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The Potential Impact of Agouti Related Peptide and Asprosin on Metabolic Parameters and Eating Behavior in Attention Deficit Hyperactivity Disorder

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ABSTRACT

Introduction: We aimed to evaluate Agouti-Related Peptide (AgRP) and asprosin levels in adults with Attention Deficit Hyperactivity Disorder (ADHD), and to examine the relationship between eating behavior, metabolic parameters, AgRP and asprosin.

Methods: Forty-five adult ADHD patients and 45 controls were included in the study. The Adult Diagnostic Interview Scale for ADHD (DIVA 2.0) and Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders-5 Clinician Version (SCID-5/CV) were administered to the participants. The Adult Attention Deficit Hyperactivity Disorder Self-Report Scale (ASRS) and the Dutch Eating Behavior Questionnaire (DEBQ) were completed by the participants. Biochemical parameters, AgRP and asprosin levels of the participants were measured.

Results: Adults with ADHD had significantly higher HbA1c, body mass index (BMI), and waist circumference. Eating behaviors and lipid profile were impaired in the patients. A significant positive correlation was found between the patients' ASRS/hyperactivity-impulsivity scores and DEBQ/emotional eating and DEBQ/external eating. A significant positive correlation was found between ASRS/total score and DEBQ/emotional eating, DEBQ/external eating, and DEBQ/total eating scores. AgRP and asprosin levels were significantly lower in the patients. The effect sizes of AgRP and asprosin were 0.526 and 0.839, respectively. A negative correlation was found between AgRP and asprosin levels of the patients and BMI. It was seen that AgRP and asprosin were confounding factors for each other, and the significance between the groups was due to asprosin. Asprosin defined ADHD at a higher rate than AgRP.

Conclusion: The study emphasizes the link between eating behavior and the hedonic system in ADHD. It also showed that AgRP and asprosin levels are low in adult ADHD. Low AgRP and asprosin levels may be an indication of impaired energy homeostasis and/or a structural cause for ADHD.

Keywords: Agouti-related peptide, asprosin, attention deficit/hyperactivity disorder, disordered eating behaviors, hedonic system, homeostatic system

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INTRODUCTION

In the literature, it is stated that attention deficit hyperactivity disorder (ADHD) is associated with overweight, impaired lipid profile, diabetes, metabolic syndrome, eating disorders and obesity. (1–6). Attention deficit hyperactivity disorder has also been associated with emotional eating, disordered eating, and addictive-like eating behavior, although it is not an eating disorder diagnosis (7,8). Many hypotheses have been proposed to explain this relationship. Abnormal eating habits, reduced physical activity (less participation in sports activities), impairments in emotion regulation processes, impulsive behaviors leading to disordered eating behavior, the contribution of accompanying mental disorders to eating behavior, poor eating habits and the presence of common genetic features are some of them (1,7–12).

Compulsive eating is regulated by homeostatic and non-homeostatic (hedonic) processes that integrate reinforcing and rewarding aspects of food as well as energy needs (13,14). Nutrition to meet energy needs is called homeostatic nutrition. The homeostatic pathway controls energy balance by increasing motivation to eat after energy stores are depleted. (13–15). The hypothalamus is the primary brain region involved in the homeostatic regulation of energy intake (14). The arcuate nucleus (nucleus arcuatus – arcuate nucleus) located in the hypothalamus plays an important role in maintaining the body's balance between

Highlights

- **BMI (body mass index) was higher; lipid profile and eating behavior were impaired in ADHD.**
- **Hyperactivity/impulsivity were positively correlated with disordered eating.**
- **AgRP and asprosin levels were lower in ADHD and negatively correlated with BMI.**
- **It was determined that asprosin defined ADHD more than AgRP.**
- **Our results support that the hedonic system is dominant in adults with ADHD.**

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food intake and energy expenditure (16). In the arcuate nucleus, two different neuron systems are working in opposition to each other. Neuropeptide Y and Agouti-related Peptide (AgRP) activation; increases appetite (16). Pro-opiomelanocortin (POMC), cocaine and amphetamine regulated transcript (CART) peptide; reduces appetite (16). Neurons in this region are involved in the regulation of energy homeostasis in response to stimuli from both the adipose tissue and the gastrointestinal tract. Some of these hormones and neuropeptides are appetite stimulating (adiponectin, ghrelin, acyl-CoA binding protein, nicotinamide phosphoribosyl transferase, asprosin), some are appetite inhibitors (adrenomedulin, apelin, cholecystokinin, leptin, nesfatin, pancreatic polypeptide, vasoactive intestinal polypeptide) (17). Paradoxically, while most appetite inhibitors increase obesity, it has been reported that most appetite stimulants decrease. In the literature, there are only three appetite stimulants in obesity that follow a consistent pattern and increase (Immediate Co-A binding protein, nicotinamide phosphoribosyl transferase and asprosin) (17). Asprosin; It is mainly produced and released by adipocytes in white adipose tissue during fasting. Asprosin crosses the blood-brain barrier and subsequently increases the activity of AgRP neurons in the arcuate nucleus. Thus, food intake is stimulated and energy homeostasis is regulated (18). It has been reported that patients with lipodystrophy in asprosin deficiency due to a mutation in the Fibrillin-1 gene consume less food and become extremely weak (18).

Apart from their effects on homeostatic mechanisms, nutrients also affect brain regions associated with pleasure and reward (13–15). Nowadays, eating often happens even if there is no hunger. This is "non-homeostatic" or "hedonic" eating; refers to food intake not regulated by metabolic feedback and by cognitive, reward-related, and emotional factors (19). The hedonic diet is the result of the powerful reinforcing and motivating properties of food, which is closely related to dopamine release in the limbic system, particularly stimulated by fatty and sugary foods (15). Today, the easy accessibility of a delicious diet and the consumption of pleasurable foods result in hedonic mechanisms dominating homeostatic pathways and increasing food consumption, which is an important risk factor for obesity (14). Low hedonic tone; has been associated with a variety of psychopathologies, including depressive disorder, substance use disorder, and ADHD (20). It has been suggested that disruption of the dopaminergic system in ADHD includes impulse-control disorders, inattention, and reward sensitivity, and that this may increase the risk of consuming delicious, sugary foods, which are seen as natural rewards, and even food addiction (7).

Asprosin is an appetite stimulant that plays a role in the regulation of the homeostatic system and shows its effect via AgRP and its serum level increases in obesity (17). Considering that ADHD is often accompanied by disordered eating behaviors, increased body mass index (BMI), and obesity, it is not surprising that serum AgRP and asprosin regulation are impaired in people with this disorder. In the literature review on disordered eating behaviors, metabolic problems and obesity in adult ADHD, it was seen that AgRP and asprosin levels were not studied, except for our recently published study looking at AgRP levels (1). Evaluation of the relationship between ADHD severity, AgRP and asprosin levels and eating behaviors may contribute to our knowledge of hedonic/homeostatic mechanisms in ADHD.

We hypothesized that adults with ADHD would have disordered eating behaviors and metabolic parameters, disruptions in AgRP and asprosin regulation, and that food intake in ADHD would be associated with emotion and stress-sensitive pathways rather than energy needs. In our study, we aimed to investigate whether the clinical characteristics, serum fasting AgRP and asprosin levels and biochemical parameters of adults with ADHD and controls differed and to evaluate the relationship between AgRP and asprosin levels, eating behavior, clinical characteristics and biochemical parameters in ADHD.

METHOD

Research Sample

Taking into account similar studies in the literature, according to our sample calculation using the G* power statistical program, it was calculated that 90 participants, 45 in each group, should be included for a 10-unit difference to be significant at 90% power and 95% confidence level (effect size=0.70) (21). The patient group consisting of 45 adults with ADHD diagnosis was composed of patients who applied to the Erzurum Regional Education and Research Hospital Psychiatry outpatient clinic between April 2022 and December 2022. The control group was composed of individuals who applied to our clinic for consultation or status reports without psychiatric disorder.

Procedure

Our study focused on the cross-sectional clinical characteristics, routine biochemical parameters, and serum fasting AgRP and asprosin analyses of 90 participants. The research protocol was approved by the Erzurum Regional Education and Research Hospital Clinical Research Ethics Committee with the decision dated 18.04.2022 and numbered 2022/05–46 and carried out in accordance with the Helsinki Declaration. Written informed consent was obtained from all participants before the first interview. The sample of the study consists of 45 adult patients who meet the ADHD diagnostic criteria and have not received any treatment before, and 45 controls with similar sociodemographic characteristics such as age, gender, and education level. The diagnosis of ADHD was made using Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5)-Clinician Version (SCID-5/CV) and Adult Diagnostic Interview Scale for ADHD (DIVA) 2.0 diagnostic interview test. Additional psychopathologies were excluded in all participants by psychiatric interview and SCID-5/CV. Participants were evaluated twice by two different psychiatrists at different times. The Adult Attention Deficit Hyperactivity Disorder Self-Report Scale (ASRS) and the Dutch Eating Behavior Questionnaire (DEBQ) were completed by all participants. The clinical and sociodemographic data of the participants were recorded. Fasting blood samples were taken from all participants between 08:00–10:00. The weight, height, waist circumference and blood pressure of all participants were measured.

Being diagnosed with ADHD according to DSM-5, not having received any treatment for ADHD and not having any additional psychopathology other than ADHD were determined as inclusion criteria for the patient group. Additionally, being between the ages of 18–65, not having a physical and/or mental disability that would prevent the completion of the tests, not having an acute/chronic physical illness and having given written consent to participate in the research were also included in the inclusion criteria. The inclusion criteria for the control group were determined as being between the ages of 18–65, not having any psychopathology, not having an acute/chronic medical illness, not having a physical and/or mental disability that would prevent the completion of the tests and giving written consent. No changes were made in the treatment of patients who were included in the study or who did not want to participate in the study.

Data Collection Tools

Sociodemographic-Clinical Data Form: It is a form developed by researchers to record the characteristics of the patient and control groups such as age, gender, education, marital status, employment status, alcohol-tobacco use, height, weight, BMI.

SCID-5/CV: The Structured Clinical Interview for DSM (SCID) is one of the most widely used diagnostic tools in clinical research worldwide. The

latest version is SCID-5. SCID-5-CV is a comprehensive, standardized tool for evaluating major psychiatric disorders according to the definitions and criteria of DSM-5. This structured clinical interview includes 32 diagnostic categories with detailed diagnostic criteria and 17 diagnostic categories with research questions (22). The validity and reliability study of the Turkish version of SCID-5/CV has been conducted (23).

DIVA 2.0: It is a diagnostic interview form developed for adults according to DSM-IV diagnostic criteria. DIVA consists of three sections applied separately for childhood and adulthood, including A1- attention deficit criteria, A2- hyperactivity and impulsivity criteria, the onset of symptoms and dysfunction resulting from symptoms (24).

ASRS: It was developed by the World Health Organization (25). The scale has two sub-dimensions, 'attention deficit' and 'hyperactivity/impulsivity', and each sub-scale consists of nine questions. The questions aim to determine how often each symptom has occurred in the last six months. The items on the scale are scored between 0–4. The Turkish validity and reliability of the scale was conducted by Dogan et al. in 2009 (26). In the reliability analysis, it was found that the internal consistency of the scale was high (Cronbach's alpha=0.88). Cronbach's alpha value was reported as 0.78 for hyperactivity/impulsivity and 0.82 for attention deficit. Test-retest reliability is high (r=0.85 for total scores; r=0.73–0.89 for sub-scales).

DEBQ: It was developed by Van Strein and friends in 1986 (27). The questionnaire consists of 33 items and is composed of three subscales evaluating emotional eating, external eating and restricted eating behaviors. The items are scored between 1–5. There is no cut-off point in scoring the test. There are three sub-scale scores evaluated within themselves and a total score. A high total score indicates a disruption in eating behaviors. In the original study of DEBQ, Cronbach's alpha internal consistency coefficients were 0.95 for the emotional eating behavior sub-scale, 0.81 for the external eating behavior sub-scale and 0.95 for the restricted eating behavior sub-scale (27). The Turkish validity and reliability study of the scale was conducted by Bozan and colleagues in 2009. Cronbach's alpha values for sub-scales vary between 0.90 (external eating) and 0.97 (emotional eating). The internal consistency coefficient of the entire scale was reported as 0.94 (28).

Biochemical Analysis

After ensuring that the controls and ADHD patients were resting in a sitting position, blood was taken into a biochemistry tube for routine biochemical parameters; Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Gamma Glutamyl Transferase (GGT) activities, glucose, cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglyceride and glycated hemoglobin (HbA1c) levels and AgRP and Asprosin measurements using a vacutainer by experienced individuals from the antecubital region. After allowing the samples to clot for 30 minutes at room temperature, they were centrifuged and ALT, AST, GGT activities, glucose, cholesterol, HDL, LDL, and triglyceride levels were determined using a spectrophotometric method on a Beckman Coulter AU 5800 clinical chemistry analyzer (Beckman Coulter, CA, USA). HbA1c levels were measured by high-performance liquid chromatography method on Trinity Biotech brand Premier Hb9210 HbA1c (Trinity Biotech Plc, Jamestown, USA) device in whole blood samples taken into EDTA hemogram tubes. After blood was drawn into yellow-capped biochemistry tubes and coagulation was finished, sera were separated by centrifuging at 3000 rpm for 10 minutes for AgRP and asprosin levels. Serum samples were aliquoted and frozen at -80° until analysis. For analysis, after the serum samples were thawed under appropriate conditions, all analyses were performed in a single session at the Atatürk University Health Research and Application Center Medical Biochemistry Laboratory. AgRP levels in serum samples were analyzed using commercially purchased SunRed brand (USA) ELISA kits and asprosin levels were analyzed using BT Lab brand (China) Elisa kits according to the manufacturer's recommended standard protocol on a Dynex brand automatic ELISA reader (Dynex Technologies Headquarters, Chantilly, USA). The measurement range of the kit was 5–1500ng/L and 0.5–100ng/mL, respectively.

Statistical Analysis

The analyses were performed using the IBM Statistical Package for Social Sciences (SPSS) program version 20 statistical analysis program. Data were presented as mean, standard deviation, median, minimum, maximum, percentage and number. The normal distribution of continuous variables was examined using the Shapiro Wilk-W test, Kolmogorov Smirnov test, Q-Q plot, skewness and kurtosis. In comparisons between two independent groups, the independent samples t-test was used when the normal distribution condition was met, and the Mann-Whitney U test was used when it was not met. The effect sizes between the two groups were calculated using Cohen's d statistic. Pearson's Chi-square test was employed for 2×2 comparisons between categorical variables, if the expected value was >5, Yates' Chi-square test if the expected value was between 3–5, and Fisher's Exact test if the expected value was <3. For comparisons between categorical variables larger than 2×2, Pearson's Chi-square test was used if the expected value was >5, and the Fisher-Freeman-Halton test was used if the expected value was <5. In the comparison of two quantitative variables, Pearson's correlation was used if the normal distribution condition was met, and Spearman's correlation test was used if it was not met. ANCOVA was used in multiple comparisons to examine the effects of cofactors on the dependent variable. Receiver operating characteristic (ROC) curve analysis was performed to determine whether the continuous variable could be used in diagnosis. In the model created to determine the relationships between the scales, the significance level of indirect effects was tested using the structural equation modeling bootstrapping method. Path coefficients (β) were calculated for the model. The statistical significance level was taken as $p<0.05$.

RESULTS

Forty-five ADHD patients and 45 controls with similar age, gender and education level were included in the study. Among the 45 patients included in the study, 33 patients (73.3%) were diagnosed with combined presentation and 12 (26.7%) with inattentive presentation.

The history of mental disorders in the family was found to be higher in the patient group compared to the control group (p=0.005). A relationship was found between alcohol use and patient and control groups (p=0.014). Of the nine participants who used alcohol, eight (88.9%) had ADHD. A relationship was found between the patient and control group and the reversal of the day-night cycle, feeling more energetic at night and more productive in the morning (p<0.001). All five participants diagnosed with metabolic syndrome were ADHD participants. The comparison of sociodemographic-clinical characteristics and biochemical parameters of patient and control groups is shown in Table 1.

Dutch Eating Behavior Questionnaire scores (restrictive eating, emotional eating, external eating and total DEBQ score) were found to be higher in the patient group compared to the control group (p<0.001). AgRP (p=0.015) and asprosin levels (p<0.001) were observed to be lower in patients compared to controls. The effect sizes of AgRP and asprosin were 0.526 and 0.839, respectively. The comparison of ASRS and DEBQ Scale scores, clinical characteristics, AgRP and asprosin levels and biochemical parameters of patient and control groups is shown in Table 2.

Table 1. Comparison of sociodemographic and clinical characteristics of the patient and control groups

		Patient group n-(%)	Control group n-(%)	Chi-square	Mean ± SD	p
Age (year)	Patient				28.71±7.44	0.30
	Control				27.20±6.22	
Gender	Female	19–(42.2)	22–(48.9)	0.179		0.67
	Male	26–(57.8)	23–(51.1)			
Marital status	Married	9–(20)	10–(22.7)	0.067		0.79
	Single	36–(80)	35–(77.8)			
Job	Student	28–(62.2)	30–(66.7)			
	Employee	14–(31.1)	15–(33.3)			
	Not Working	3–(6.7)	0–(0)			
Cigarette smoking	Yes	16–(5.6)	10–(22.2)	1.947		0.16
	None	29–(64.4)	35–(77.8)			
Alcohol use	Yes	8–(17.8)	1–(2.2)	6.049		**0.014**
	None	37–(82.2)	44–(97.8)			
Presence of mental illness in the family	Yes	19–(42.2)	7–(5.6)	7.788		**0.005**
	None	26–(57.8)	38–(64.4)			
Living the night-day cycle reversed	Never	4–(8.9)	20–(44.4)	33.593		**<0.001**
	Rarely	9–(20.0)	18–(40.0)			
	Sometimes	7–(15.6)	5–(11.1)			
	Mostly	25–(55.6)	2–(4.4)			
Feeling more productive in the morning	Never	14–(31.1)	3–(6.7)	35.711		**<0.001**
	Rarely	24–(53.3)	7–(15.6)			
	Sometimes	4–(8.9)	5–(11.1)			
	Mostly	3–(6.7)	30–(66.7)			
Feeling more energetic at night	Never	1–(2.2)	15–(33.3)	41.461		**<0.001**
	Rarely	8–(17.8)	17–(37.8)			
	Sometimes	6–(13.3)	11–(24.4)			
	Mostly	30–(66.7)	2–(4.4)			

p<0.05; Statistical significance level in comparison of two groups; Mean ± SD: Mean ± standard deviation; n: number of participants.

AgRP (p=0.022) and Asprosin (p=0.05) levels were found to be lower in patients with high waist circumference than in patients with normal waist circumference. There was no difference between genders in AgRP (p=0.153) and asprosin (p=0.700) levels in the patient group. A high level of positive correlation was found between AgRP and asprosin (p<0.001). A moderate negative correlation was found between AgRP (p=0.040) and asprosin (p=0.035) levels and BMI. A moderate positive correlation was found between ASRS/hyperactivity-impulsivity scores of patients and DEBQ/emotional eating (p=0.041) and DEBQ/external eating (p=0.014) scores. A moderate positive correlation was found between the total clinical severity of ADHD (ASRS/T) and DEBQ/emotional eating (p<0.001), DEBQ/external eating (p<0.001) and DEBQ/total eating scores (p=0.001).

When AgRP was a covariate, it was found that there was a relationship between asprosin and AgRP, that AgRP was a confounding factor and that asprosin was significant between groups. When asprosin was a covariate, it was found that there was a relationship between asprosin and AgRP, that asprosin was a confounding factor and that AgRP was not significant between groups. ANCOVA analysis for AgRP and asprosin is shown in Table 3.

Receiver operating characteristic curve analysis was performed to reveal the role of AgRP and asprosin in distinguishing ADHD. The analysis results showed that AgRP (Area under curve (AUC) ± Standard Error (SE); 95% Confidence Interval (CI); 0.643±0.059; 0.527–0.759) and asprosin (AUC ± SE; 95% CI; 0.733±0.054; 0.628–0.838) can be used to identify ADHD and that low levels of AgRP and asprosin increase the likelihood of identifying ADHD. When looking at AgRP and asprosin, it was found that asprosin identified ADHD at a higher rate than AgRP (Table 4 and Figure 1).

It was found that asprosine had an intermediary effect between the total ASRS score of all participants and AgRP (β=-0.218; Z=-3.292; p<0.001). The intermediary effect of asprosine is shown in Table 5.

Table 2. Comparison of ASRS scale scores, DEBQ scale scores, clinical characteristics, AgRP, asprosin and other biochemical parameters of the patient and control groups

	Patient Group n=45	Control Group n=45			
	Mean ± SD	Mean ± SD	t, Z	p	Effect size
ASRS Total Score	43.64±6.54	14.84±2.54	-27.522	**<0.001**	5.802
ASRS Attention Score	24.38±3.63	7.09±1.44	-29.716	**<0.001**	6.265
ASRS Hyperactivity/ Impulsivity Score	19.27±6.24	7.69±1.82	-11.950	**<0.001**	2.519
DEBQ restrained eating score	25.60±6.83	18.96±3.12	-5.936	**<0.001**	1.251
DEBQ emotional eating score	40.84±9.11	25.56±3.87	-10.364	**<0.001**	2.185
DEBQ external eating score	26.16±5.00	19.76±3.66	-6.931	**<0.001**	1.461
DEBQ total score	92.56±16.87	64.31±7.35	-7.315	**<0.001**	0.601
Height cm	172.04±10.36	171.09±8.79	-0.178	0.859	0.000
Weight (kg)	75.26±14.17	69.44±12.74	-1.805	0. 071	0.037
BMI	25.37±4.10	23.59±3.12	-2.223	**0.026**	0.056
Waist Circumference (cm)	83.07±11.19	77.09±10.14	-2.556	**0.011**	0.073
Glucose	85.71±13.12	83.67±5.79	-0.956	0.343	0.202
HbA1c	5.18±0.31	4.98±0.36	-2.475	**0.013**	0.069
HDL	50.49±10.83	47.62±9.26	-1.131	0.258	0.014
Triglyceride	134.24±122.66	96.73±44.48	-1.929	0.059	0.407
Cholesterol	189.87±38.87	156.24±25.32	-4.862	**<0.001**	1.025
LDL	125.80±25.81	98.98±21.81	-4.755	**<0.001**	0.254
ALT	23.31±18.25	18.71±17.86	-1.209	0.230	0.255
AST	23.29±7.97	19.73±6.52	-2.316	**0.023**	0.488
GGT	27.13±17.91	19.73±11.26	-2.346	**0.022**	0.495
AgRP	574.54±431.25	781.92±353.80	2.494	**0.015**	0.526
Asprosin	18.97±17.49	34.04±18.44	3.978	**<0.001**	0.839

Note: p<0.05; Statistical significance level in comparison of two groups; Effect size=Cohen's d (0.2-small, 0.5-medium, and 0.8-large effect size).
AgRP: Agouti-related peptide; ALT: Alanine aminotransferase; ASRS: Adult attention deficit hyperactivity disorder self-report scale; AST: Aspartate aminotransferase; BMI: Body mass index; DEBQ: Dutch Eating Behavior Questionnaire; GGT: Gamma glutamyl transferase; HbA1c: Glycosylated hemoglobin; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; Mean ± SD: Mean ± standard deviation; n: Number of participants; t: Independent samples t-test, Z; Mann-Whitney U test.

Table 3. ANCOVA for AgRP and asprosin

Tests of between-subjects effects				
Dependent Variable: Asprosin				
Source	**Type III Sum of squares**	**Mean square**	**F**	**p**
Corrected model	14388.665[a]	7194.332	32.720	0.000
Intercept	1751.986	1751.986	7.968	0.006
AgRP	9280.010	9280.010	42.206	**0.000**
Group	1964.687	1964.687	8.935	**0.004**
Error	19129.258	219.877		
Total	96760.179			
Corrected total	33517.922			
Dependent variable: AgRP				
Source	**Type III Sum of squares**	**Mean square**	**F**	**p**
Corrected model	5439733.941[b]	2719866.971	25.669	0.000
Intercept	3332760.813	3332760.813	31.453	0.000
Asprosin	4472106.327	4472106.327	42.206	**0.000**
Group	6402.729	6402.729	0.060	0.806
Error	9218532.856	105960.148		
Total	56057507.386			
Corrected total	14658266.797			

[a]R squared=0.429 (Adjusted R squared=0.416);
[b]R squared=0.371 (Adjusted R squared=0.357).
p<0.05; Statistical significance level, AgRP: Agouti-related peptide.

Table 4. ROC curve analysis result for AgRP and asprosin

Test Result Variable (s)		Area under curve	Standard Error[a]	Asymptotic significance[b]	Asymptotic 95% Confidence Interval	
					Lower Bound	Upper Bound
	AgRP	0.643	0.059	**0.019**	0.527	0.759
	Asprosin	0.733	0.054	**0.000**	0.628	0.838

[a]Under the nonparametric assumption
[b]Null hypothesis: true area=0.5
p<0.05; Statistical significance level, AgRP; Agouti-related peptide.

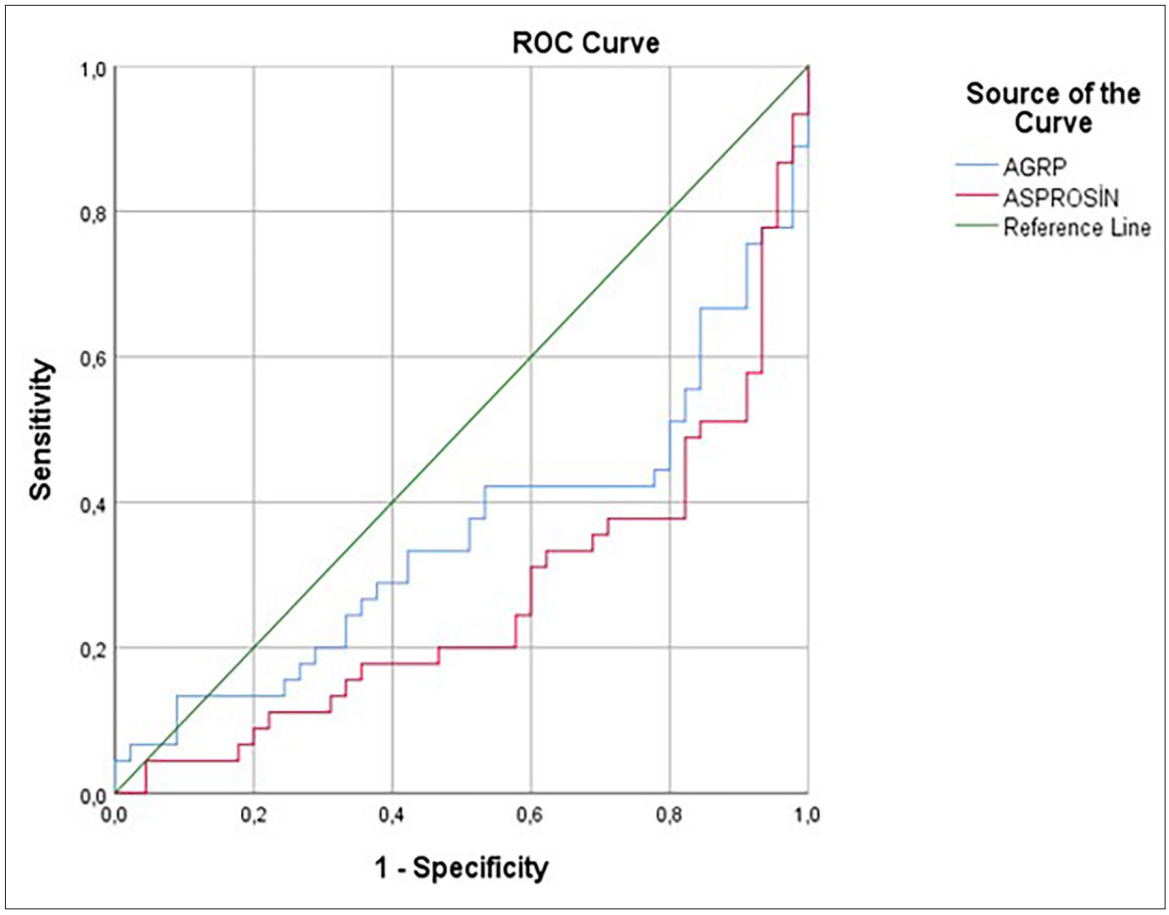

Figure 1. Receiver operating characteristic curve analysis for AgRP and asprosin (AgRP: Agouti-related peptide).

Table 5. Mediator effect of asprosin between ASRS total score and AgRP

				95% CI				
Type	**Effect**	**Estimate**	**SE**	**Lower**	**Upper**	β	**z**	**p**
Indirect	ASRS Total Score → Asprosin → AgRP	-5.804	1.763	-9.260	-2.348	-0.2188	-3.292	<0.001
Component	ASRS Total Score → Asprosin	-0.473	0.124	-0.716	-0.230	-0.3728	-3.812	<0.001
	Asprosin → AgRP	12.272	1.880	8.587	15.957	0.5868	6.527	<0.001
Direct	ASRS Total Score → AgRP	-1.565	2.385	-6.239	3.110	-0.0590	-0.656	0.512
Total	ASRS Total Score → AgRP	-7.369	2.701	-12.663	-2.074	-0.2778	-2.728	0.006

Confidence intervals computed with method: Standart (Delta method).
Betas are completely standardized effect sizes.
p<0.05; Statistical significance level in comparison of two groups; AgRP: Agouti-related peptide; ASRS: Adult Attention Deficit Hyperactivity Disorder Self-report Scale, CI: Confidence Interval, SE: Standard Error..

DISCUSSION

In our study, it was found that there are irregular eating behaviors in adult ADHD, BMI and waist circumference measurements are higher and lipid profile is impaired. It was determined that serum fasting AgRP and asprosin levels were lower in patients. Waist circumference was significantly lower in patients with high waist circumference compared to patients with normal waist circumference. A significant relationship was found between the severity of hyperactivity/impulsivity and the clinical severity of ADHD and irregular eating behaviors (emotional eating and external eating).

Irregular eating habits (overeating, guilt after overeating, difficulty to plan meals, meal skipping) are poor eating behaviors that don't meet the diagnostic criteria of eating disorders and are considered risk factors for eating disorders. (1,29). It is reported that there is a relationship between ADHD and irregular eating behaviors, that both impulsive and inattentive components of ADHD can reinforce irregular eating behaviors, and that inattention and inadequate planning can cause difficulties in adhering to irregular eating habits and diet practices (1,9,29). In the study, it was found that the patients' eating behaviors were impaired, and that restrictive eating, external eating and emotional eating scores were significantly higher than controls. In addition, a significant and positive relationship was observed between the severity of hyperactivity/impulsivity and emotional eating and external eating scores in patients. Impulsivity is one of the main symptoms of ADHD and it has been reported that impulsivity can reinforce irregular eating behaviors and increase obesity (1,4,9,30).

According to the reports, there is a bidirectional relationship between ADHD and obesity in adults, the prevalence of ADHD is higher in obese people and obesity is more common in maturity (4,7–9). It has been shown that obesity increases by 70% in adults with ADHD compared to those without ADHD, and by 40% in children (7,8). In our study, it was found that BMI, waist circumference, HbA1c, total cholesterol and LDL levels were significantly higher in patients compared to controls. In line with our findings, it has been reported in the literature that there is a significant relationship between ADHD and overweight, that BMI, HbA1c and LDL levels are higher in patients, and triglyceride and HDL levels are similar (1,4,8). It is also stated in the literature that high blood lipid levels are associated with an increased risk of ADHD in obese children (4,5).

It has been observed that serum asprosin levels are pathologically elevated in obese adults, children and mice, and when a specific antibody to asprosin is used in obese mice, there are decreases in body weight and food intake (18,31). In our study, although the BMI and waist circumference of the patients were higher than the controls, serum AgRP and asprosin levels were found to be significantly lower. The AgRP and asprosin levels of the patients showed a negative correlation with BMI. In addition, in the patient group; AgRP and asprosin levels of those with high waist circumference were significantly lower than those with normal waist circumference. This may be an indicator and/or structural cause of impaired energy homeostasis in ADHD. In line with the literature, it was observed that AgRP and asprosin are related and confounding factors, but the significance between groups was due to asprosin (31).

When we reviewed the literature, we found that in addition to studies supporting the appetite-stimulating effects of AgRP and asprosin, studies were reporting that low asprosin levels were detected in obese children and interestingly, asprosin levels increased in patients with anorexia (31–34). AgRP levels were found to be significantly lower in patients during manic periods compared to euthymic periods and the control group, and it was suggested that this is an indicator of impaired energy homeostasis during manic periods and that AgRP may be a state marker (35). In another study, it was reported that patients diagnosed with bipolar disorder in remission had higher serum AgRP levels than controls, but no relationship was found between increased AgRP levels and BMI in patients (34).

The outcomes of the studies conducted with appetite hormones in ADHD also included conflicting results (36–38). In a study involving 50 adolescents with ADHD, it was found that patients had higher insulin and leptin levels than controls, and there was no difference in ghrelin and adiponectin levels (37). In a study conducted with 44 patients with ADHD, it was reported that there was a decrease in serum adiponectin levels in patients compared to controls (38). In a study conducted with 30 patients diagnosed with ADHD, there was no significant difference between leptin and ghrelin levels, while Neuropeptide Y levels were found to be low in the group with ADHD group (36). In our literature review, we did not find any studies that examined AgRP and asprosin levels, except for our study that looked at AgRP levels in adult ADHD (1). Within our study regarding the investigation of the relationship between impaired eating attitudes and night eating syndrome and AgRP in adults with ADHD, we demonstrated that patients who did not receive treatment did not show a significant difference with controls, although their AgRP levels were low, there was no relationship between impaired eating behavior and AgRP, and impulsivity severity was effective on impaired eating behavior (1). In our current study, we found that there was no relationship between irregular eating behaviors and AgRP and asprosin levels in patients, and there was a significant and positive relationship between the severity of hyperactivity/impulsivity in ADHD and emotional eating. These results point to the relationship between feeding behavior in ADHD and the hedonic system. It has been reported that impairment of the dopaminergic system in ADHD may increase the consumption of tasty and sugary foods seen as natural rewards (7). In line with our results, it has been reported in the literature that patients diagnosed with ADHD are more prone to irregular and/or impulsive eating habits. There is also information in the literature that this may lead to increased BMI and related metabolic disorders (1,6).

Hedonic nutrition, defined as appetite stimulation, desire to eat and enjoyment without eating while there is no metabolic need, affects people's nutritional orientation and nutritional behavior (14). In mouse models where transient or chronic loss of AgRP neuron activity was created, it was observed that feeding behavior on a normal food diet depended on AgRP neurons and that AgRP neurons were not needed when a tasty diet was given. Mice with AgRP neuron ablation experienced rapid weight loss when subjected to a normal food diet and this resulted in deep anorexia, and it has been reported that AgRP neurons are a critical component of the homeostatic circuit. It has been found that mice with AgRP neuron ablation exhibit exaggerated hyperphagia with a tasty diet, supporting the hypothesis that in the absence of AgRP neurons, feeding is less motivated by energy demand and more sensitive to changes in the stress and reward pathway. When AgRP neuron activity is disrupted, emotion and stress-sensitive neural pathways are activated and food intake is modulated by food aroma and dopamine signaling (15).

Our results (irregular eating behaviors, increase in BMI and waist circumference, deterioration in lipid profile, no relationship between impaired eating behaviors and AgRP and asprosin levels in patients, on the other hand, deterioration in eating behaviors being related to the severity of hyperactivity/impulsivity and clinical severity of ADHD, low AgRP and Asprosin levels, negative correlation between AgRP and asprosin levels and BMI and waist circumference) support that food intake in ADHD is closely related to emotional and stress-sensitive neural circuits rather than energy needs, with hedonic mechanisms becoming dominant by invalidating homeostatic pathways.

Performing diagnostic evaluations based on structured clinical interviews, the validity and reliability of the scales completed by the participants in Turkish, the evaluation of the participants by two different psychiatrists, the fact that the study was conducted taking into account many variables together with AgRP and asprosin, and the use of an appropriately selected control group are the strengths of the research.

The limitations of our study include its cross-sectional nature, the fact that some of the data are based on personal reporting scales, the lack of detailed discussion of nutritional characteristics, and the lack of a full investigation of appetite stimulants and inhibitors. It should not be forgotten that the study results may not represent the entire population.

As a result of this study, it has been revealed that serum AgRP and asprosin levels are significantly lower in adult ADHD, and there are irregular eating behaviors, weight gain and impairments in lipid profile. Considering the increasing prevalence of obesity, revealing and effectively treating the role of ADHD in the development of obesity will positively affect both the physical and mental health of individuals and reduce societal costs. Although we do not know for sure whether hedonic feeding in adult ADHD is a cause or a consequence of irregular eating behaviors, we believe that future studies should consider both homeostatic energy-focused and non-homeostatic reward-focused feeding as a whole and conduct longitudinal studies to better understand the relationship between ADHD and obesity.

Ethics Committee Approval: The research protocol was approved by the Clinical Research Ethics Committee of Erzurum Regional Education and Research Hospital with the decision dated 18.04.2022 and numbered 2022/05–46.

Informed Consent: Written informed consent was obtained from the participants.

Author Contributions: Concept– NG, SZ; Design– NG, SZ, EL, KK; Supervision– NG, SZ, EL, KK; Resource– NG, SZ; Materials– NG, SZ, EL, KK; Data Collection and/or Processing– NG, SZ, EL, KK; Analysis and/or Interpretation– NG, SZ, EL, KK; Literature Search– NG, SZ; Writing– NG, SZ, EL, KK; Critical Reviews– NG, SZ, EL, KK.

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