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The assessment of serum omentin levels of children with autism spectrum disorder and attention-deficit/hyperactivity disorder

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ABSTRACT

Objectives: We aimed to investigate plasma omentin concentrations in non-obese, drug-free patients with autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) in comparison with healthy volunteers.

Methods: Sixty children with ASD, 60 children with ADHD, and 60 control subjects were recruited. Plasma omentin levels were determined by the enzyme-linked immunosorbent assay.

Results: Plasma levels of omentin (479.0 ng/ml) were found to be significantly higher in patients with ASD (median = 422.6, min/max; 220–800) than in controls (382.5 ng/ml) (median = 322.0, min/max 184–800). No significant difference was found between ADHD and control groups with respect to plasma omentin levels. There was no significant correlation between omentin levels and age of children, ABCL, AbBC, CARS, CPRS, and CTRS scores.

Conclusions: To our knowledge, this is the first study that demonstrated the association between omentin and ASD and ADHD. The present results suggest that plasma omentin levels are increased in non-obese and drug-free patients with ASD when compared with in ADHD and healthy children. The omentin levels in ADHD and ASD need further refinement with larger samples and long-term follow-up periods.

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Introduction

Autism spectrum disorder (ASD) is characterized by developmental abnormalities in social interaction and communication, reciprocity and language use, as well as the occurrence of repetitive and stereotypical behaviours and area of interests [1]. ASD affects nearly 1% of the population worldwide [2,3]. Thus far, a number of genetic, perinatal, and biochemical pathways have been suggested for the aetiology and pathogenesis of this neurodevelopmental disorder, although its exact mechanism remains unclear [4].

Attention-deficit/hyperactivity disorder (ADHD) is characterized by inattention, hyperactivity, and impulsivity. It is accepted to be one of the most common neuropsychiatric disorders, with a global prevalence of around 5–10% in childhood [5]. Similar to ASD, the aetiology of ADHD is not yet clear [6].

Due to the relatively high frequency of both disorders and the inadequacy of the common treatment approaches, which can cause severe economic burdens and negative effects for both children and their family, researchers' interest in the clarification of the aetiologies of these two disorders is increasing. Some studies that have investigated the commonalities of ASD and ADHD have supported the notion that these disorders have similar biological features [7,8]. Thus, the common aetiological and pathophysiological factors of the two disorders should be investigated systemically.

In recent years, the tissue thought to play a role in the aetiology of psychiatric disorders is the adipose tissue. Adipose tissue is a dynamic structure that plays a role in the regulation of the metabolism in humans by means of secreting adipokines [9]. The adipokines are responsible for several physiological functions, including nutrition, appetite, energy balance, insulin, glucose and lipid metabolism, blood pressure regulation, vascular remodelling, coagulation, and inflammation. There is some evidence supporting the association between the adipokines and anorexia and bulimia nervosa, depression, anxiety disorders, ASDs, ADHD, and schizophrenia [10–15]. However, due to various methodological differences, the results in this regard are inconsistent and hence need to be confirmed. The adipokines are known to have a pro-inflammatory function [16], which is suggested to be one of the biological factors that play a role in the aetiology of both ASD and ADHD [4,7,8].

Prior studies have mostly investigated the levels of adiponectin, leptin, resistin, and ghrelin in neuropsychiatric disorders [17,18] although a few studies have

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examined the omentin levels. Omentin is a novel adipocytokine that was first isolated from intestinal paneth cells, although it was later also isolated from cardiac, ovarian, adipose tissue, lungs, and placenta [19]. It is known to be secreted to a greater extent by the cells of the visceral adipose tissue than the subcutaneous adipose tissue [20]. The regulatory mechanisms of omentin in humans are not yet fully understood, but the circulating levels of omentin are known to be negatively associated with metabolic risk factors [21].

Omentin regulates the nitric oxide synthase enzyme and affects the dysfunction of the endothelium [22]. It also antagonizes vasoconstriction due to the effect of noradrenaline through nitric oxide (NO) [23]. NO is a neurotransmitter that regulates many biological processes, including immunity and vasodilatation [24]. The effects of vascular NO are reduced by the presence of free oxygen radicals [25]. These free oxygen radicals occur as a result of various biological reactions, for example, phagocytic activation and synthesis reactions, while an increase in the free radicals causes oxidative stress that may lead to cell damage and endothelial dysfunction [26,27].

There is some evidence to suggest that the oxidative mechanism plays a role in the aetiology of both ASD and ADHD, although the exact biological pathways affecting this mechanism are not yet clear [28–31]. In this context, we hypothesized that the possible effects of omentin on microcirculation and the oxidative system may play a role in the aetiology of ASD and ADHD. Although the relationships between the adipose tissue and various psychiatric disorders have previously been investigated, to the best of our knowledge no prior studies have investigated the omentin levels of children with these two common neurodevelopmental disorders.

Thus the aims of this study were;

(1) To determine and compare the omentin levels of children with ASD and ADHD,
(2) To assess the relationship between omentin levels and sociodemographical features and symptom severity of children with ASD and ADHD.

Methods

The ASD group and ADHD group each consisted of 60 Caucasian children aged from 9 to 13 and admitted to the Department of Child and Adolescent Psychiatry, Ankara Pediatric Hematology-Oncology Training and Research Hospital between December 2016 and February 2017. These children were diagnosed with ASD or ADHD according to DSM-5 criteria. They have not taken any medication for at least six months and they were not obese according to body mass indexes (BMI). The control group consisted of 60 Caucasian healthy children who were matched with clinical groups by gender and age.

The BMI was calculated using the formula kg/m^2. Normal weight was defined as a BMI between 5th and 85th percentile for age and sex. Centers for Disease Control and Prevention (CDC) data were used for the calculation of the BMI standard deviation score (BMISDS) [32].

All participants and their parents were informed about the study. Written and verbal consents were obtained prior to testing.

The children with mental retardation (Intelligence quotient < 70) were excluded from the groups according to the Wechsler Intelligence Scale for Children – evised and clinical evaluation. Additionally, the children with chronic medical diseases (metabolic, neurological, allergic, or endocrinological diseases), obesity, taking vitamin or any medication in past six months and had an infection in last month were excluded from the study.

Firstly, Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version was applied to the clinical sample. Gökler [33] studied the reliability and validity of Turkish version of this instrument. Conner's parents and teachers rating scales were fulfilled by the parents and teachers of children diagnosed with ADHD. Autism behaviour control checklist and problematic behaviour checklist were filled by parents of children diagnosed with ASD and childhood autism checklist scale was applied to all autistic children by the interviewers.

After obtaining 10 cc venous samples from all participants at 8:00–10:00am, they were kept at room temperature for 20 min and centrifuged at 3000 rpm for 10–20 min and then stored at −20°C until the time of assay. The samples were analysed by using the enzyme-linked immunosorbent assay (ELISA) method which is a biochemistry assay that is used to detect and quantify the presence of the substance. The Human Omentin ELISA kit was used to determine serum concentrations of omentin. The sensitivity of the kit was 0.5 ng/ml. The intra- and inter-assay coefficients of variations were 3.6% and 4.6%, respectively.

This study was approved by the ethic committee of Ankara Pediatric Hematology-Oncology Training and Research Hospital (2015/043).

Instruments

Aberrant Behaviour Checklist (AbBC)

It is an instrument initially used for determining the effects of treatment in children with mental retardation, but it is currently used for measuring the severity of behavioural problems of children with autism [34]. Parents score the problematic behaviour on 58 items of a four-point Likert scale. Turkish validity

and reliability studies were completed by Karabekiroglu and Aman [35].

Childhood Autism Rating Scale (CARS)

It is an autistic behaviour rating scale which consists of 15 items and used for diagnosis and determination of the severity of autism. Each item is a score from 1 to 4. The total score should be minimum 30 if the child has autism [36,37]. The validity and reliability studies for a Turkish sample were completed [38].

Autism Behaviour Checklist (ABCL)

It is a scale used for assessment of autism symptoms and their severity [39]. There are 57 items and 5 categories to determine the behaviours associated with autism. The validity and reliability studies have been conducted on a Turkish sample [40].

Conners' Parent Rating Scale-Revised Long Form (CPRS)

This is a parent-reported scale used for assessment of behavioural problems, ADHD symptoms and their severity of children aged 3–17 [41]. It is a four-point Likert scale and consists of 80 items. Turkish validity and reliability studies of the scale were performed [42].

Conners' Teacher Rating Scale – Revised Long Form (CTRS)

This is a teacher-reported scale used for determining the ADHD symptoms and their severity among ADHD children aged 3–17 [41]. Turkish validity and reliability studies were performed [43].

Statistical analyses

Statistical analyses of the study were performed using the SPSS (version 17.0) statistical program. Shapiro–Wilk testing was used to assess the distribution of variables. It revealed that there was no normal distribution of parameters except for BMI which used for its comparison among three groups by the use of the ANOVA test. The Kruskal–Wallis test was used to compare the variables among the ASD, ADHD, and control groups, and if needed a Mann–Whitney U test was used with the Bonferroni correction, $p < .017$ was accepted as the level of significance. The chi-square test was used to compare the gender which is a dichotomic parameter. To determine the correlation of the continuous variables Spearman's test was used and $p < .05$ was accepted as the significance level.

Results

The study sample was composed of 180 children and 71.1% ($n = 128$) were male and 28.9% ($n = 52$) were female. The three groups (ASD, ADHD, and control) were similar in terms of distribution of gender ($X^2 = 0.379$, $p = .828$), mean age ($p > .05$), and BMI distribution ($p > .05$).

There was found no significant difference between groups with respect to age or education level of mothers and fathers ($p > .05$). Sociodemographical features of children are shown in Table 1.

The omentin levels of groups were compared. The median levels of omentin were 479.0, 385.9, and 382.5 ng/ml for those with ASD, ADHD, and healthy subjects, respectively. The difference between groups was significant ($X^2 = 13.619$, $p = .001$). Dichotomic analysis of the groups with the use of a Mann–Whitney U test revealed that the significance in the ratio of omentin was due to the comparison between those with ASD and healthy subjects ($z = -3.043$, $p = .002$), and ASD and ADHD ($z = -3.268$, $p = .001$). The median omentin levels of children with ASD were

Table 1. Sociodemographical findings of participants.

	ASD ($n = 60$) n (%)	ADHD ($n = 60$) n (%)	Healthy ($n = 60$) n (%)	Total ($n = 180$) n (%)	X^2, F	p
Gender						
Boys	44 (73.3)	43 (71.1)	41 (68.3)	128 (71.1)	0.379	.828
Girls	16 (26.7)	17 (28.3)	19 (31.7)	52 (28.9)		
	Mean ± SD (min-max)	Mean ± SD (min-max)	Mean ± SD (min-max)	Mean ± SD (min-max)	X^2	p
Age (months)	124.2 ± 10.4 (103–151)	121.5 ± 9.4 (99–141)	118.7 ± 9.1 (96–132)	121.5 ± 9.9 (96–151)	5.813	.055
BMI (kg/m^2)	21.7 ± 1.9 (18–25)	21.5 ± 1.9 (18–25)	21.6 ± 1.7 (18–25)	21.6 ± 1.8 (18–25)	0.109	.897
Mothers' age (year)	32.8 ± 5.1 (23–48)	33.1 ± 4.4 (23–42)	33.5 (4.1) (27–42)	33.1 (4.5) (23–48)	1.223	.542
Fathers' age (year)	36.5 ± 5.8 (27–57)	37.1 ± 4.9 (30–51)	36.9 ± 5.5 (27–49)	36.8 ± 5.4 (27–57)	1.078	.583
Mothers' Education (year)	10.3 ± 3.3 (5–15)	10.9 ± 3.7 (5–15)	11.0 ± 3.4 (5–15)	10.8 ± 3.5 (5–15)	1.625	.444
Fathers' Education (year)	11.7 ± 3.2 (5–17)	11.1 ± 3.3 (5–15)	11.2 ± 3.0 (4–17)	11.3 ± 3.1 (4–17)	1.574	.455

Note: SD, standard deviation; min, minimum; max, maximum; BMI, body mass index; X^2, Kruskal–Wallis; F, ANOVA for BMI analysis; ASD, autism spectrum disorder and ADHD, attention-–deficit/hyperactivity disorder.

Table 2. Omentin levels of participants.

	Total M (min-max) Mean ± SD	ASD M (min-max) Mean ± SD	ADHD M (min-max) Mean ± SD	Healthy M (min-max) Mean ± SD	First analysis Kruskal–Wallis	Dual comparisons Mann–Whitney U
Omentin (ng/ml)	327.6 (134–800) 415.8 ± 201.0	422.6 (220–800) 479.0 ± 201.2	293.5 (219–800) 385.9 ± 201.5	322.0 (134–800) 382.5 ± 188.1	X^2=13.619 p = .001	ASD vs. ADHD: z=−3.268, p = .001 ASD vs. Healthy: z=−3.043, p = .002 ADHD vs. Healthy: z=−0.728, p = .476

Note: M, median; min, minimum; max, maximum; SD, standard deviation; ASD, autism spectrum disorder and ADHD, attention-deficit/hyperactivity disorder.

significantly higher (422.6 mg/ml) than those of healthy subjects (322 ng/ml) and children with ADHD (293.5 ng/ml). The omentin levels of children with ADHD and healthy subjects were similar (z = −0.728, p = .467) (see Table 2).

The correlation between variables was analysed and shown in Table 3:

- There was no significant correlation between omentin levels and age (r = −0.014, p = .852).
- There was no correlation between omentin levels and total scores of ABCL (r = 0.104, p = .443), AbBC (r = –0.055, p = .679), and CARS (r = 0.184, p = .159).
- There was no correlation between omentin levels and CPRS (r = 0.136, p = .302) and CTRS (r = −0.056, p = .669).
- There was a negative correlation between ABCL scores and age (r = −0.422, p = .001).

Discussion

In this study, the omentin levels of children diagnosed with ASD and ADHD were compared with those of healthy subjects (Table 4). The most remarkable finding was the significantly high levels of omentin in the ASD group when compared to the levels in both the ADHD and control groups. However, there was no correlation between the omentin levels and the scores for the CARS and ABCL scales, which are associated with the symptom severity of ASD. Similarly, there was no correlation between the omentin levels and the CPRS and CTRS. Additionally, there no significant correlation was found between omentin levels and age. This result may be related to the insufficient variation of omentin levels and needs to be investigated.

Table 3. Spearman correlation analysis of the variables in ASD group (n = 60).

	BMI	Omentin	ABCL	AbBC	CARS
Age	−0.259 0.045	−0.035 0.792	−0.422 0.001	−0.018 0.889	−0.228 0.079
BMI		0.080 0.542	−0.068 0.608	−0.112 0.394	−0.203 0.119
Omentin		1	0.104 0.443	−0.055 0.679	0.184 0.159
ABCL			1	0.149 0.255	0.544 0.000
AbBC				1	0.255 0.049

Note: Significance at the 0.01 level. ABCL, Autism Behavior Checklist; AbBC, Problematic Behavior Checklist and CARS, Childhood Autism Rating Scale.

Being active substances that are thought to have anti-inflammatory functions, the adipokines arise from the adipose tissue and may play a role in the onset of ASD and ADHD as well as other psychiatric diseases [16,44]. In recent years, studies investigating that potential role have mainly focused on the levels of adiponectin, leptin, ghrelin, and resistin, which are the most commonly known adipokines. Such studies have demonstrated that the serum levels of adiponectin are decreased in adult patients with panic disorder [10], major depression [11], schizophrenia [12], obsessive-compulsive disorder [45], and autism [13]. The serum ghrelin levels have been assessed in patients with an eating disorder and major depressive disorder, and increased levels have been reported [14,46].

According to the results of a study that compared the serum adiponectin levels of adult ADHD patients with those of control subjects, the levels of adiponectin were decreased in the ADHD patients [15]. In another study, it was reported that the leptin levels of ADHD children were increased, while the adiponectin levels were decreased [47]. It has been suggested that this result supports the notion that obesity occurs frequently in the ADHD population [48].

The studies that focused on the relation between the adipokines and ASD reported decreased plasma levels of resistin [18] and adiponectin [13] as well as increased levels of leptin [18,49]. The levels of leptin were also assessed in patients diagnosed with ASD who were undergoing risperidone treatment, and it was shown that the increased leptin levels were not associated with the medication [50].

No previous studies have demonstrated changes in the levels of omentin in autism or ADHD patients, although the role of omentin in the aetiology of cardiovascular and endocrinological diseases has been investigated in a number of prior studies [23,51]. Indeed, the relation between omentin and

Table 4. Spearman correlation analysis of the variables in ADHD group (n = 60).

	BMI	Omentin	CPRS	CTRS
Age	−0.108 0.412	−0.167 0.203	−0.064 0.625	−0.097 0.459
BMI		−0.056 0.669	0.138 0.294	−0.074 0.577
Omentin		1	0.136 0.302	−0.056 0.669

Note: Significance at 0.01 level. CPRS, Conner's Parent Rating Scale; CTRS, Conner's Teacher Rating Scale and ADHD, attention-deficit/hyperactivity disorder.

neuropsychiatric disorders represents a new area of research and hence there are presently only a few studies concerning this issue.

Increased levels of omentin have been shown in patients with anorexia nervosa [9,52], as well as after weight loss [53] and aerobic training in obese patients with metabolic risk factors [54].

Decreased levels of omentin were observed in diseases characterized by chronical inflammation, for example, Crohn's disease [55], rheumatoid arthritis [56] and Type 1 diabetes mellitus [57] and omentin is suggested to play a role in the regulation of inflammatory processes [23].

The serum levels of omentin have previously been found to be normal in patients diagnosed with major depression, although there was arguably insufficient investigation supporting these results [58]. Yıldırım and colleagues [59] reported that the omentin levels of patients with schizophrenia were significantly lower than those of healthy subjects. Additionally, a negative correlation was detected between the omentin levels and the symptom severity of these patients. It has further been suggested that common aetiological factors at a molecular level (e.g. oxidative stress and immunological mechanisms) that affect similar areas of the brain may play a role in the development of ASD and psychotic disorders [29,60].

Omentin was firstly described in paneth cells and it may be implicated in the defensive mechanisms against pathogenic gut bacteria [61]. Recently, the involvement of both the gut bacteria and dysbiosis in ASD has been well researched in relation to the aetiology of autism [62]. The gut microflora is suggested to have an association with the onset and symptomatology of ASD [63]. The higher serum levels of omentin found in children with ASD may be associated with the role of omentin in the regulation of the intestinal flora. In addition to oxidative stress and immune dysregulation [64], the dysfunction of the mitochondria might play a role in the metabolism of glucose, fatty acids, and energy [65] that occurs in ASD. The dysfunction of the mitochondria is suggested to have possible effects on the functions of the gastrointestinal system due to it being a high-energy organ [4]. Increased levels of omentin have positive effects on insulin sensitivity, oxidative stress, revascularisation, and microcirculation [23] which could point to a protective bias that occurs as a reaction to the differences in the metabolism in ASD patients. The metabolic changes in autism and their relationship with omentin, therefore, require further investigation.

Taking the BMI into consideration, non-obese participants were included in our study and, despite the high levels of omentin found in children with ASD, no correlation was found between the omentin levels and the symptom severity. It is important to note, however, that this result does not provide definitive support for excluding from consideration the relationship and etiopathogenetic connection between the symptom severity of ASD and the omentin levels. The symptom severity of obese and non-obese children with ASD should thus be investigated further in order to confirm the validity of these results.

In the current study, BMI was used to define obesity among the participants. In order to assess the weight in relation to height, BMI is the most frequently used measure. But there are some disadvantages of using BMI to define paediatric obesity. Because of the variation of BMI distribution according to ethnicity, sex, age, and level of maturity, the significance is more difficult to determine the differences among children and adolescents than within adult populations [66,67]. Statistical approaches for a particular population have often been used due to unclear cut-off values to use in order to define obesity in children and adolescents [68].

In our study, the omentin levels of physically healthy, non-obese, non-smoking, and drug-free participants diagnosed with ASD and ADHD were compared with the omentin levels of the control group. The strengths of the present study include the inclusion of a gender and age-matched control group and the fact that semi-structured clinical interviews were conducted with all the participants. However, the study did have some methodological limitations. First, the participants included in the study were all recruited from one centre. Second, the assessment of the omentin levels was cross-sectional and there was no long-term follow-up period. Hence, it is not clear whether the omentin levels change during growth. Further, the relatively small sample size represents another limitation of this study. Additionally, it has previously been reported that the serum omentin concentrations were higher in women than in men [52], although the serum concentration of omentin has been shown to be negatively correlated with 17β-oestradiol [56]. In our study, the groups were not compared with each other according to the gender and age of onset of puberty variables. On the other hand, as another limitation, some factors that could be effective on omentin levels, such as fasting [69], physical exercise [70], maternal obesity [71], obstructive sleep apnea syndrome [72], pain [73], and non-obese polycystic ovary syndrome [74], food rituals and nutritional status of children have not been assessed in our study. Thus, these results must be confirmed by other studies with larger samples of different age ranges and by taking these factors into consideration.

Conclusions

The findings of our study seem to suggest the role of omentin in ASD. To the best of our knowledge, this is the first study to investigate the omentin levels of

children with ASD and ADHD. These results may inspire further studies on the aetiology of both ASD and ADHD featuring larger samples and long-term follow-up periods. The relation between the adipose tissue and mental disorders represents a new area of research and there is currently only limited information available on this issue. Biochemical studies concerning the aetiopathogenesis of both ASD and ADHD are needed to develop more effective treatment approaches for these disorders.

Disclosure statement

No potential conflict of interest was reported by the authors.

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