Original article / *Araştırma*

Decreased serum levels of total and high molecular weight adiponectin in treatment-naïve children with ADHD

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ABSTRACT

Objective: *Attention deficit hyperactivity disorder (ADHD) is considered to be one of the most common childhood psychiatric disorders. The aim of this study was to examine serum levels of total and High Molecular Weight (HMW) adiponectin, and also HMW/total adiponectin ratio with respect to ADHD symptomatology in children.* ***Methods:*** *Serum levels of total adiponectin and HMW adiponectin were measured by commercial enzyme-linked immunesorbent assay kits in 44 treatment-naïve children with ADHD and age, gender matched 44 healthy controls. ADHD symptoms were scored by Conners' Parent Rating Scale-Revised Short (CPRS-RS) and ADHD Rating Scale (ADHD-RS). Body Mass Index-Standart Deviation Scores (BMI-SDS) of all children were evaluated.* ***Results:*** *There were no significant difference in terms of gender, age and BMI-SDS between ADHD and healthy control groups (respectively, p=1, p=0.475, p=0.097). We found that serum total, HMW adiponectin levels and HMW adiponectin/ total adiponectin ratio were significantly lower in ADHD group compared to controls (p<0.001). In logistic regression analysis, adjusting for age, gender and BMI-SDS, we observed that serum total and HMW adiponectin levels as well as HMW/total adiponectin ratio were associated with ADHD (p<0.001). Additionally, in partial correlations adjusting for age and BMI-SDS in ADHD group, we detected significantly negative correlations between total adiponectin, HMW adiponectin, HMW/total adiponectin ratio and CPRS-RS hyperactivity (p=0.031, p=0.016, p=0.007, respectively), ADHD-RS hyperactive-impulsive (p<0.001), ADHD-RS total symptom scores (p=0.015, p=0.010, p=0.005, respectively).* ***Discussion:*** *To our knowledge, the present study is the first to examine serum HMW adiponectin levels in ADHD children and also to investigate the relationship between ADHD symptoms and serum levels of total and HMW adiponectin. The results of our study indicate that total and HMW adiponectin may be associated with ADHD.* ***(Anatolian Journal of Psychiatry 2020; 21(6):633-640)***

Keywords: *attention deficit hyperactivity disorder, total adiponectin, high molecular weight (HMW) adiponectin*

Dikkat eksikliği hiperaktivite bozukluğu olan çocuklarda serum toplam ve yüksek moleküler ağırlıklı adiponektin düzeyleri

ÖZ

Amaç: *Dikkat eksikliği hiperaktivite bozukluğu (DEHB), en sık görülen çocukluk çağı psikiyatrik bozukluklarından biri olarak kabul edilir. Bu çalışmanın amacı, DEHB'li çocuklarda, toplam ve yüksek moleküler ağırlıklı (YMA) adiponektin serum düzeylerini, YMA/toplam adiponektin oranını ve bu parametrelerle DEHB belirtileri arasındaki ilişkiyi incelemektir.* ***Yöntem:*** *DEHB tanısını yeni konmuş 44 çocuk ve yaş, cinsiyet açısından DEHB grubuyla eşleştirilmiş 44 sağlıklı çocukta, toplam adiponektin ve YMA adiponektinin serum düzeyleri, enzim bağlı immünosorban test kitleri (ELISA) ile ölçülmüştür. Tüm çocuklarda, DEHB belirtileri Conners Ebeveyn Derecelendirme Ölçeği-Yenilenmiş Kısa (CPRS-RS) ve DEHB Derecelendirme Ölçeği (ADHD-RS) ile değerlendirilmiştir. Beden kitle indeksi standart sapma puanları (BMI-SDS) hesaplanmıştır.* ***Sonuçlar:*** *DEHB ve sağlıklı kontrol grupları arasında cinsiyet, yaş*

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ve BMI-SDS açısından anlamlı fark bulunmadı (sırayla, p=1, p=0.475, p=0.097). Serum toplam, YMA adiponektin düzeyleri ve YMA adiponektin/toplam adiponektin oranının, DEHB grubunda kontrollere göre anlamlı olarak düşük olduğu bulundu (p<0.001). Lojistik regresyon analizinde yaş, cinsiyet ve BMI-SDS kontrol edildiğinde, serum toplam ve YMA adiponektin düzeylerinin yanı sıra, YMA/toplam adiponektin oranının DEHB ile ilişkili olduğu saptandı (p<0.001). DEHB grubunda, yaş ve BMI-SDS kontrol edilerek bakılan kısmi korelasyonlarda toplam adiponektin, YMA adiponektin, YMA/toplam adiponektin oranı ile CPRS-RS hiperaktivite (sırayla, p=0.031, p=0.016, p=0.007), ADHD-RS hiperaktivite-dürtüsellik (p<0.001) ve ADHD-RS toplam ölçek puanları (sırayla, p=0.015, p=0.010, p=0.005) arasında istatistiksel yönden anlamlı ilişkiler saptandı. ***Tartışma:*** *Bildiğimiz kadarıyla bu çalışma, DEHB'li çocuklarda serum YMA adiponektin düzeylerini inceleyen ve DEHB belirtileri ile toplam ve YMA adiponektin serum düzeyleri arasındaki ilişkiyi araştıran ilk çalışmadır. Çalışmamızın sonuçları, toplam ve YMA adiponektinin DEHB ile ilişkili olabileceğini göstermektedir.* ***(Anadolu Psikiyatri Derg 2020; 21(6):633-640)***

Anahtar sözcükler: *Dikkat eksikliği hiperaktivite bozukluğu, toplam adiponektin, yüksek moleküler ağırlıklı (YMA) adiponektin*

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is one of the most common psychiatric disorders with a worldwide prevalence of %3-5 in childhood.[1,2] ADHD is considered to be a heterogeneous and complex disorder,[3] highly variable with regard to impairment, associated comorbidities and etiology.[4] Although, a large number of neurobiological factors have been proposed to take part in the etiology of ADHD**,** the precise neurobiological mechanisms of ADHD and comorbid psychiatric and medical disorders remain largely unknown.[5] It has been proposed that the link between ADHD and obesity can be regarded as well-established and ADHD may possibly share some common etiological factors with obesity.[6]

Adiponectin, a plasma protein, consists of oligomeric complexes, including trimer, hexamer or multimer (high molecular weight, HMW) forms, and the HMW form has been reported to be the most active form.[7] Adiponectin is well-known for its anti-oxidant,[8] anti-inflammatory activities,[9,10] and considered as a metabolic regulator.[11,12] In addition, adiponectin receptors are widely expressed in different regions of the brain.[13] Consequently, there have been several studies investigating circulating levels of adiponectin in different psychiatric disorders including autism,[14] and ADHD.[15,18-20]

Mavroconstanti et al. examined serum levels of total adiponectin, HMW adiponectin and HMW/total adiponectin ratio in young adults with ADHD. The researchers found that all three parameters were decreased in ADHD group compared to controls. However, in further analysis, they implicated that HMW adiponectin and HMW/total adiponectin ratio were associated with ADHD.[15] Moreover, a number of studies have revealed associations between single nucleotide polymorphisms in the region of an ADHD candidate gene, CDH13, coding for adiponectin receptor T-cadherin, and alterations in serum levels of adiponectin.[16,17] In children with ADHD, circulating total adiponectin level has been explored in three studies.[18-20] We have encountered no study investigating HMW adiponectin and HMW/total adiponectin ratio in children with ADHD.

We conducted this study to determine whether serum levels of total adiponectin, HMW adiponectin and HMW/total adiponectin ratio are altered in treatment-naive children with ADHD and whether there is an association with ADHD symptoms.

METHODS

Participants

Forty four treatment-naïve children aged between 8 and 12 years old diagnosed with ADHD according to DSM-5 criteria (APA, 2013) and semi-structured interviews (via K-SADS-PL-Turkish) were enrolled in the study. The control group consisted of age and gender matched 44 healthy children free of life-time psychopathologies as evaluated via K-SADS-PL. Exclusion criteria included obesity, intellectual disability, medical comorbidities (with pediatric consultation), comorbid psychopathologies and history of taking psychotropic medications. Children attending exercise programs were also excluded. Weschler Intelligence Scale for Children-Revised (WISC-R) was used to eliminate any intellectual disability in case of having an academic achievement lower than average, developmental delay or poor adaptive functioning. All children were weighted in light clothing without shoes. Height was measured to the nearest 0.5 cm on a standardized height board and weight was measured to the nearest 0.1 kg on a standard scale. BMI was calculated as weight in kilograms divided by squared height in meters. Pediatric obesity cut off was defined ≥95th

percentile according to BMI percentile curves established for Turkish children.[21] On the basis of Turkish reference data for children,[21] BMIs were transformed into standard deviation scores (BMI-SDS) using the least mean square method by Cole.[22] This study was conducted at the outpatient clinics of Child Psychiatry Department of Düzce University Medical Faculty. All of the participant children gave verbal assent and parents provided informed consent. The study was approved by the Medical Ethics Committee of Düzce University and performed in accordance with the ethical standards established in the Declaration of Helsinki.

Measures

Kiddie Schedule for Affective Disorders and Schizophrenia for School Age Children- Present and Lifetime Version (K-SADS-PL): This semi-structured interview evaluate present and lifetime psychopathology in children and adolescents.[23] Reliability and validity studies of Turkish versions according to DSM-IV and DSM-5 criteria were conducted.[24,25]

Conners' Parent Rating Scale-Revised Short (CPRS-RS): CPRS-RS includes inattention/cognitive problems, hyperactivity and oppositional behavior subscales.[26] Reliability and validity study of CPRS-RS was established for Turkish population.[27]

Attention Deficit/Hyperactivity Disorder Rating Scale (ADHD-RS): This 18-item, 4-point Likert type scale evaluates inattention and hyperactivity/impulsivity domains.[28] The clinician rated version of the scale used in this study was also used in previous studies conducted in Turkish children with ADHD.[29,30]

Blood sampling and analysis

Venous blood samples of patients and controls were drawn between 8:00 and 10:00 a.m. after a 12-h overnight fasting to avoid circadian variation. Participants also instructed to refrain from heavy exercise and eating/drinking prior to blood sampling. Blood samples were centrifuged and the sera were stored in deep freezer at -80°C until the day of analysis. Serum levels of total and HMW adiponectin were measured using commercial enzyme-linked immunosorbent assay (ELISA) kits (Elabscience, USA, cat. No: E-EL-H0004, E-EL-H5621, respectively) following the protocols of the manufacturer. Analysis results were expressed in µg/ml.

Statistical analyses

SPSS version 22 (SPSS™, IBM Inc., Armonk, NY) was used for the statistical analyses. Descriptive statistics of the data are summarized as means, standard deviations for normally distributed variables and medians, inter-quartile ranges for non-normally distributed variables. The distribution of each variable was examined by normality tests both in total sample and in each group. Differences of adiponectin levels, as well as differences of other continuous variables between groups, were analyzed using either independent samples t-test for normally distributed variables or Mann-Whitney U test for non-normally distributed variables.

We used univariate binary logistic regression analysis to evaluate whether ADHD diagnosis could be predicted by total adiponectin, HMW adiponectin or HMW/total adiponectin ratio. In addition, we subsequently used multivariate binary logistic regression model to further evaluate whether ADHD diagnosis could be predicted by adiponectin levels adjusting for the effects of age, gender and BMI-SDS. Lastly, we performed partial correlations controlling for the effects of age and BMI-SDS in order to study the correlations between adiponectin levels and psychiatric symptoms in ADHD group. P was set at 0.05 (two-tailed).

RESULTS

Eighty-eight children, 44 children with ADHD with a median age of 113 months (IQR=28.7) and 44 control children with a median age of 117 months (IQR=26.5) were enrolled in the study. ADHD and control groups were one to one matched according gender (both groups 75% male, 25% female, p=1) and age (p=0.475). No statistically significant difference was observed for BMI-SDS between ADHD (0.19±0.45) and control (0.04±0.40) groups (p=0.097). Children with ADHD scored significantly higher compared to controls on parent and clinician rated ADHD symptoms (p<0.001) except for CPRS-RS oppositional behavior score. No statistically significant difference was detected for CPRS-RS oppositional behavior score (p=0.353). The last result was obtained possibly due to the fact that we had excluded Oppositional Defiant Disorder in addition to the other comorbid psychiatric disorders. (Table 1).

ADHD patients had significantly lower levels of total and HMW adiponectin as well as a lower HMW/total adiponectin ratio compared to controls (p<0.001) (Fig 1). In univariate binary logistic regression analysis, total adiponectin (OR= 0.213, 95% CI=0.105-0.431, p<0.001), HMW

Table 1. Clinical parameters of ADHD and control groups

	Median (IQR) ADHD group (n=44)	Control group(n=44)	p*
ADHD-RS inattentive score	16.0 (7.0)	3.0 (1.75)	**<0.001**
ADHD-RS hyperactive-impulsive score	13.5 (4.75)	2.0 (2.0)	**<0.001**
ADHD-RS total score	30.0 (5.75)	5.0 (2.0)	**<0.001**
CPRS-RS inattention score	12.0 (3.0)	2.0 (2.0)	**<0.001**
CPRS-RS hyperactivity score	9.0 (4.0)	1.0 (1.0)	**<0.001**
CPRS-RS oppositional behavior score	2.0 (1.0)	2.0 (1.0)	0.353
Total adiponectin	10.91 (2.11)	15.64 (3.5)	**<0.001**
HMW adiponectin	2.63 (1.91)	6.06 (2.3)	**<0.001**
HMW/total adiponectin ratio (%)	23.69 (11.96)	38.97 (5.76)	**<0.001**

**: Mann-Whitney U test; CPRS-RS: Conners' Parent Rating Scale-Revised Short; ADHD-RS: Attention Deficit/ Hyperactivity Disorder Rating Scale; HMW adiponectin: High Molecular Weight adiponectin*

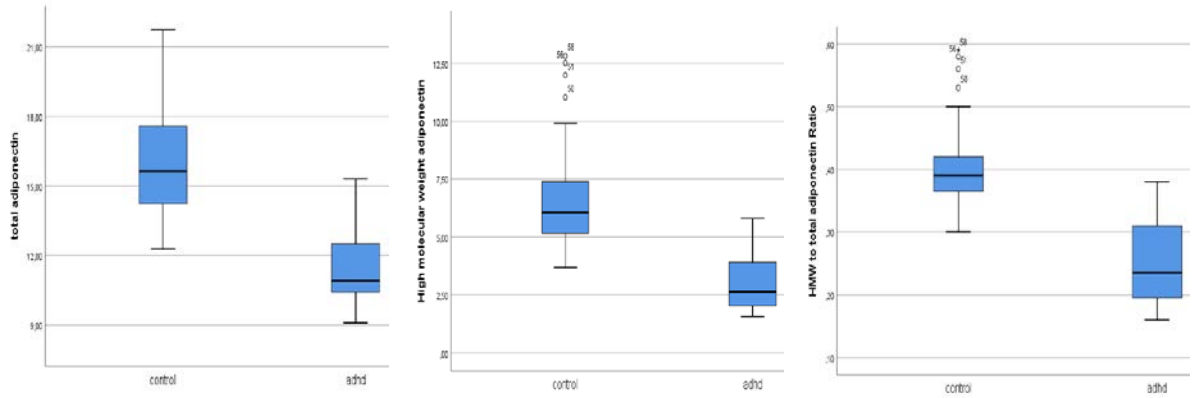

Figure 1. Boxplots of adiponectin parameters according to groups (µg/ml). The boxes indicate the first, second (median) and third quartiles and the vertical bars indicate the range. The open circles indicate individual values that are outside the range.

Table 2. Partial correlations between adiponectins and ADHD symptom scores controlling for age and BMI-SDS in ADHD group

	Total adiponectin r	p	HMW adiponectin r	p	HMW/total adiponectin r	p
CPRS-RS IA	-0.006	0.970	0.035	0.827	0.031	0.844
CPRS-RS H	-0.334	**0.031**	-0.371	**0.016**	-0.411	**0.007**
CPRS-RS OB	-0.018	0.912	0.006	0.969	0.019	0.906
ADHD-RS IA	0.118	0.458	0.134	0.397	0.132	0.403
ADHD-RS H	-0.542	**<0.001**	-0.585	**<0.001**	-0.628	**<0.001**
ADHD-RS T	-0.375	**0.015**	-0.394	**0.010**	-0.424	**0.005**

HMW adiponectin: High Molecular Weight adiponectin; CPRS-RS: Conners' Parent Rating Scale- Revised Short; ADHD-RS: Attention Deficit/Hyperactivity Disorder-Rating Scale; IA: Inattention score, H: Hyperactivity score, OB: Oppositional Behavior score

adiponectin (OR=0.147, 95% CI=0.062-0.349, p<0.001), and HMW/total adiponectin ratio (OR= 0.650, 95% CI=0.531-0.797, p<0.001) were found to be associated with ADHD diagnosis,

before adjustments. In multivariate binary logistic regression analysis, after adjustments for gender, age and BMI-SDS, total adiponectin (OR=0.168, 95% CI=0.072-0.395, p<0.001), HMW adiponectin (OR=0.111, 95% CI=0.039-0.315, p<0.001) and HMW/total adiponectin ratio were found to be predictive for ADHD diagnosis. (OR=0.614, 95% CI=0.481-0.783, p<0.001).

We also examined the correlations between adiponectin levels and ADHD symptoms (CPRS-RS and ADHD-RS) in addition to the categorical diagnoses. The results of partial correlation analysis between ADHD symptoms and adiponectin levels, adjusted for the effects of age and BMI-SDS are shown in Table 3. We detected significantly negative correlations between total adiponectin, HMW adiponectin, HMW/total adiponectin ratio and CPRS-RS hyperactivity (p= 0.031, p=0.016, p=0.007, respectively), ADHD-RS hyperactive-impulsive symptom subscale scores (p<0.001) and ADHD-RS total scores (p=0.015, p=0.010, p=0.005) in ADHD children (Table 2).

DISCUSSION

In this study, we investigated serum levels of total and HMW adiponectin and HMW/total adiponectin ratio in treatment-naive children with ADHD with respect to ADHD symptomatology. Our findings showed decreased serum total and HMW adiponectin levels as well as HMW/total adiponectin ratio in treatment-naïve children with ADHD compared to healthy controls. In further analysis, we observed statistically significant changes in serum total, HMW adiponectin levels and HMW/total adiponectin ratio in ADHD children, and that those changes were inversely correlated with hyperactivity symptoms. To the best of our knowledge, this is the first study reporting on serum HMW adiponectin levels in ADHD children and also investigating the relationship between ADHD and serum levels of both total and HMW adiponectin with regard to the severity of ADHD symptoms in children.

Consistent with our findings, two recent studies have reported decreased circulating levels of total adiponectin in ADHD.[15,18] In one of those studies conducted in 36 drug-naïve children with ADHD and 40 controls, Özcan et al. revealed decreased plasma level of total adiponectin in ADHD children compared to controls.[18] In the other study conducted in young adults with ADHD, decreased levels of total, HMW adiponectin levels and HMW/ total adiponectin ratio were reported. In further statistical analysis of this study controlling for age, gender and BMI, serum levels of HMW adiponectin and HMW/ total adiponectin ratio were found to be associated with ADHD and inversely correlated with ADHD symptoms.[15] Nevertheless, in a study conducted in drug-naïve 30 children with ADHD and 20 controls, Sahin et al. reported similar total adiponectin levels in children with ADHD and controls. The conflicting results may be due to differing sample sizes, different characteristics of participants and methodological variation. However, in this naturalistic follow-up study, the authors also reported a significant increase for serum total adiponectin after two months methylphenidate treatment.[19] Torabi et al. also reported increased serum levels of total adiponectin after six weeks high-intensity intermittent training in 50 adolescents with ADHD.[20]

In our study, we found that ADHD symptom severity was negatively correlated with levels of total, HMW adiponectin and HMW/total adiponectin ratio. Similar to the results of our study, Mavroconstanti et al. revealed negative correlations between ADHD symptoms and both HMW adiponectin and HMW/total adiponectin ratio in young adults.[15] The mechanisms underlying the association between ADHD and possible reduction in adiponectin parameters are unclear, but some possible mechanisms might be proposed.

Adiponectin has anti-oxidative properties[8] and pro-oxidation has been reported to decrease adiponectin secretion in adipocytes.[31] Therefore, Bonvicini et al. proposed that dysregulated oxidative stress mechanisms might be associated with decreased adiponectin levels identified in ADHD.[32] Moreover, adiponectin is considered to be involved in adipocyte-brain-cross-talk and brain functions.[13,33] More specifically, adiponectin has been implicated to be associated with neurogenesis.[34] Therefore, the involvement of adiponectin in brain functions should be considered for decreased adiponectin levels detected in ADHD patients.

Another disclosure may be attributed to the inflammatory mechanisms. Inflammatory processes have been widely reported to be involved in ADHD.[35,36] Of note, IL-6 is supposed to play a major role in the immune response and inflammation as a pro-inflammatory cytokine. Importantly, IL-6 is considered to be crucial for homeostasis of the nervous system, normal development and function of glial cells and neurons.[37] Furthermore, serum IL-6 has been demonstrated to increase in ADHD children.[38] In a recent study conducted in 52 children and ado-

lescents with obesity, IL-10 and TNF-alfa has been found to be correlated with hyperactivity/impulsivity symptoms even after controlling for BMI.[39] In our study, we also found that hyperactive/impulsive symptom severity was negatively correlated with adiponectin parameters. Interestingly, adiponectin has been identified to have anti-inflammatory effects.[9] More specifically, adiponectin has been indicated to reduce the macrophage production of pro-inflammatory cytokines IL-6 and TNF-alpha,[11] cytokines that have been reported to be involved in ADHD by aforementioned studies. Considering proposed inflammatory influences in ADHD and well-known anti-inflammatory effects of adiponectin, inflammatory mechanisms should also be considered for decreased adiponectin levels in ADHD.

Additionally, adiponectin is considered to be a protective factor for metabolic conditions due its anti-inflammatory effects.[40] It is plausible that decreased adiponectin levels detected in ADHD patients in our study might reinforce the vulnerability for obesity in our patients in course of time.

The strengths of our study are including only treatment-naïve children, using standardized tools for the assessment of psychiatric symptoms and controlling for the possible confounding effects of age, gender and BMI. On the other hand, this study has a number of limitations, including relatively small number of patients and cross-sectional design. In addition, although we excluded comorbid psychiatric disorders, we did not collect data on other possible confounders, such as subclinical anxiety, depression symptoms or subtle problems in social communication. Furthermore, other possible confounding factors such as socioeconomic status, inflammatory and metabolic parameters could not be controlled.

In conclusion, the results of our study indicate that total and HMW adiponectin may be associated with ADHD. Further studies investigating the role of adiponectin parameters in ADHD are required.

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