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# Serum Copper and Ceruloplasmin Levels in Children and Adolescents with Attention Deficit Hyperactivity Disorder

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# Serum Copper and Ceruloplasmin Levels in Children and Adolescents with Attention Deficit Hyperactivity Disorder

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**ÖZET:**

Dikkat eksikliği hiperaktivite bozukluğu olan çocuk ve ergenlerde serum bakır ve seruloplazmin düzeyleri

**Amaç:** Dikkat Eksikliği Hiperaktivite Bozukluğu (DEHB) çocukluk çağının en sık psikiyatrik hastalığı olup, çocuğun yaşına ve gelişim düzeyine uygun olmayan dikkatsizlik, hiperaktivite ve dürtüsellik ile karekterizedir. DEHB'nin nörobiyolojik temellerine yönelik araştırmaların sayısı ve elde edilen veriler artmasına karşın bu konu henüz aydınlatılamamıştır. Bakır ve seruloplazmin hem dopamin ketakolamin sistem üzerine olan etkileri nedeni ile hem de oksidatif mekanizmalar üzerine olan etkileri nedeni ile DEHB nörobiyolojisinde rol oynayabilir. DEHB hastalarında serum bakır düzeyini saptamaya dönük az sayıdaki çalışmanın sonuçları çelişkilidir. Serum seruloplazmin düzeylerini saptamaya yönelik çalışma ise bulunmamaktadır. Bu çalışmanın amacı DEHB tanısı alan çocuk ve ergenlerin serum bakır ve seruloplamin düzeyinin sağlıklı çocuk ve ergenler ile karşılaştırılmasıdır.

**Yöntem:** Bu çalışmada; nörolojik ya da sistemik hastalığı olmayan, karşı olma karşı gelme bozukluğu (KOKGB) dışında eşlik eden psikopatolojisi bulunmayan, normal zekaya sahip, DSM-IV'göre DEHB tanısı konulan 43 çocuk ve ergen hasta (32 erkek, 11 kız), yaş ve cinsiyet bakımından benzer 32 sağlıklı kontrolle (23 erkek, 9 kız) serum bakır ve seruloplazmin düzeyleri bakımından karşılaştırıldı. DEHB hastalarının %47'sinde KOKGB eş tanısı vardı. Serum bakır düzeyleri atomik absorpsiyon yöntemi ile, serum seruloplazmin düzeyleri ise nefelometrik yöntem ile çalışıldı.

**Bulgular:** DEHB grubunda bakır düzeyi ortalaması 17.3±3.2 µg/dl iken kontrol grubunda bakır düzeyi ortalaması(±SS) 16.9±2.6 µg/dl olup her iki grup bakır düzeyleri ortalamaları arasında istatistiksel olarak anlamlı fark yoktu (p=0.538). DEHB grubunda seruloplazmin düzeyi ortalaması 37.6±6.9 µg/dl iken kontrol grubunda seruloplazmin düzeyi ortalaması (±SS) 36.9±6.4 µg/dl olup her iki grup seruloplazmin düzeyleri ortalamaları istatistiksel olarak benzer bulundu (p=0.685). Yalnız DEHB olan grup, KOKGB eş tanısı olan DEHB grubu ve kontrol grubu arsında da bakır (p=0.845) ve seruloplazmin (p=0.878) değerleri açısından istatistiksel olarak anlamlı fark gözlenmedi.

**Sonuç:** Çalışmamız DEHB hastalarının serum bakır ve seruloplazmin düzeylerinin sağlıklı kontrollerden farklı olmadığını göstermiştir. Sonuçlarımız DEHB nörobiyolojisinde serum bakır ve seruloplazmin düzeylerinin doğrudan rolü olmadığını düşündürmekle beraber bu konuda daha geniş hasta grupları ile yapılacak çalışmalara ihtiyaç vardır.

**Anahtar sözcükler:** dikkat eksikliği ve hiperaktivite bozukluğu, bakır, seruloplazmin

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**ABSTRACT:**

Serum copper and ceruloplasmin levels in children and adolescents with attention deficit hyperactivity disorder

**Objective:** Attention deficit hyperactivity disorder (ADHD) is the most common neuropsychiatric disorder seen in childhood. It is characterized by inattention, hyperactivity, and impulsivity that is inappropriate for the age and developmental level of the child. Although the number of studies investigating the neurobiological basis of ADHD is increasing, there is still no clear understanding of the mechanisms of the disorder. Serum copper and ceruloplasmin levels may play a role in the neurobiology of ADHD due to their effects on oxidative mechanisms and the dopaminergic-catecholaminergic system. However, the results of studies investigating the serum levels of copper in patients with ADHD are contradictory. Moreover, serum ceruloplasmin levels have not yet been studied. The aim of the current study was to compare the serum copper and ceruloplasmin levels in children and adolescents with ADHD to the levels found in healthy controls.

**Method:** This study included 43 children and adolescents (32 males, 11 females) with ADHD, who did not have any neurological, systemic, or comorbid psychiatric disorders, except for oppositional defiant disorder (ODD), and 32 gender and age-matched healthy controls (23 males, 9 females). Levels of serum copper and ceruloplasmin were compared between the two groups. Approximately 47% of the children with ADHD had comorbid ODD. The level of serum copper was measured using atomic absorption spectrophotometry, and serum ceruloplasmin was measured using nephelometry.

**Results:** The mean level of serum copper was 17.3±3.2 µg/dL in the ADHD group, and 16.9±2.6 in the control group. This difference was not significant (p=0.538). The mean serum ceruloplasmin level was 37.6 ± 6.9 µg/dL in the group with ADHD, and 36.9±6.4 µg/dL in the control group; this difference between groups was not significant (p=0.685). Moreover, no significant difference was observed between the groups with ADHD with or without ODD comorbidities and the control group for either levels of serum copper (p=0.845), or ceruloplasmin (p=0.878).

**Conclusion:** This study showed that serum copper and ceruloplasmin levels do not differ between children and adolescents with ADHD compared with controls. Although our results suggest that serum ceruloplasmin and copper do not have a direct role in the neurobiology of ADHD, there is a need for future studies with larger patient groups.

**Keywords:** attention deficit hyperactivity disorder, copper, ceruloplasmin

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## INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by attention deficit, hyperactivity, and impulsivity, which are inappropriate for the age and developmental level of the child. Although the neurobiological mechanisms responsible for ADHD have not been fully elucidated, results from relevant studies investigating the pathogenesis of the disease point to a role for abnormalities in the dopaminergic and noradrenergic systems[1]. Favorable responses have been observed in individuals with ADHD to psychostimulant agents that increase levels of dopamine and noradrenaline in the brain. The efficacy of selective noradrenaline reuptake inhibitors in the treatment of ADHD, which increase levels of dopamine and noradrenaline in the prefrontal cortex, supports this observation[2].

In recent studies, it has been demonstrated that in a number of psychiatric diseases, in particular autistic disorders, ADHD, schizophrenia, and bipolar disorder, oxidative balance is disturbed and antioxidant defense mechanisms are weakened, factors which might play a role in the pathogenesis of these diseases[3-7]. The strongest assumption regarding this mechanism stems from the interaction between oxidants and cell membrane proteins. This interaction leads to the obstruction of cellular uptake of enzymes and/or neurotransmitters, which functions as a predisposing factor for ADHD. It has been reported that deterioration of the membranes of neurons that are targeted by increased oxidative stress may lead to abnormalities in the binding affinities of neurotransmitters including serotonin, norepinephrine, opiates, and dopamine, and also the dysregulation of neurotransmission[8,9]. Moreover, it has been suggested that impairment in the integrity of the membrane induces potential deterioration in both the structure and function of neuronal receptors[10].

Copper is involved in the structure of dopamine beta hydroxylase and monoamine oxidase (MAO) enzymes, which directly exert their effects on dopamine-catecholamine metabolism. Dopamine beta hydroxylase converts dopamine into noradrenaline, and MAO enzyme systems also affect the degradation of catecholamines. Therefore, copper plays a role in the oxidation of dopamine, epinephrine, and norepinephrine. Copper is also incorporated into the structure of the enzymes thyrosinase, catalase, uricase, and superoxide dismutase (SOD), which exert important effects on antioxidant defense mechanisms.

Ceruloplasmin constitutes more than 90% of serum copper, and is thus a multifunctional protein that supports copper transport. Ceruloplasmin is an acute phase reactant, the concentration of which increases during inflammatory reactions. In addition, it is an antioxidant that plays an important role in the antioxidant defense mechanism of human plasma, which is mediated by iron and copper elements. Ceruloplasmin oxidizes $Fe^{+2}$ to $Fe^{+3}$ via activity of ferroxidase, and facilitates binding of $Fe^{+3}$ to transferrin, resulting in the prevention of iron-dependent lipid peroxidation. It also binds copper ions to inhibit copper-induced lipid peroxidation. These two mechanisms form the basis of its antioxidant efficacy.

Ceruloplasmin also exhibits antioxidant efficacy via various mechanisms, including inhibition of both the formation of hydrogen peroxide ($H_2O_2$), and superoxide ($O_2$-), and the production of hydroxyl radicals (OHs) from hydrogen peroxide[11,12]. It has been suggested that ceruloplasmin and related changes occurring in the levels of copper are potential mechanisms underlying the development of neurodegenerative disease[13]. Because of the critical role they play in both synthesis and metabolism of catecholamines, as well as their impact on antioxidant defense mechanisms, alterations to copper and ceruloplasmin metabolism are thought to be influential in the pathophysiology of ADHD.

The outcome of alterations in copper-ceruloplasmin metabolism is most frequently observed in the psychiatric symptoms manifested in Wilson's disease. In this disease, synthesis of ceruloplasmin, which binds and transports copper, is decreased. Biliary excretion of copper decreases, and it accumulates in various tissues, including the liver. Wilson's disease is associated with cognitive

and behavioral changes, and psychiatric symptoms are observed in two-thirds of patients, with nearly one-third receiving psychiatric treatment prior to receiving a diagnosis[14,15]. In children with Wilson's disease, behavioral changes, a decrease in school performance, impaired concentration, and failed hand-eye coordination, may occur over time[16]. Silva et al. have reported the case of a patient, who underwent 6 years of drug therapy before further tests were able confirm a diagnosis Wilson disease[17].

Serum copper and ceruloplasmin levels have been investigated by a number of researchers, and different levels have been reported across studies. It has been suggested that these differences might be effective in the development of disease. However, a number of studies have not detected any difference between serum copper and ceruloplasmin levels in ADHD patients and controls. Inconsistencies observed across these results have been commonly interpreted as the consequence of methodological differences between studies.

Serum copper and ceruloplasmin levels have been most frequently studied in patients with schizophrenia. Some authors have demonstrated that serum copper and ceruloplasmin levels were decreased or remained the same, while others have indicated an increase in the serum levels of their metabolites[18-21]. Diverse results have been reported in patients with autism. Copper levels in hair were found to be unchanged in studies by Jackson and Garrod, and Blaurock-Busch et al.[22,23], in contrast to other studies that reported relatively low hair copper concentrations in patients with autism[24,25]. Atasoy et al. found a comparative increase in copper levels in hair samples of children with autism compared with healthy children[26]. Chauhan et al. compared patients with autism to their healthy relatives and found lower serum ceruloplasmin concentrations in the patient group[27]. However, Parellada et al. demonstrated decreased serum copper and ceruloplasmin levels in a group of patients with psychosis[28].

A limited number of studies have tried to determine the levels of serum copper that affect the etiopathogenesis of ADHD, either directly via metabolism of the catecholaminergic-dopaminergic system, or indirectly through oxidative metabolism, with conflicting outcomes. Moreover, serum levels of ceruloplasmin, which has an important role in copper metabolism and a strong antioxidant activity, have not been investigated to date. The present study was designed to compare plasma copper and ceruloplasmin levels in children and adolescents with ADHD, to those of age-matched healthy individuals. We predicted that plasma copper and ceruloplasmin levels in the ADHD group would be lower when compared to the control group.

## METHODS

Forty-three patients, who had received a diagnosis of ADHD based on DSM-IV criteria and had undertaken psychiatric evaluation at the outpatient clinic of Hacettepe University Faculty of Medicine's Department of Pediatric and Adolescent Mental Health and Diseases, volunteered to participate in the study. The control group consisted of 32 children and adolescent volunteers, who had no psychopathological disorder based on psychiatric evaluations following referral to the outpatient clinic at the Hacettepe University Faculty of Medicine, Department of Pediatric and Adolescent Mental Health and Diseases. The study was approved by the Ankara Third Ethics Committee of Clinical Investigations. Participants and their families provided written informed consent to participate in the study.

All participants were evaluated using a semi-structured survey questionnaire, the Schedule for Affective Disorders and Schizophrenia for School Aged Children - Present and Lifetime Version (K-SADS-PL). The diagnostic phase of the study was confirmed using the Conners' Teacher Rating Scale (CTRS-28), and parents completed the DSM-IV Based Disruptive Conduct Disorders Screening and Rating Scale in Children and Adolescents (DBD-STS A; Atilla Turgay).

Exclusion criteria for the group with ADHD included other concomitant psychiatric, neurological, and metabolic disorders, with the exception of oppositional defiant disorder (ODD).

**Table 1: Serum copper, and ceruloplasmin levels for the patient and control groups**

| | | n | Mean | Standard Deviation | p |
|---|---|---|---|---|---|
| Copper | Control Group | 32 | 16.9 | 2.6 | 0.538 |
| | ADHD Group | 43 | 17.3 | 3.2 | |
| Ceruloplasmin | Control Group | 32 | 36.9 | 6.4 | 0.685 |
| | ADHD Group | 43 | 37.6 | 6.9 | |

For both the control and patient groups, participants with growth retardation, obesity, or those who were receiving a special nutrient-rich diet for any reason, were excluded from the study. Participants who had experienced infection, inflammation, trauma, and/or drug use within the previous week were also excluded. All participants were evaluated using the Wechsler Intelligence Scale for Children (WISC-R) scoring system, to rule out a diagnosis of mental retardation. After overnight fasting, 5 cc venous blood samples were drawn from the left forearm, and were centrifuged in the Central Laboratory of Hacettepe University to separate their sera. For the analysis of serum copper and ceruloplasmin levels, atomic absorption and nephelometric methods (Beckman Coulter) were used, respectively.

### Statistical Analysis

Statistical analysis was performed using SPSS v.15.0. Normality of the data distribution was assessed using the Kolmogorov-Smirnov and the Shapiro–Wilk tests, and visual histograms. Student's t-test was employed to compare continuous variables between the two independent groups, and analysis of variance (ANOVA) was used to compare the three groups. For the comparison of categorical variables, crosstabs were constructed, and a chi-square test was used to assess the difference. Pearson's correlation analysis was used to determine any association between scores on the psychometric scales and serum levels. In all statistical procedures, $p \leq 0.05$ was considered the criterion for significance.

## RESULTS

The study population consisted of patients with ADHD (n=43), and a control (n=32) group. The difference between the mean age (±SD) of the patients with ADHD (119.5±29.8 months) and the control (119.7±23.3 months) groups was not significantly different (p=0.973). The group with ADHD consisted of 11 (25.6%) female, and 32 (76.4%) male children, while the control group comprised of 9 (28.1%) female, and 23 (71.9%) male participants. This gender difference between groups was not significant (p=0.805). The two groups shared similar socioeconomic status characteristics.

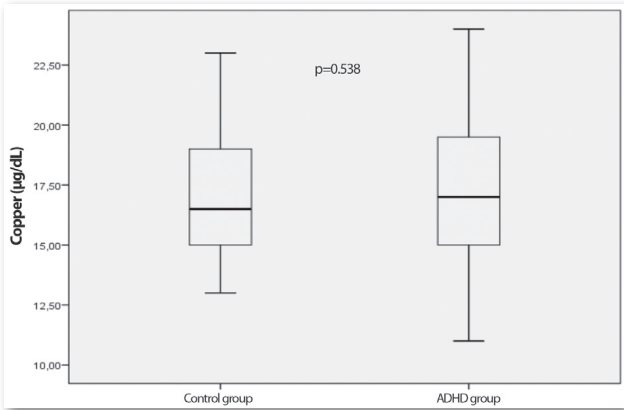


**Figure 1: Mean (±SD) and 95% CI for serum copper levels in the patient and control groups**

The serum copper and ceruloplasmin levels of both groups were comparable, and there was no statistically significant intergroup difference. Serum copper and ceruloplasmin levels for the ADHD and control groups are shown in Table 1 and Figures 1 and 2, respectively.

Twenty (46.5%) patients with ADHD had an ODD comorbidity. There was no significant difference between patients in the ADHD groups with or without ODD comorbidity and the control group for either serum copper (p=0.845) or ceruloplasmin (p=0.878) levels. Data for each of the three groups are summarized in Table 2. There was

**Table 2: Ceruloplasmin levels in the ADHD groups with or without ODD comorbidity, and the control group**

| | | n | Mean | Standard Deviation | P |
|---|---|---|---|---|---|
| Copper | ADHD | 23 | 17.3 | 3.3 | 0.845 |
| | ADHD+ODD | 20 | 17.3 | 3.1 | |
| | Control Group | 32 | 16.9 | 2.6 | |
| Ceruloplasmin | ADHD | 23 | 37.9 | 6.7 | 0.878 |
| | ADHD +ODD | 20 | 37.2 | 7.3 | |
| | Control Group | 32 | 36.9 | 6.4 | |

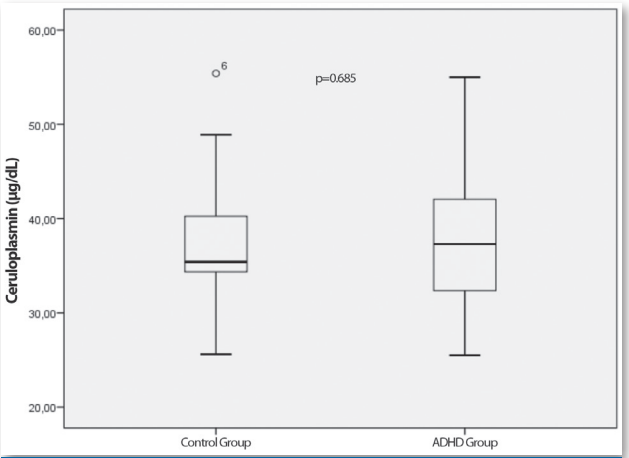


**Figure 2: Mean (± SD) and 95 % CI for serum ceruloplasmin levels in the patient and control groups**

no correlation (r=0.104, p=0.529) between either serum copper or ceruloplasmin levels with scores on the CTRS-28 for the ADHD group, and no correlation between serum copper (r=0.128, p=0.414) or ceruloplasmin (r=0.07, p=0.629) levels and scores on the DBD-STS scale.

## DISCUSSION

In a number of previous studies, levels of serum copper and ceruloplasmin levels have been analyzed separately, and in a limited number of studies both have been studied together. When investigated in combination, it has been asserted that changes to one of these metabolites in healthy individuals might reflect a corresponding change in the other. However, studies have shown that serum levels of these two metabolites do not correlate with each other in clinical conditions which result from abnormalities of serum copper and ceruloplasmin levels, such as Wilson's disease. In the present study, we analyzed both serum copper and ceruloplasmin levels in patients with clinically manifesting ADHD, in order to demonstrate probable differences between concentrations of these two metabolites.

Our data showed that serum ceruloplasmin levels of patients diagnosed with ADHD were comparable to those measured in healthy individuals. In our review of the literature, we did not encounter any studies investigating serum ceruloplasmin levels in children or adolescents. Ceruloplasmin levels in patients with ADHD have only been examined by Archana et al.[29]. In their study, sputum samples of the patients were analyzed, and, consistent with our findings, there was no difference found between serum ceruloplasmin levels in patients with ADHD compared to healthy controls. In our study, serum copper levels from patients with ADHD and healthy controls were also similar. In the medical literature, a limited number of studies have investigated serum copper levels in patients with ADHD. For example, similar to the results reported here, Mahmoud et al. reported no difference between serum copper levels in patients with ADHD and healthy controls[30]. Additionally, Yorbık et al. demonstrated that in a group with ODD, of whom half had also been diagnosed with ADHD, serum copper levels did not differ[31]. Contrary to these results, a study conducted by Kozilec et al. detected relatively lower copper values, in descending order of concentrations, for the hair, plasma, erythrocytes, and urine samples, in a group of patients with ADHD[32]. In a study performed by Bekaroğlu et al. relatively lower, but still above normal, serum copper levels were detected in a group with ADHD when compared with a control group,[33]. Furthermore, Starabrot

reported decreased serum copper levels in patients with ADHD, and Yorbık et al. found similar results in male children with ADHD[34,35].

This study has demonstrated comparable serum copper and ceruloplasmin levels in patients with ADHD and their healthy peers. This outcome supports the view that development of ADHD is effected by complex biochemical mechanisms taking place in the brain, rather than a difference in serum concentration of a specific biological molecule. However, it is important to note that this interpretation does not exclude the role of copper and ceruloplasmin in the pathophysiology of ADHD. Normal concentrations of specific molecules do not refute molecular dysfunction, and therefore further studies should be performed that focus on the function of specific molecules, rather than their concentrations, in bodily samples. The conflicting results obtained from studies investigating serum copper levels in patients with ADHD might also be related to the inadequate numbers of patients tested. Future studies investigating this issue should therefore be performed with larger patient groups. Larger patient populations are also required to investigate potential differences between ADHD subtypes. It is important to note the possible differences in biochemical parameters for subtypes of ADHD that have diverse clinical manifestations.

Investigating only the plasma levels of copper and ceruloplasmin constitutes an important limitation to this study. However, the exclusion of comorbidities using the K-SADS-PL, and mental retardation using the WISC-R, in conjunction with the combined analysis of serum copper and ceruloplasmin levels, are methodologically strong factors of our study.

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