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# No Effect of Antidepressant Treatment on Elevated Serum Ceruloplasmin Level in Patients with First-Episode Depression: A Longitidunal Study

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*Background and Aims.* Ceruloplasmin, an acute phase reactant with antioxidant capacity, has been found to be increased in some psychiatric disorders like schizophrenia and obsessive compulsive disorder. However, studies in depression are very scarce. We undertook this study determine the serum ceruloplasmin levels of depressive patients before and after treatment, to compare them with those of healthy control subjects, and to assess any possible association of ceruloplasmin and treatment response.

*Methods.* Nineteen (8 male, 11 female) patients with major depressive disorder and 40 (17 male, 23 female) healthy control subjects were included in the study. The patients received naturalistic antidepressant treatment for 8 weeks after diagnosis. Serum ceruloplasmin levels and Hamilton Depression Rating Scale (HAM-D) scores of the patients were measured before and after their antidepressant treatment. Blood collection for ceruloplasmin measurement was done only once for healthy control subjects.

*Results.* Patients' ceruloplasmin levels before and after antidepressant treatment were significantly higher than control subjects ($t = 7.569$, $p < 0.001$ and $t = 6.764$, $p < 0.001$, respectively). Despite clinical improvement, ceruloplasmin did not show any significant change after treatment in patients with depression ($t = -1.163$, $p = 0.260$) and remained higher than levels of control subjects. No correlation was found between HAM-D score, presence of response, and ceruloplasmin levels.

*Conclusions.* Compared to healthy control subjects, ceruloplasmin level seemed to be higher in patients with depression and remained high, despite acute antidepressant treatment. Improvement in clinical measurements of depression after antidepressant treatment was not reflected as significant alterations in serum ceruloplasmin levels. 

*Key Words:* Antioxidant, Depression, Oxidative Stress, Ceruloplasmin, Antidepressant treatment.

## Introduction

Ceruloplasmin is a serum protein mainly synthesized by hepatocytes and, to a lesser extent, by testis, spleen, and lungs, and neuronal, astroglial, and microglial cells of the central nervous system. Ceruloplasmin binds almost 90% of the total copper amount found in the body (1). It is an acute phase reactant known to play a role as an antioxidant in both iron and copper metabolism (2,3).

Abnormalities in serum ceruloplasmin level are usually found among the conditions that underlie neurodegenerative disorders. Its deficiency in neuronal cells may lead to damage secondary to diminished mitochondrial energy production, increased lipid peroxidation and iron-associated free radicals (4). Previous studies suggested

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a causal role of ceruloplasmin deficiency or ceruloplasmin gene variations in the development of neurodegenerative disorders such as idiopathic Parkinson's disease (2,5). Ceruloplasmin is involved in the oxidation process of some neurotransmitters such as serotonin, noradrenaline and dopamine. These neurotransmitters are known to play an important role in the development of many psychiatric disorders including depression (2,6,7).

Association of ceruloplasmin with neurodegenerative disorders and its involvement in the metabolism of neurotransmitters suggest a possible association of this protein and psychiatric disorders. In fact, some studies have found increased ceruloplasmin levels in schizophrenia and obsessive compulsive disorder (OCD) (8,9). Few studies have investigated ceruloplasmin in depression (10,11). These studies had a cross-sectional design or did not include a control group, which limits the generalizibility of their results.

To the best of our knowledge, ceruloplasmin (before and after treatment) has not yet been investigated in a longitudinal study. In an attempt to fill this gap, we aimed to determine the serum ceruloplasmin levels of patients with depression before and after pharmacological treatment and compare them with those of control subjects.

## Materials and Methods

### *Participants*

Twenty one drug-naive patients from the Gaziantep University Hospital Psychiatry Outpatient Clinic with diagnosis of major depressive disorder (MDD) according to DSM-IV were enrolled.

Exclusion criteria were as follows: a) patients with known previous depressive episode, b) comorbid psychiatric conditions such as substance abuse, dementia, mental retardation, anxiety disorders, mood disorders other than MDD, psychotic disorders, eating disorders, and tardive dyskinesia, c) any concomitant severe medical conditions like infectious diseases, any neurological disorders, severe obesity, and use of drugs with known antioxidant effects.

Forty healthy age- and gender-matched volunteers were included in the study as a control group. Any patient with a psychiatric disorder and medical condition were excluded from the control group by a meticulous psychiatric interview along with an extensive neurological and physical examination of each participant.

### *Psychiatric and Biochemical Measurements*

The Turkish version of Hamilton Depression Rating Scale (HAM-D) was used to assess the severity of depressive symptoms of the patients. The original scale was first developed by Hamilton et al. in 1960 (12). Validity and reliability of its Turkish version was demonstrated by Akdemir et al. in 2001 (13). HAM-D is composed of 17 items and provides scores between 0 and 51. Treatment response was defined as 50% or more decrease in the HAM-D score (14).

Venous blood samples from the left forearm vein were collected once into 5 ml vacutainer tubes at 7−8 a.m. after overnight fasting. Blood samples were centrifuged at 7000 rpm for 5 min to obtain sera. Samples were stored frozen at −40°C prior to analyses. Biochemical analyses were conducted at the Harran University Biochemistry Laboratory after collecting all the blood samples. Ceruloplasmin measurement method is automated, colorimetric, and based on the enzymatic oxidation of ferrous ion to ferric ion (15). The results were expressed in milligrams per deciliter, and the precision of this assay has been previously demonstrated. For a detailed understanding of measurements, readers may review our previous studies (15,16).

### *Procedure*

All patients and control subjects provided informed consent prior to study inclusion. Two patients were excluded from the analysis due to insufficient sampling of venous blood. Patients were given naturalistic antidepressant treatments for 8 weeks including selective serotonin reuptake inhibitors. Patients were also evaluated before and at the end of their antidepressant treatment with the HAM-D. Venous blood sampling from healthy control subjects was done only once after providing informed consent. Ceruloplasmin levels of 19 patients before and after their antidepressant treatment and also those of healthy control subjects were compared with each other. For comparison of continuous variables, *t* test for independent samples was used and *t* test for repeated measures was also used where appropriate. Correlations were analyzed using Pearson's correlation test. For comparison of categorical variables, Fisher's $\chi^2$ test was used; $p < 0.05$ was accepted as statistically significant.

## Results

Demographic and clinical data including age, gender, mean HAM-D scores and serum ceruloplasmin levels before and after antidepressant treatment are shown in Table 1. Both groups were similar in terms of age and gender. The mean ceruloplasmin levels in the patient group before and after their antidepressant treatment were significantly higher than those of healthy control subjects ($t = 7.569$, $p < 0.001$ and $t = 6.764$, $p < 0.001$, respectively). The antidepressants used were venlafaxine in six patients (31.6%), sertraline in four patients (21.1%), escitalopram in three patients (15.8%), fluoxetine in two patients (10.5%), paroxetine in two patients (10.5%), citalopram in one patient (5.3%), and mirtazapine in one patient (5.3%).