

## Depression and Copper

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Major depressive disorder (MDD) is a chronic illness that causes long-term deterioration in mental status, manifested by the inability to enjoy work as much as before and the constant sadness. The individual takes on a pessimistic mood, cannot find the energy to fulfill his responsibilities, has a lack of sleep, cannot overcome his problems and becomes withdrawn. It is a condition that can occur in every stage of life, from childhood to old age. Studies have shown that the prevalence of MDD in adults and children is between 1-3%. Among the causes of depression, factors such as stress in daily life, genetic factors, and social environment are shown. If the applied treatment methods are not effective, it may cause temporary or permanent damage to the individual's body and even result in suicide.<sup>[1-4]</sup> As a result of a study carried out on 318 subjects between 1978-1981, it was seen that after the first improvement, the probability of recurrence in 1 year was 25%, the probability of recurrence in 2 years was 42%, and the probability of recurrence in 5 years was 60%. After the second recurrence, it was determined that the probability of recurrence within 1 year was 41%, the probability of recurrence within 2 years was 59%, and the probability of recurrence within 5 years was 74%.<sup>[5]</sup> In the light

### ABSTRACT

Major depressive disorder (MDD) is a long-term mood disorder that occurs in an individual's mood. It is a disease that is mostly encountered in the adolescence period of living things, but it can also occur in other life stages. Social environment or genetic factors can be effective in the emergence of depression. The person constantly feels sad and tired, changes in eating habits, not being able to enjoy the work done, loss of concentration, and this process may result in suicide. MDD is medically treatable, but relapses occur in most individuals. Copper mineral, which plays a role in the strengthening of the skeletal-muscular system and the regeneration of tissues, is the most abundant mineral in the tissues after zinc and iron and is taken into the body through diet. It is known that in cases where copper homeostasis is not provided, it causes the development of diseases by affecting many cellular processes. In this article, the link between depression and high copper concentration in the organism will be discussed.

**Keywords:** Copper, depression, major depressive disorder.

of these data, it can be said that there is no direct proportionality between the recovery period of the individual and the probability of relapse, and that it increases the probability of recurrence in case of recurrence. Electroconvulsive therapy (ECT), one of the treatment methods of major depressive disorder, is based on the treatment of mental disorders by applying electric shock. A 1008 mC stimulus was applied bilaterally from the temporal lobe of the brain to a group of depressed individuals with a mean age of 52.8 years, twice a week. After the treatment process, when the cognitive functions and brain structures of the individuals were examined, it was observed that there was a volumetric increase in both hemispheres of the amygdala and hippocampus regions, which are responsible for controlling the mood, as a result of the electrical current applied, and cognitive disorders improved.<sup>[6]</sup> In addition to zinc and iron, the most abundant copper in the body is known

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**Cite this article as:** Tekin E, Güneş B, Erbaş O. Depression and Copper. JEB Med Sci 2021;2(2):181-187.

doi: 10.5606/jebms.2021.75655

**Received** : July 12, 2021

**Accepted** : August 17, 2021

**Published online** : September 29, 2021

as a micronutrient necessary for the fulfillment of biological processes and the maintenance of life. It has been understood that copper and supplementary selenium, zinc and molybdenum are involved in increasing the amount of DNA and RNA, regulating cellular processes such as the use of oxygen in respiration, and ensuring the continuity of the cell membrane. Too little or too much copper has been associated with many other diseases. In case of excess, it shows its toxic effect mainly on the liver. As a result of poisoning, nausea and vomiting, fever, cough, and diarrhea symptoms are detected. In case of low levels, it is known to trigger Menkes syndrome and Wilson's disease, causing fatigue, loss of appetite, skin lesions and infection. It is necessary to provide copper homeostasis in order to prevent the occurrence of diseases associated with this and similar copper. As a result of the researches, it was found that the amount of copper that should be taken daily should be 1 milligram.<sup>[7-9]</sup>

### MDD PATHOPHYSIOLOGY

Changes in an individual's stress hormone levels are among the most important causes of MDD. In response to the psychological stress exposed, corticotropin-releasing hormone, or CRH, is secreted from the hypothalamus region of the brain. It is known that most depressed individuals have high levels of CRH hormone in their cerebrospinal fluid (CSF). In addition, it has been understood that it causes symptoms such as sleep disturbance, loss of appetite, and decrease in psychomotor reactions, which are related to MDD. High cortisol level, which occurs as a result of excessive secretion of CRH hormone, is an important factor in the development of heart disease, osteoporosis or diabetes, as well as depressive disorder. Although it cannot be based on definitive evidence, it is thought that genetic factors are also among the causes of depressive disorder. Considering twin siblings or close relatives, it would not be wrong to say that it is a genetically based disease. When the midbrain and brainstem nuclei are examined, it is seen that some monoamines cause changes in the cognitive function of the individual. Among these monoamines, noradrenergic, dopaminergic, and serotonergic neurons can be given as examples. As a result of the researches, it has been observed that with the decrease in the amount of serotonin, there are losses in the function of the serotonergic system, with the increase in the hydroxylase activity, there is a decrease in the norepinephrine

activity and therefore the function of the noradrenergic system is lost, and the depression increases with the decrease in the dopamine neurotransmission. In the light of this information, it has been understood that the basis of the pathophysiology of major depressive disorder is the change in the amount of neurotransmitters. It has been observed that the loss of function of the GABA-A receptor is associated with the stress factor exposed, and depression decreases with decreasing GABA concentration. It has been observed that there are changes in the hormone level as a result of factors such as irregular sleep, social environmental conditions, and nutrition in the biochemical and psychological behaviors of the creature during the 24-hour period, and accordingly, it causes MDD.<sup>[10]</sup>

### PATHOPHYSIOLOGICAL MECHANISM MARKERS

*Inflammatory markers:* As a result of the research carried out at Vrije University in Amsterdam, blood samples taken from the subjects in the morning were examined. As a result of the examinations, it was understood that the amount of CRP protein, which is responsible for reversing the inflammation caused by the entry of foreign substances into the body, is higher in depressed individuals than in non-depressed individuals.

*HPA axis (hypothalamic-pituitary-adrenal axis) markers:* The HPA axis is a pathophysiological mechanism involved in the stress response. When the saliva samples taken from the subjects in 7 different time periods of the day were examined, it was understood that the amount of cortisol was higher in the evening than in the daytime. It has been observed that the cortisol level, which triggers depression, increases even more in the evening hours in depressed individuals.

*BDNF (Brain-derived neurotrophic factor) level:* When the serum blood samples of the subjects who did not use antidepressant drugs but were depressed were examined, it was understood that the level of BDNF, which contributes to the development of the neuron and nervous system, was lower than that of the other subjects of the same age who were using antidepressant drugs and were depressed.

*Vitamin D level:* When the vitamin D levels of 2514 subjects were measured, it was understood that non-depressed individuals had higher levels of vitamin D than depressed individuals.<sup>[11]</sup>

## MDD PATHOGENESIS

Although it is known that there is no clear information about the details and functioning of the mechanisms of MDD pathogenesis, it is thought that BDNF plays a role in this mechanism and that at least one out of every five people will suffer from MDD at any stage of life. In order to understand depression in humans, a model of depression in experimental animals has been developed. As a result of these studies carried out in experimental animals; It has been understood that the conditions affecting the emotional state such as separation from parents at an early age, exposure to violence in childhood, and repeated exposure to stress factors cause the individual to be isolated from the social environment, and as a result, depression occurs. When different rat groups were examined, it was seen that the defense mechanism against stress was transferred to the offspring with genetic factors. It has been proven that the phenotype before and after depression in one group of rats showed more variation than in the other group of rats. Studies in this area allow for the examination of all aspects of depression and the development of new drugs and treatments.<sup>[12]</sup>

## MDD ETIOLOGY

When the etiology of MDD is examined, it is understood that some changes occur in the mental states of living things that show full development in the evolutionary process, depending on environmental conditions, social life, stress factors and biological processes. When the etiology of MDD was examined, it was understood that there was a disruption in the development of neurons and the formation of new neurons due to various stress factors. It has been observed that the estrogen hormone and the increased education level with learning to encourage the formation of new neurons, while the traumatic events experienced, cortisol, and therefore the increase in corticosterone prevent the formation of new neurons in the hippocampus. Therefore, regulation of neurogenesis is important for coping with depression.<sup>[13]</sup>

## MDD EPIDEMIOLOGY

When the epidemiology of MDD is examined, the most common psychiatric disorder in medical clinics is Major depressive disorder. It has been understood that it is a disease that can be caused

by various factors, which victimizes almost 50% of the whole society.<sup>[14-16]</sup>

## MDD SYMPTOMS

There are some symptoms sought in the individual to understand the presence of MDD. Among these symptoms, there are pains in certain parts of the body, especially in the head and back, slowing of the digestive system, loss of appetite, and sleep disorders. In addition, psychomotor symptoms should also be considered when diagnosing depression. While it is seen that depressed individuals touch themselves more frequently and communicate with small head movements, it is seen that there is an increase in the decision-making process in the face of events.<sup>[17,18]</sup>

## GENETIC FACTOR IN MDD

It has emerged as a result of studies that the symptoms of anxiety and depression are mostly common and that these symptoms occur together. Therefore, it is thought that these two diseases trigger each other or occur through genetic factors. When the presence of this disease was tested in the relatives of the individual with MDD, it was observed that there was a relationship between them and the same relationship was established between twin siblings. In the later stages of the study, it was concluded that MDD is not only caused by genetic factors, but may also arise as a result of environmental or physical factors.<sup>[19]</sup>

## THE LINK BETWEEN MDD AND OTHER DISEASES

When examining whether there is a relationship between depression and vascular disease, a relationship was found between them. Vascular disease is the narrowing or occlusion of the arteries as a result of various factors. As a result of the study conducted on the subjects, it was found that depression does not have a clear effect on the occurrence of vascular disease, but vascular disease causes depression at a high rate in individuals. It has also been observed that depression occurs in individuals who have had a stroke.<sup>[20]</sup>

Although it cannot be based on conclusive evidence, it is believed that there is a relationship between AD and depression, and that depression is a symptom that causes the onset of AD.<sup>[21]</sup>

It has been noticed that some cancer diseases also start after people with MDD are diagnosed

with depression, and therefore cancer disease has been associated with depression. Although no relationship was found between depression and stomach cancer as a result of studies, it was found that there was a relationship between lung, breast, pancreatic, oral and pharyngeal cancers.<sup>[22]</sup>

In an experiment conducted with 2049 people aged 20-75, who are known to have diabetes, it was found that the rate of depression was 77.6%. In addition, in this study, it was determined that individuals without diabetes were 2 times less likely to develop depression than individuals with diabetes.<sup>[23]</sup>

### NEUROANATOMY OF MAJOR DEPRESSIVE DISORDER

The symptoms that are one of the most critical symptoms of MDD and that must be present in the individual for the diagnosis of this disease; being indifferent to events, showing a careless attitude and not finding energy in himself to fulfill his responsibilities. These changes in the mood of the individual during the process of major depression cause some effects in regions of the brain such as the thalamus, hippocampus, prefrontal cortex, and amygdala. Disruption of coordination between brain parts that work in coordination with each other can be due to some psychological or physical effects. As a result of the researches, it was explained that the depression process, which negatively affects the mood, causes a decrease in the activation of the anterior cingulate cortex and left ventro-lateral prefrontal cortex in the brain. The anterior cingulate cortex is a part of the brain that is in communication with regions of the brain such as the amygdala, thalamus, and prefrontal cortex, and is responsible for controlling emotional behaviors. The left ventro-lateral prefrontal cortex, similar to the anterior cingulate cortex, is the region responsible for the regulation of movements depending on emotional processes.<sup>[24]</sup>

### EVALUATION OF MDD

Based on the data obtained as a result of a study conducted in 18 countries, it was determined that the countries with the highest prevalence of MDD were France and the United States, respectively. Although the response to major depressive disorder, which occurs as a result of factors such as social environment, insufficient economic income,

education level, age, gender, and marital status, may vary from person to person, it has been observed that women tend to be depressed twice as much as men. It is known that the most used method in this disease, which is tried to be treated with various methods, is the use of antidepressant drugs, but it has often been understood that this treatment method alone is not sufficient, no curative effect is observed, and there are individuals who are resistant to treatment. Individuals with treatment-resistant depression (TRD) are individuals who do not respond positively to existing treatment methods.

As a result of the studies, it was concluded that keeping the amount of neurotransmitters in the body at the required level has a preventive effect on the formation of MDD. It has been understood that the amount of neurotransmitter substances should be kept under control with a balanced diet in cases where current treatment methods cannot be effective alone. Depression can be prevented by taking enough vitamins and minerals and consuming vegetables, fruits and grain foods. Among the most important minerals to be taken through the diet are copper, zinc and magnesium.<sup>[25,26]</sup>

### PREVENTION, DIAGNOSIS AND TREATMENT OF MAJOR DEPRESSIVE DISORDER

It has been previously stated that conditions such as introversion, constipation, lack of appetite, tendency to communicate with small head movements instead of using sentences, constant fatigue, and sleep disturbance are among the symptoms of MDD.<sup>[17,18]</sup>

Among the methods used in the treatment of MDD are psychotherapy, well-being therapy, pharmacotherapy, and psychodynamic psychotherapy. Psychotherapy and well-being therapy aim to restore individuals' communication with their environment and instill self-confidence in order to prevent individuals from experiencing difficulties in their social life. Psychodynamic psychotherapy is a method used in the treatment of individuals who experience anxiety and are overly attached to their social environment. In pharmacotherapy, with the use of antidepressant group drugs, it is possible to cope with depression by affecting the amygdala region of the brain, increasing the production of positive emotions and reducing the production of negative emotions.<sup>[27]</sup>

## THE RELATIONSHIP BETWEEN COPPER AND MAJOR DEPRESSIVE DISORDER

It is known that copper is a reactive element that takes part in reactions based on the exchange of a single electron and is carried in the body by the ATP7A protein belonging to the ATP7A gene. Copper, which can be found free or bound to proteins, can cause damage to cells as a result of free radical reactions, causing damage to DNA and protein. Therefore, the amount in the body should always be kept stable at the required level.<sup>[28-30]</sup> As an important component of lysyl oxidase (LOX), copper, which mediates the transport of oxygen to the necessary tissues by oxidation, takes part in maintaining the form of organs and forming connective tissue. In addition, as an important component of tyrosinase, it takes part in the formation of color pigment depending on the formation of melanin.<sup>[31]</sup> After absorption of the copper element, it is stored in the liver via transcuprein or serum albumin, where it is stored in the form of ceruloplasmin, plasma copper-protein, superoxide dismutase or copper-metallothionein. Ceruloplasmin, which mediates the transport of the element copper; It carries the copper element to the tissues so that copper enzymes such as LOX or cytochrome c oxidase can be synthesized.<sup>[32]</sup>

After iron and zinc, copper is the most abundant mineral in tissues. In addition to being a cofactor in the structure of many enzymes, it plays a role in many biochemical processes such as the regulation of the functioning of the central nervous system, the formation of color pigment (melanin), the structure of bones, and the control of cellular respiration. It has been understood that problems in the bone structure occur as a result of copper deficiency due to nutritional deficiency and may cause diseases such as anemia, Huntington's disease and Menkes disease. It is known that due to the increase in its amount in the body, it creates imbalances in cellular processes and causes Parkinson's and Alzheimer's disease. Although it has not been proven with definite data, it is among the possibilities that an increase in the amount of copper may cause MDD. Copper is transported from the blood to the brain via the blood-brain barrier (BBB), and excess copper is transported to the blood via the blood-cerebrospinal fluid barrier (BCB). In this way, it is tried to keep the copper concentration in the body in balance and to provide homeostasis.<sup>[33,34]</sup>

Proton magnetic resonance spectroscopy (H-MRS) method can be used to understand whether brain biochemistry changes depending

on the concentration of copper and whether this situation causes MDD. The H-MRS method is a non-invasive, non-surgical and non-invasive method used to detect biochemical changes in the brain. As a result of studies conducted with 32 healthy individuals with 29 MDD, it was determined that the copper concentration in sick individuals was higher than in healthy individuals. Based on these data, it was concluded that changing copper concentration prevents the prefrontal cortex of the brain, which controls mood and emotions, and the amygdala region, which is responsible for the fight-flight response, from working in coordination with each other.<sup>[35]</sup>

It is among the information in some scientific data that the brain function is affected as a result of the increase in the blood due to the decrease in the concentration of copper in the brain, which has a role in many important cellular processes, up to the creation of neurotransmitters, and that it triggers the occurrence of AD. When the changes that occur as a result of zinc concentration are examined, it is understood that the mood changes positively with the elimination of the deficiency, and it has positive effects on the cognitive process of the individual. Based on this and similar information, scientists concluded that copper and zinc are effective in the process of oxidative stress, and high copper concentration has been associated with major depressive disorder.<sup>[36]</sup>

In a study carried out on rats, 33 adult male rats were kept under suitable conditions for 1 week. After this process, the rats were randomly divided into 3 groups. Group 1 received 20 mg/kg corticosterone and 1 mL/kg saline, group 2 received 7 mg/kg copper gluconate and 20 mg/kg corticosterone, and group 3 received only 1 mL/kg saline injection daily for 3 weeks. At the end of 3 weeks, 5 rats from each group were killed, and serum copper concentrations were determined. The remaining rats were treated with memantine for 2 weeks. After the end of the study, it was understood that the high copper concentration caused the rats to exhibit depressive movements. After the administration of memantine, it was understood that NMDAR function improved, and it could be a means of achieving a positive result against depression.<sup>[37]</sup>

In another study conducted in Japan, the relationship of some minerals with depression was investigated. In this study, it was understood that individuals who took high copper and manganese in their body showed symptoms of depression, while

individuals who took low copper and manganese did not show symptoms of depression. However, it has been determined that individuals with low copper and zinc concentrations at the same time show signs of depression 3 times more than other individuals. It has been clearly seen that the mineral concentration in the diet has important effects on the mental health of the individual.<sup>[38]</sup>

Contrary to scientists who suggest that high copper levels cause MDD, there are also scientists who suggest that copper levels of depressed individuals are lower than those who are not depressed, and there are studies supporting this idea.<sup>[39]</sup> Because of these contradictions, it is not possible to reach definite conclusions about the relationship between copper and depression.

## CONCLUSION AND DISCUSSION

Creating a strong social environment, increasing the quality and level of education, engaging in physical activities by doing sports, staying calm and solution-oriented in the face of unexpected situations, sleeping and eating habits are critical points in minimizing the possibility of getting MDD.

As a result of the studies, it has been started to be thought that MDD is associated with many other diseases, although it cannot be based on definitive evidence. It has been observed that some types of cancer, AD or vascular disease occur following the diagnosis of MDD.

It is known that in addition to genetic, physical and environmental conditions, which are the causes of MDD, improper eating habits can also cause depression. It has been understood that many protein-rich foods have an effect on increasing serotonin levels and thus reducing depression. Furthermore, it is proven that the incidence of diseases changes depending on the increase and decrease in the level of vitamins and minerals taken with food.

There are many scientific studies investigating the relationship between nutritional mineral intake and depression. As a result of some studies, it has been found that increased copper level prevents the amygdala and prefrontal cortex from working with each other regularly and thus causes MDD, while in some studies it has been found that increased copper level does not cause any negative effects on the brain and is not associated with the occurrence of MDD.

Considering these conflicting studies, it is not possible to make a clear interpretation that an increase or decrease in copper level increases or decreases depression, since the relationship between copper level and depression cannot be based on definitive evidence.

### Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

### Funding

The authors received no financial support for the research and/or authorship of this article.

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