The Importance of Iron, Copper, Zinc, and Magnesium Dyshomeostasis in terms of Alzheimer’s Disease and Possible Mechanisms

Alzheimer Hastalığı Açısından Demir, Bakır, Çinko ve Magnezyum Dishomeostazisinin Önemi ve Olası Mekanizmalar

ABSTRACT

Alzheimer’s disease (AD) affects many people around the world, and its incidence is increasing. In addition to the amyloid cascade hypothesis, different mechanisms are discussed for AD, which has no definitive treatment. Studies have shown that the levels of metal cations such as iron, copper, zinc, and magnesium vary and their metabolism are impaired in patients with AD. Metal cation dyshomeostasis is believed to be one of the mechanisms that contribute to the development of AD. In this review, we aimed to evaluate various metal cations in terms of AD.

Keywords: Alzheimer’s disease, dyshomeostasis, iron, copper, zinc, magnesium

INTRODUCTION

Dementia is a neuropsychiatric medical condition that causes deterioration in people’s cognitive abilities compared to a few months or a few years ago and is characterized by deterioration in activities of daily living (1). The incidence of dementia increases with the prolongation of the human lifespan. Alzheimer’s disease (AD) is the most common cause of dementia and affects many people worldwide. Although AD is a disease that usually occurs in advanced age, it cannot be considered as a part of normal aging (2). While AD causes behavioral and speech changes by disrupting the cognitive activities of patients, it also negatively affects the quality of life of patients’ relatives (1,2).

In addition to the large number of people affected, there is still no curative treatment for AD (3). Acetylcholine esterase inhibitors such as donepezil, rivastigmine, galantamine, and the N-methyl D-aspartate (NMDA) receptor antagonist memantine are used in this treatment. These treatments are only aimed at slowing the disease progression. They are insufficient to treat the disease, and there is a problem of tolerance to these drugs (3,4). The effectiveness of the monoclonal antibody aducanumab, which was approved by the US Food and Drug Administration (FDA) in 2021, for treating the disease is controversial (4). Lecanemab, another anti-Aβ monoclonal antibody, was approved by the FDA in 2023. It is emphasized that lecanemab, which targets the soluble and insoluble forms of the Aβ peptide accumulated in AD, can reduce Aβ aggregates in the brain.

Address for Correspondence/Yazışma Adresi: Mustafa Arslan MD, Gazi University Faculty of Medicine Department of Anesthesiology and Reanimation, Ankara, Türkiye

E-mail / E posta: mustarslan@gmail.com

ORCID ID: orcid.org/0000-0003-4882-5063
It has been stated that lecanemab can be effective, especially in the early stages of AD, and results are needed to demonstrate its clinical benefit (5,6). There is currently no curative treatment for AD. In addition to the lack of an effective treatment for AD, no biomarker can make a definitive diagnosis alone. Although various biomarkers have been tried for the diagnosis of AD, these options do not provide high specificity and sensitivity criteria and remain far from making a definitive diagnosis (7). The fact that the biomarker considered for AD is blood-based and minimally invasive will provide a great advantage in terms of ease of application (8). Therefore, various plasma parameters have been evaluated for their potential as biomarkers for AD.

Metal cations such as iron, copper, and zinc are currently being investigated because of their association with AD (9,10). In addition, in recent years, it has been emphasized that various forms of magnesium are important for AD. With its anti-inflammatory properties, magnesium is believed to be beneficial in AD, as in many other neurological diseases (11).

Changes in plasma and urinary metal cation levels in patients with Alzheimer’s have led scientists to work on this issue. For example, in various studies, plasma copper levels in patients with Alzheimer’s were found to be significantly higher than in controls. It has been reported that urinary copper excretion is also high in patients with AD. These findings indicate the presence of metal cation dyshomeostasis in patients with AD (12).

This review aims to evaluate various metal cations (iron, copper, zinc and magnesium) in terms of AD. The specified metal cations are the most important for AD, and their dyshomeostasis further influences disease development. This study aimed to review the literature by examining the metals that may be related to AD, which does not have a definitive diagnosis and curative treatment yet. Explaining the mechanism could lead to the development of future AD treatments targeting metal cations.

**Alzheimer’s Disease and Metal Cations**

AD is the most common form of dementia and affects many people around the world. Pathological accumulations are observed during the development of AD. These are intracellular neurofibrillary tangles and extracellular amyloid plaques. The accumulation of amyloid plaque and the accumulation of hyperphosphorylated tau protein act as triggers for each other. In the continuation of the process, clinical signs of AD are observed due to neuronal loss and deterioration of synaptic transmission (13).

Although age is the most prominent factor in the development of AD, life expectancy is increasing in many countries. In addition, AD cannot be considered as a result of normal aging (2). Therefore, studies should be conducted for AD, which has not a curative treatment and a biomarker that will provide a definitive diagnosis. However, it will be beneficial to elucidate the unknown parts of the development mechanisms of the disease.

In recent years, mechanisms other than the amyloid cascade hypothesis have been investigated for the development of AD. This is caused by the ineffectiveness of treatments targeting amyloid deposition and the fact that AD is a multifactorial disease (14).

Balance of metal cations in the central nervous system is necessary for healthy brain function. For this reason, metal cation homeostasis was investigated for AD using different mechanisms (Figure 1) (14). Metals cross the blood-brain barrier endothelium via active or receptor-mediated transporters to serve essential roles as secondary messengers, enzyme activators, and gene expression regulators in the brain. Therefore, the delicate brain balance of metal concentrations must be maintained (15).

In this review, the possible relationships between some metal cations and AD were investigated.

**Iron in Alzheimer’s Disease**

Iron, the most abundant transition metal in the brain, is essential for healthy living and proper functioning of the brain. Iron is a cofactor in many processes, including gene expression, neuronal development, enzymatic reactions, enzyme formation, and electron transport (16). However, iron dyshomeostasis is closely related to oxidative stress. When the amount of iron exceeds the detoxification capacity of the cell, increased iron levels cause the amplification of oxidative stress by the Fenton reaction and the Haber-Weiss cycle. Therefore, oxidative stress due to iron accumulation in the brain causes neuronal damage (17).

Iron levels vary in Alzheimer’s patients. Iron binds directly to Aβ and tau, causing biochemical modifications that generate oxygen radicals that amplify cell-wide oxidative stress (14). Alternative treatments are sought because amyloid-targeted therapies cannot...
show the desired efficacy in AD. Homeostatic regulation of iron is a viable avenue for therapeutic targeting and has been observed to be impaired in many neurodegenerative disorders in addition to AD (18).

Amyloid precursor protein (APP) and tau proteins, which play a role in AD development, are associated with iron metabolism (19). In neurons, the concentration of iron ions is effective in APP gene expression. APP mRNA has a segment of 11 bases in the 5' region called the iron regulatory element (IRE). Iron regulatory proteins (IRPs) associate with IRE to regulate APP synthesis (20). Iron regulatory proteins associate with IREs in the untranslated region of mRNA transcripts of iron metabolism-related genes, thereby regulating iron concentration in cells. High iron concentrations increase APP expression by causing conformational changes in the IRE region of APP mRNA. In addition, high concentrations of iron in the neurons cause APP to be proteolyzed to form amyloid deposits (21).

The iron regulatory proteins IRP1 and IRP2 are intracellular iron sensors. The regulation of brain iron homeostasis at the cellular level includes IRPs that regulate the expression of related proteins. A decrease in IRP2 expression levels leads to an imbalance in brain iron. In addition, oxidative stress caused by iron accumulation in the brain increases IRP1 activity, causing a further increase in intracellular free iron (22,23). This increase in iron can lead to the development of neurodegenerative diseases such as AD (24).

Iron accumulates in the brain with age, and several neurodegenerative conditions are associated with increased iron levels in affected areas of the brain. Iron accumulation is observed in the parietal cortex, motor cortex, and hippocampus, which are brain regions of primary importance in AD (25,26). Age-related iron deposition in brain regions associated with AD has made iron dyshomeostasis a therapeutic target for AD (18).

In addition, iron-dependent programmed cell death, called ferroptosis, causes many diseases, particularly neurodegenerative diseases. Iron dyshomeostasis and lipid peroxidation, which are hallmarks of ferroptosis, play an important role in the development of AD, a neurodegenerative disease (27,28).

**Copper in Alzheimer's Disease**

Aβ senile amyloid plaques in Alzheimer’s patients contain high levels of metal cations. These metal cations are especially iron, copper, and zinc. Metal accumulation in amyloid plaques demonstrates the effect of metal cation dyshomeostasis on AD development (12,29). Senile amyloid plaques contain high concentrations of iron, copper, and zinc, and these ions can trigger Aβ accumulation (30).

In a study conducted with 336 healthy controls, 385 Alzheimer’s patients, and 9 Wilson’s patients, plasma copper levels were found to be higher in Alzheimer’s patients, similar to Wilson’s patients. These findings have been interpreted as an indicator of deterioration in copper homeostasis in AD. In the same study, urinary copper excretion was high in Alzheimer’s patients compared with healthy controls in 24-h urine measurements (12).

In another study conducted with 50 patients with AD and 50 healthy controls, plasma iron, copper, and zinc levels were found to be significantly lower in patients with AD. In this study, trace elements and antioxidant enzymes associated with these elements were also evaluated in AD. Metals act as cofactors in the realization of many reactions in our body and participate in the structure of many enzymes (31). We evaluated superoxide dismutase, catalase, and glutathione peroxidase, which are antioxidant systems that prevent damage caused by reactive oxygen species in the body. These levels were found to be low in AD. Changes in the levels of metals associated with these enzymes confirm metal cation dyshomeostasis in AD (31).

Transthyretin, a carrier protein in the blood, mediates the transport of various substances. One of these substances is Aβ and transthyretin mediates the removal of amyloid derivatives from the central nervous system (32). In addition, transthyretin undergoes a conformational change when exposed to metal cations such as copper, iron, zinc, and manganese. These metal ions change the binding affinity of transthyretin to Aβ. Transthyretin is converted to a protease that scavenges Aβ, thereby increasing Aβ elimination. It is one of the hypotheses that metal cations exert their effect on AD through transthyretin (30).

Copper homeostasis is regulated by two different activities. The first is enzymes that use copper as a cofactor, and the second is the proteins that transport copper. When copper is not used for vital catalytic functions, it participates in redox reactions. It generates hydroxyl radicals through the activation of the Haber-Weiss cycle and Fenton reactions (33). Copper bound to ceruloplasmin is associated with redox-mediated toxicity. Ceruloplasmin-bound copper contains 5-10% of plasma copper and is in dynamic equilibrium with albumin, peptides, and amino acids (34). Metal accumulates in the mitochondria of copper-overloaded cells, and mitochondrial copper alterations are involved in neurodegenerative processes and apoptotic signaling (35).

Therefore, when the copper balance is disturbed, this may contribute to the development of AD, or the development of AD may disrupt copper homeostasis and the process may be exacerbated. The details of this mechanism are not fully known and need to be clarified. Knowing the mechanism will enable the production of metal cation-related treatment options.

**Zinc in Alzheimer’s Disease**

Zinc is the second most abundant trace element after iron in the human central nervous system. Because of the multifunctional properties of zinc, zinc dyshomeostasis can affect different biological activities. Zinc-based therapies are considered for AD because of the changes observed in zinc levels in human and animal studies (36).

Zinc is essential for brain function and participates in catalytic reactions for the continuation of life (19). High zinc influx at synapses contributes to synaptic plasticity, and zinc modulates long-term potentiation in the hippocampal CA3 region. The synaptic zinc cycle deteriorates with age. Therefore, zinc dysregulation contributes to cognitive impairment in AD (37,38).

Zinc levels affect APP processing, function, and degradation. NF-κB and p53, zinc-containing transcription factors, regulate APP synthesis. In addition, zinc correlates with the expression of secretases that are effective in APP proteolysis (39). Park et al. (40) showed that zinc reduced presenilin1 synthesis in mouse primary cortical culture and APP/P51 mice. In this study, zinc induced cell death in a dose-dependent manner, and the increase in presenilin 1 synthesis was thought to be specifically related to zinc-induced cell death (40). Zinc
binding can regulate the polymerization properties of Aβ. Because zinc is mainly released from synaptic vesicles in the central nervous system, it plays a key role in controlling the formation of synaptic Aβ oligomers and targeting Aβ oligomers to synaptic terminals (41). The ZnAβ oligomer is a cytotoxic Aβ oligomer, more toxic than the zinc-free form and has toxic effects on synaptic plasticity and long-term potentiation (42).

Zinc accumulation, as well as other metal cations, has been demonstrated in amyloid plaques in AD (29). It is also stated that Aβ exposed to the +2 form of zinc undergoes conformational changes (43). In metal cation dyshomeostasis in AD, the levels of some metals increase while those of others decrease. In a study conducted with 44 patients with AD and 41 healthy controls, it was determined that plasma zinc levels were significantly reduced in patients with AD. The researchers in this study interpreted this finding as a decrease in zinc in plasma due to its accumulation in the central nervous system (44).

It is emphasized that while zinc at low concentrations reduces amyloid aggregation, +2 loaded zinc at high concentrations can increase toxicity (45). As with other metal cations, the most important issue with zinc is balance. Disruption of this balance appears to be associated with diseases. Metal cation dyshomeostasis is accepted as one of the development mechanisms of AD and is among the future therapeutic targets.

**Magnesium in Alzheimer’s Disease**

Magnesium is a very important metal ion that participates in more than 300 enzymatic reactions in the human body. It is necessary for the regulation of muscle contraction, blood pressure, and insulin metabolism. In addition, magnesium must be present for the synthesis of DNA, RNA, and proteins (46).

Magnesium is also important for the nervous system. This is mainly due to the interaction of magnesium with the NMDA receptor, which contains a calcium channel with magnesium blockade. Low magnesium levels could theoretically be thought to amplify glutamatergic signaling. This may result in glutamate excitotoxicity, which leads to oxidative stress and neuronal death. Abnormal glutamatergic transmission is a predisposing factor in many neurological diseases, the most important of which is AD (47,48). Therefore, magnesium supplements are believed to be beneficial for many neurological diseases, especially AD. It is stated that inadequate and/or irregular nutrition may lead to magnesium deficiency, which is a risk factor for AD (48-50).

Studies have shown that plasma, cerebrospinal fluid, and erythrocyte magnesium concentrations are low in Alzheimer’s patients (51-54). In another study conducted with 15 Alzheimer’s patients, 15 mild cognitive impairment patients, and 15 healthy controls, magnesium levels were low in Alzheimer’s patients and patients with mild cognitive impairment. These findings were explained by the fact that magnesium deficiency may cause glutamate excitotoxicity (49). However, in several studies, no significant difference was found in magnesium levels between Alzheimer’s patients and healthy controls (55,56). Therefore, the relationship between AD and magnesium should be clarified by experimental and clinical studies. Barbagallo et al. (57) reported that the ionized form of magnesium is related to cognitive function rather than physical function, and the ionized form of magnesium should be considered when evaluating neurological diseases such as AD.

In addition, improvement in cognitive impairment was observed following magnesium administration in a mouse model of AD. The results of this study have been interpreted as suggesting that elevation of brain magnesium exerts synaptoprotective effects in AD, and magnesium supplementation may have therapeutic potential for the treatment of AD (58). In a study conducted in rats, it was emphasized that magnesium deficiency may lead to an increase in free radical oxygen species. The reducing effect on oxidative stress products may be considered as one of the mechanisms of the positive effects of magnesium supplementation in AD. In addition, intraperitoneal administration of magnesium sulfate showed a protective effect on cognitive functions in a streptozotocin-induced sporadic AD rat model (59). Magnesium supplements are being considered as therapeutic targets for AD. It is necessary to clarify both the prophylactic and therapeutic efficacy of magnesium in AD.

**CONCLUSION**

The mechanism of AD and its relationship with metal cations are not fully understood, but metal dyshomeostasis is effective in AD. The inability of treatments based on the amyloid cascade hypothesis, which is the most accepted hypothesis in the development of AD, to show sufficient efficacy in AD indicates the existence of different mechanisms. Iron, copper, zinc, and magnesium dyshomeostasis is common in AD. Therefore, metal cation dyshomeostasis appears to be associated with AD. Through the mechanisms investigated in this review and future studies, iron, copper, zinc, and magnesium-based treatments may be particularly beneficial for AD.

**Ethics**

**Peer-review:** Externally peer-reviewed.

**Authorship Contributions**


**Conflict of Interest:** No conflict of interest was declared by the authors.

**Financial Disclosure:** The authors declared that this study received no financial support.

**REFERENCES**


15. Choi BS, Zheng W. Copper transport to the brain by the blood-brain barrier and blood-CSF barrier. Brain Res 2009; 1248: 14-21


34. Linder MC. Ceruloplasmin and other copper binding components of blood plasma and their functions: an update. Metallomics 2016; 8: 887-905


