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REVIEW

Role of micronutrients in Alzheimer's disease: Review of available evidence

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Abstract

Alzheimer's disease (AD) is one of the most common age-related neurodegenerative disorders that have been studied for more than 100 years. Although an increased level of amyloid precursor protein is considered a key contributor to the development of AD, the exact pathogenic mechanism remains known. Multiple factors are related to AD, such as genetic factors, aging, lifestyle, and nutrients. Both epidemiological and clinical evidence has shown that the levels of micronutrients, such as copper, zinc, and iron, are closely related to the development of AD. In this review, we summarize the roles of eight micronutrients, including copper, zinc, iron, selenium, silicon, manganese, arsenic, and vitamin D in AD based on recently published studies.

Key Words: Alzheimer's disease; Iron; Micronutrient; Zinc

Core Tip: Significant advances have been made in characterizing the relationship between Alzheimer's disease (AD) and micronutrients copper, zinc, iron, selenium, silicon, manganese, and arsenic. This study provides a new perspective and direction for future scientific research, development of new drugs, and routine preventive measures against AD.

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INTRODUCTION

Alzheimer's disease (AD) is a common age-related neurodegenerative disease[1,2]. Owing to progressive population aging, the incidence of AD will continue to increase[3,4]. In China, an estimated 14% of the general population over the age of 65 years and approximately 30% general population over the age of 85 years were affected by AD. In China, the estimated annual cost of medical care for AD approaches one hundred billion RMB, as the conventional diagnosis of AD is based on expensive investigations such as magnetic resonance imaging, positron emission tomography, and analysis of cerebrospinal fluid[5].

Individuals with AD typically suffer from loss of learning ability and memory, impaired judgment and reasoning[6,7], and loss of analytical ability[8], which can seriously affect their quality of life. This imposes a heavy economic and psychosocial burden on the affected families and the society. Clinical treatment of AD is typically challenging[9]. Currently, clinical research on AD in China and overseas is only at the stage of exploration, while the basic research on AD is still at the stage of hypotheses or theories. Studies have shown that AD is closely related to the dynamic changes in body micronutrients, such as decrease in iron and zinc content, and increase in copper content[10-12]. This article reviews the evidence from contemporary research conducted across the world on the link between AD and micronutrients.

This article is primarily based on a literature search conducted in the NCBI database for studies investigating the link between AD and micronutrients published in the last five years.

AD AND MICRONUTRIENTS

AD and copper

Copper is a ubiquitous element. Red meat, nuts, and vegetables are rich sources of copper. Copper is one of the most abundant transition metals in the human body. It is involved in collagen synthesis, antioxidant defense, skin pigmentation, neurotransmitter synthesis, and iron homeostasis[13]. Thus, it plays an important role in human physiology.

Copper is closely related to AD[14,15]. The most common neuropathic lesions in AD are plaques of neurofibrillary tangle, amyloid, and soluble oligomers with large amounts of copper at their core. Patients with AD were shown to have significantly higher levels of copper in their brain tissue than the general population, which promotes the formation of neurofibrillary tangle, amyloid, and other proteins [16-18].

Copper promotes the neurofibrillary tangle of hyperphosphorylation Tau, which aggravates homeostatic disorders; in addition, copper promotes oxidative stress, which has been observed in the brain tissue of many patients with AD[19]. Rosmarinic acid is a commonly used anti-AD drug. Rosmarinic acid has been shown to reduce copper-induced neurotoxicity due to its antioxidant effect *in vitro* and *in vivo*, by preventing the binding of amyloid protein with copper[20]. The properties of copper-bound amyloid proteins have been employed for auxiliary positron emission tomography in the diagnosis of AD in mouse models[21].

Detection of copper is useful in the diagnosis and prevention of AD[22,23]. In addition, long-term exposure to copper is associated with cognitive decline and microglia degeneration[24]. TDMQ20 was shown to reduce the copper content in the cerebral cortex of mice[25], and ameliorate oxidative stress in the cerebral cortex of mice, further attenuating the neurotoxicity of amyloid[26]. High affinity metal ion chelating agents such as chitosan can be an effective treatment for AD. The therapeutic effect of chitosan is related to its ability to absorb copper ions[27].

AD and zinc

Zinc is one of the essential micronutrients in the body and the second most abundant micronutrient in the central nervous system[28,29]. Zinc is involved in growth and development, wound healing, immune regulation, catalytic reactions, and substance synthesis. Zinc also regulates excitatory and inhibitory neurotransmitters in brain tissue[30,31]. As the zinc content in the body decreases with age, abnormal zinc metabolism may serve as a therapeutic target for AD. In particular, zinc and selenium or iron and zinc have been concomitantly used to treat AD[32,33].

Studies have shown that zinc release increases with age, especially in female rats, and that zinc deficiency leads to neuronal death; this phenomenon is related to the involvement of zinc in the

recognition of neuronal receptors and ligands, which is one of the main risk factors for AD and its associated brain neuropathology[34]. On the contrary, zinc supplementation was shown to improve cognitive deficit and rescue the decline in key molecular targets of synaptic plasticity and insulin signaling in the hippocampus of rats with sporadic AD[35]. Oxidative stress plays a key role in neurodegeneration and impaired cognitive function. Diet rich in antioxidants is a novel strategy for prevention of AD. Compared with healthy individuals, patients with AD showed significantly lower serum levels of Se, Cu, and Zn[36].

Studies have shown that the disorder of zinc dynamic equilibrium can cause abnormal synthesis and increased deposition of amyloid protein in brain tissue, and increase the degree of neuronal damage. The underlying mechanism involves binding of zinc to histidine residues of brain tissue-amyloid protein leading to the formation of amorphous aggregates of-amyloid protein, which then leads to the formation of age spots[37]. The combination of zinc and copper was shown to accelerate the formation of amorphous aggregates of amyloid protein[38], and the high saturation magnetization of zinc ferrite was found to improve the formation of amorphous aggregates of amyloid protein[39].

An increasing body of evidence has shown that the basal level of extracellular zinc in hippocampus is typically in the low nanomolar range, and that the increase in zinc content aggravates the neurotoxicity of amyloid protein[40]. Zinc was shown to increase the expression of amyloid precursor protein in a mouse model of AD, which in turn increased amyloid synthesis.

Pathological dynamic equilibrium of copper, iron, and zinc promotes the deposition of amyloid proteins in brain tissue and affects structural changes in Tau Proteins. S100B is one of the most abundant proteins in the brain[41], which is involved in the regulation of amyloid deposition and zinc homeostasis. Use of zinc chelating agents can improve amyloid deposition levels by interfering with S100B[42]. Klotho protein is a zinc-rich protein which has neuroprotective, anti-inflammatory, anti-oxidant, and promyelination effects. Increasing serum Klotho protein can play a role in neuroprotection, anti-inflammation, and anti-oxidation[43]. Evidence suggests that AD is associated with increased levels of Tau, which is related to the presence of multiple zinc binding sites in the Tau protein. Low zinc levels stimulate Tau, leading to increased neurofibrillary tangle in the neurons[44]. The antioxidant zinc carboxylate inhibits the activity of acetylcholine esterase (ACHE) and butylcholinesterase and plays an anticholinesterase role, which indicates the benefit of zinc carboxylate in the treatment of AD[45]. Zinc homeostasis is involved in the pathogenesis of AD. Zinc can significantly increase the activity of carnosine, which is beneficial in the treatment of AD[46].

Zinc deficiency can lead to a decrease in learning ability and memory in AD. Zinc supplementation (3 mg/kg) was shown to improve learning and memory in a mouse model of AD, which may be related to the decrease in inflammatory activity in NLRP3[47]. Zinc can promote the aggregation of SFPQ in cultured neurons by regulating the nuclear SFPQ protein, which is an important marker of AD[48].

AD and iron

Iron is one of the essential trace metal elements which is widely distributed in the human body. Iron is involved in material transportation, growth and development, cell differentiation, gene expression, and lipid peroxidation. Abnormal heme content and deranged iron homeostasis are more common in AD [49].

Accumulation of iron in the brain is a common phenomenon in many neurodegenerative disorders. Postmortem studies have documented markedly increased concentration of ferritin and hemosiderin aggregates in the brain tissues of patients with severe AD[50]. Inadequate iron intake during pregnancy may cause iron deficiency in fetal brain tissue, increasing the risk of neurological defects. With the increase in age, accumulation of iron in brain tissue can also occur because of brain tissue-amyloid protein deposition and plaque, which in turn promotes further iron deposition[51].

A growing body of evidence suggests that iron dysregulation in brain neurons plays a key role in AD [52]. Studies have documented high iron concentrations in deep gray matter structures of brain tissue in patients with AD[53]. Iron deposition promotes increased Tau levels in brain tissue and neurofibrillary Tangle Tau formation[10,54]. Iron also accelerates the deposition of amyloid proteins in brain tissue[55]. Increased concentration of iron-rich pollutants in the air predisposes people to AD[56].

Studies have shown that-amyloid precursor protein can be hydrolyzed to-amyloid, which is dependent on iron transporter transmembrane transport[57]. *CISD2* gene encodes CDGSH FT-DOMAIN Protein 2, and up-regulation of CDGSH FT-DOMAIN PROTEIN 2 can improve mitochondrial structure and synaptic function, which plays a neuroprotective role[58].

Research has shown that oxidative stress promotes iron deposition in brain tissue, which plays an important role in the development of AD. In a study, scanning electron microscope and transmission electron microscope were used to examine specific iron-rich areas in the hippocampus of anatomical specimens of brain tissue from patients with AD. The authors found a significant increase in both Tau and amyloid proteins in brain tissue, which suggests that the effect of oxidative stress on AD is related to the oxidation of iron[59].

Endothelial cells in brain tissue can promote the formation of new blood vessels in the environment of embryonic development, and they rely on specific metabolic pathways to achieve different cellular functions. Pilin-1, a transmembrane protein of endothelial cells, regulates mitochondrial function and iron homeostasis, thus affecting the development of AD[60]. Use of iron chelating agents such as desfer-

rioxamine mesylate (desferrioxamine) was shown to reduce the iron content in brain tissue in animal models of AD. This effect was related to the ease with which desferrioxamine crosses the blood brain barrier[61].

Multi-functional nanoparticles w20xd4-spions may contribute to the diagnosis and treatment of AD. This is related to the ability of multi-functional nanoparticles w20xd4-spions to readily cross the blood-brain barrier and enhance microglia phagocytosis[62]. Iron oxide nanoparticles have been used in clinical studies to improve AD, owing to their ability to cross the blood-brain barrier[63]. Iron deposition is a pathway that regulates cell death, initiated by glutathione and lipid peroxidation signals [64].

Ferroptosis, a recently discovered form of cell death caused by accumulation of byproducts of lipid peroxidation, is also involved in the pathogenesis of AD. Excess iron was shown to exacerbate oxidative damage and cognitive deficit in a mouse model of AD. Use of specific iron deposition inhibitors was shown to alleviate the degree of neuronal death and memory damage in mice, especially in the hippocampus[65]. Brain iron metabolism disorder is one of the main characteristics of AD. Hemagglutinin neutralizes heme toxicity, maintains iron homeostasis, enhances antioxidant capacity by breaking down metabolites, biliverdin and carbon monoxide, and alleviates iron-mediated lipid peroxidation, which improves hippocampal volume, metabolism, and cognitive function in patients with AD[66].

AD and selenium

Selenium is one of the most common micronutrients in the body. It is involved in biological oxidation, cell differentiation, protein synthesis, and gene transcription. In particular, selenium inhibits ACHE and butylcholinesterase, which has a positive effect on the treatment of AD[67]. Selenium is a central component of many antioxidant enzymes (glutathione peroxidase) that regulate redox levels in the body and have a positive effect on the immune system[68].

Selenium deficiency is believed to be involved in the causation of AD. Selenium deficiency impairs immunity and leads to overproduction of oxidized products and amyloid-beta protein. Selenium can interact with metals by using selenomethionine and improve the body's antioxidant capacity'[69]. Chondroitin sulfate selenium has been shown to improve spatial learning and memory impairment in mice with AD, reduce the degree of synaptic edema of hippocampal neurons, and protect the integrity of mitochondria. The underlying mechanism involved activation of the P38 mitogen activated protein kinase signaling pathway by chondroitin sulfate selenium[70].

Glutathione peroxidase 1 is a major antioxidant enzyme that has a protective effect against memory impairment induced by-amyloid in mice with AD; this phenomenon is related to the activation of Erk signal pathway by glutathione peroxidase-1[71]. Memory impairment is the most well-known symptom of AD. The combination of nano-selenium (0.4 mg/kg) and stem cells increased the levels of brain-derived neurotrophic factor and reduced amyloid deposition in an Alzheimer mouse model; these results suggest that the combination of selenium and stem cells can reduce neurotoxicity in mice with AD[72].

Clinical studies have shown that AD is associated with cognitive decline. Higher blood selenium levels in older people were shown to be associated with higher cognitive scores; a general linear model was observed between blood selenium concentrations and cognitive function. It is suggested that selenium ameliorates the decrease of cognitive ability[73,74]. Selenium is essential for brain health. In a study of 984 men and 1032 women conducted between 2011 and 2014, selenium was found to be associated with cognitive function. The study involved assessment of whole blood selenium concentrations; there was no correlation between blood selenium concentration and sex. The results indicated that adequate selenium was positively associated with cognitive ability in the elderly[75].

Alzheimer's and silicon

Silicon is one of the most common micronutrients in the body It is divided into amorphous silicon and crystalline silicon, which exists in the form of silicate or silicon dioxide. Silicon is involved in collagen synthesis, immune system regulation, bone mineralization, and Tau phosphorylation[76]. Silicon was shown to lower the risk of AD[77].

Recent studies have shown the health benefits of silicon in humans. Soluble silicic acid is a useful form of silicon in the human body. The absorption, distribution, and metabolic characteristics of soluble silicic acid in human body are closely related to human health. The unique cross-linking ability of soluble silicic acid and its antagonism to toxic aluminum may protect against AD[78].

Studies have shown an increase in the incidence of degenerative diseases in Western countries. Diet has a positive effect on AD. Beer, which is rich in silicon and hops, plays an important role in preventing brain disorders. This is primarily related to the ability of beer to regulate inflammation, oxidation, and cholinesterase activity[79]. Nerve growth factor (NGF) plays an important role in reducing the number of cholinergic neurons in AD. Studies have demonstrated the neuroprotective effect of NGF on rat pheochromocytoma PCL2 cells by using biodegradable porous silicon oxide carriers[80].

AD and manganese

Manganese is one of the essential micronutrients in the body. It is involved in oxidation-reduction, lipid synthesis and, protein degradation, which are mostly related to the alkylation of manganese. Various aromatic, heterocyclic aromatic, and aliphatic secondary amines, such as indole and resveratrol-derived amines, can be obtained by alkylation reaction[81]. Most studies have found that AD can occur with decreased or normal levels of manganese[82].

With rapid industrialization and the increasing environmental pollution, excessive intake of heavy metal manganese will have a neurotoxic effect and promote neurodegeneration. Astrocyte is the main stable cell type in the central nervous system. Excessive intake of manganese can affect the structure and function of astrocytes, as well as the synthesis and degradation of glutamate. Effective control of manganese neurotoxicity may be a potential strategy for preventing or slowing AD[83]. Abnormal conformation of prion proteins in normal cells can lead to their transformation into pathogenic prion proteins, which can bind to manganese, copper, zinc, and other micronutrients, and thus induce AD[84].

Studies have shown the role of manganese in the diagnosis of AD. Manganese enhanced magnetic resonance imaging can be used to assess the level of pathological Tau accumulation[85]. Treatment with Manganese chelating agents may play a role in neurodegenerative diseases such as AD, providing a new strategy for the clinical treatment of AD[86].

AD is associated with a decline in learning and memory. Use of naringin reduces amyloid accumulation, a manganese-induced form of AD in rats. It is suggested that naringin has a neuroprotective effect, which is closely related to the anti-oxidant, anti-inflammatory and anti-amyloid degeneration effect of naringin[87]. Manganese-rich nanocapsules were shown to improve cognitive ability in animal models with AD, which is related to the decrease of Tau protein in animal brain tissue[88].

AD and arsenic

Arsenic is an essential micronutrient of the body. It is widely found in nature in the form of Ash, black, and yellow arsenic. Arsenic is highly toxic, but in small amounts it is beneficial. Arsenic participates in biotransformation, protein synthesis, and material metabolism.

Sodium arsenite (1–10 mol/L) was shown to increase Tau phosphorylation and promote the formation of neurofibrils in human neuroblastoma SH-SY5Y cells, which are used to study AD. This effect was related to the activation of Erk Pathway by sodium arsenite[89].

Animal studies have shown that arsenic in drinking water can cause abnormal circadian rhythm and movement behavior in mice with AD, as well as accumulation of amyloid proteins in the frontal cortex and hippocampus. This was found to be related to arsenic-induced lipid peroxidation in mice[90]. Sodium arsenite was shown to cause behavioral disorders and memory change in male rats with AD, which was alleviated by gallic acid (100 mg/kg); this indicated the neuroprotective effect of gallic acid [91].

In a clinical study, arsenic levels were measured in the nails and hair of 40 individuals with AD using inductively coupled plasma mass spectrometry. Arsenic levels in AD were higher than those in controls. This implies that individuals with AD often have elevated levels of arsenic[92].

Alzheimer's and vitamin D

Vitamin D is an antioxidant hormone. There is a close linkage between vitamin D, human microbiome, and the immune system. Vitamin D can regulate innate and adaptive immune responses[93].

Vitamin D enhances the immune function and may delay aging; thus, it may play a role in the treatment of AD[94].

The key findings of the aforementioned micronutrients related to AD are summarized in Table 1.

CONCLUSION

AD is the most common type of dementia with an elusive etiology. An increasing number of studies have explored the effects of micronutrients on the pathogenesis and development of AD[95]. Abnormal copper homeostasis plays an essential role in the development of many neurodegenerative diseases, including AD[14]. Zinc status affects the progression of AD, as evidenced by cognitive decline observed under conditions of zinc deficiency[52]. Excessive iron contributes to the deposition of β-amyloid and the formation of neurofibrillary tangles in AD, as well as other neurodegenerative diseases[96]. Selenium may have a protective role against the development of AD[97]. Silicon may lower the risk of AD by protecting against accumulation of toxic substances in the brain[98]. Manganese is critical for neurodevelopment but has also been implicated in the pathophysiology of several neurological diseases, including AD[99]. Chronic manganese exposure increases the risk of amyloid plaques and the development of AD[100]. Increased level of arsenic was shown to be associated with brain damage and neurobehavioral changes, which may exacerbate AD symptoms[90]. Vitamin D and its receptors are fundamentally involved in neurodegenerative mechanisms and vitamin D deficiency is recognized as a risk factor for AD[101]. Collectively, these findings suggest that aberrant homeostasis of these micronutrients is a key contributor to AD progression.

Table 1 Roles of different micronutrients in Alzheimer's disease

Micronutrient	Key findings related to AD
Copper	Plaques of neurofibrillary tangle, amyloid, and soluble oligomers have large amounts of copper at their core[18]
	AD patients have significantly higher levels of copper in brain tissues[19-21]
	Copper promotes neurofibrillary tangle of hyperphosphorylation Tau and oxidative stress[22]
	Copper is useful marker for the diagnostic and prevention of AD[27]
Zinc	Zinc and selenium or iron and zinc have been concomitantly used to treat AD[35,36]
	Combination of zinc and copper accelerates the formation of amorphous aggregates of amyloid protein[40]
	High saturation magnetization of zinc ferrite improves the formation of amorphous aggregates of amyloid protein[41]
	Zinc increases the expression of amyloid precursor protein in a mouse model of AD[43]
	Zinc deficiency leads to a decrease in the learning ability and memory of AD mice[51]
Iron	Markedly increased concentration of ferritin and hemosiderin aggregates in the brain tissues of patients with severe AD[55]
	Iron dysregulation in brain neurons plays a key role in AD[57]
	Iron deposition increases Tau levels in brain tissue and promotes neurofibrillary Tangle Tau formation[10,59]
	Iron accelerates the deposition of amyloid proteins in brain tissues[60]
	Iron oxide nanoparticles have been used in clinical studies to improve AD[68]
Selenium	Chondroitin sulfate selenium improves spatial learning and memory impairment in mice with AD[75]
	The combination of nano-selenium and stem cells increases the levels of brain-derived neurotrophic factor and reduces amyloid deposition in AD mice[77]
	Selenium ameliorates the decrease of cognitive ability[78,79]
Silicon	Silicon may lower the risk of AD[82]
	The unique cross-linking ability of soluble silicic acid and its antagonism to toxic aluminum may protect against AD[83]
Manganese	Excessive intake of manganese can affect the structure and function of astrocytes, as well as the synthesis and degradation of glutamate. Effective control of manganese neurotoxicity may be a potential strategy for preventing or slowing AD[88]
	Abnormal conformation of prion proteins in normal cells can lead to their transformation into pathogenic prion proteins, which can bind to manganese, copper, and zinc, and thus induce AD[89]
	Manganese-rich nanocapsules improve cognitive ability in animal models with AD[93]
Arsenic	Sodium arsenite increases Tau phosphorylation and promotes the formation of neurofibrils in human neuroblastoma cells[94]
	Presence of arsenic in drinking water induces accumulation of amyloid proteins in the frontal cortex and hippocampus of AD mice[95]
	Sodium arsenite causes behavioral disorders and memory change in male AD rats[96]
	The levels of arsenic in the nails and hair of AD patients were higher than that in healthy controls[97]
Vitamin D	Vitamin D regulates innate and adaptive immune responses, which may play a role in the development of AD[98]
	Vitamin D enhances the immune function and may delay aging; thus, it may be used in AD treatment[99]

AD: Alzheimer's disease.

Some limitations of this review warrant mention. First, this is a narrative review, which lacks predetermined research question or specific search strategy. Future studies with a systemic design and a specified protocol are required for a more in-depth characterization of the roles of these micronutrients in AD. Secondly, the animals studies included in this review only used rodent AD models. The results from other animal AD models should be taken into account in future analysis.

In conclusion, this review summarizes the recent findings on the relationships between AD and micronutrients, which may provide a new perspective and direction for future scientific research, development of new drugs, and preventive measures against AD. Although significant advances have been made in characterizing the relationships between AD and these micronutrients, further studies are required to provide more robust evidence.

FOOTNOTES

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