Diet and Nutrition in Dementia and Cognitive Decline

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Colin R. Martin and Victor R. Preedy

Chapter 54

Magnesium and Alzheimer's Disease: Implications for Diet and Nutrition

Mario Barbagallo, MD, Mario Belvedere, MD, Delia Sprini, MD and Ligia J. Dominguez, MD
University of Palermo, Palermo, Italy

LIST OF ABBREVIATIONS

AD Alzheimer's disease
Al aluminum
APP amyloid precursor protein
ATP adenosine triphosphate
Ca calcium
cAMP cyclic adenosine monophosphate
CDR Clinical Dementia Rating
DNA deoxyribonucleic acid
ERK extracellular signal-regulated kinases
GDS Global Deterioration Scale
K potassium
MAPK mitogen-activated protein kinase
MDA malondialdehyde
Mg magnesium
NADPH nicotinamide adenine dinucleotide phosphate
NMDA *N*-methyl-D-aspartate
PHF paired helical filaments
RNA ribonucleic acid

INTRODUCTION

Magnesium (Mg) ion, the second most abundant intracellular cation after potassium (K), is the fourth most abundant element in the brain. Mg plays crucial roles in the structure and function of the human body [1]; it is an essential cofactor in a wide variety of biological processes, including protein synthesis, nucleic acid synthesis and stability, neuromuscular excitability and conduction of neural impulses, stimulus-contraction coupling, and muscle contraction [1,2].

Mg is an indispensable part of the activated MgATP complex, and it is required for adenosine triphosphate (ATP) synthesis in the mitochondria [2,3]. Cell signaling requires MgATP for the phosphorylation of proteins and for the synthesis and activation of cell-signaling molecule cyclic adenosine monophosphate (cAMP), involved in multiple biochemical processes. Mg is a necessary cofactor in over 300 enzymatic reactions; it is required for the activity of all rate-limiting glycolytic enzymes, protein kinases, and more generally, all ATP and phosphate transfer-associated enzymes. Mg may also bind the enzymes directly (i.e., RNA and DNA polymerases) and alter their structure [1,2]. Therefore, availability of an adequate quantity of Mg may be considered a critical factor for normal cellular and body homeostasis and function (Table 54.1).

MAGNESIUM METABOLISM IN OLDER ADULTS

The adult human body contains approximately 24 g (1 mol) of Mg, of which about 65% resides in the mineral phase of bone, about 27% is found in muscle, and 6–7% is found in other cells. Extracellular Mg accounts for only 1% or so of total

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TABLE 54.1 Physiological Role of Mg in the Body

Enzyme Function	
Enzyme Substrate	*Direct Enzyme Activation*
• Kinases • ATPases/GTPases • Cyclases	• Phosphofructokinase • Creatine kinase • 5-Phosphoribosyl-pyrophosphate synthetase • Adenylate cyclase • Na-K-ATPase
Structural Function	
• Proteins • Polyribosomes • Nucleic acids	• Multiple enzyme complexes • Mitochondria
Calcium Antagonist	
• Muscle contraction/relaxation • Neurotransmitter release • Action potential conduction in nodal tissue	
Membrane Function	
• Cell adhesion • Transmembrane electrolyte flux	

TABLE 54.2 Characteristics of Ionic Mg

	Mg
Element category	Alkaline earth metal
Atomic number	12
Atomic weight	24.305 g/mol
Valence	2
Normal serum	0.75–0.95 mmol/L
	1.7–2.5 mg/dL
Total body content	24 g
Distribution in serum	– Free ionized 70–80% – Protein-bound 20–30% – Complexed 1%

body Mg [4]. The normal serum Mg concentration ranges from 0.75 to 0.95 mmol/L (1.7–2.5 mg/dL or 1.5–1.9 mEq/L) and is tightly controlled and maintained in this range. In the serum, about 70–80% of Mg exists in the biologically active ionized (free) form, while the remainder is bound to circulating proteins (i.e., albumin) (20–30%) or complexed to anions (i.e., bicarbonate, phosphate) (1%). Cytosolic Mg concentration ranges between 0.5 and 1.0 mmol/L in various cell types [1] (Table 54.2).

The main determinants of Mg equilibrium in the body are the absorption through the gastrointestinal tract, the requirement of different tissues, and the renal excretion. The small intestine is the main site for Mg absorption. Healthy individuals need to ingest 0.15–0.2 mmol/kg/day to stay in balance. The kidney exerts the most predominant impact in controlling body Mg status. Diuretics, frequently used in older populations, may also modify renal Mg handling, reducing Mg reabsorption [1–4] (Table 54.3).

TABLE 54.3 Mg Equilibrium

- Main determinants are gastrointestinal absorption and renal excretion
- Healthy individuals need to ingest 0.2–0.4 mmol/kg of body weight/day to stay in balance
- Extracellular Mg is in equilibrium with that in the bone, kidneys, intestine, and other soft tissues
- Bone is the main reservoir of Mg
- Primary renal disorders cause hypomagnesemia by decreased tubular reabsorption of Mg
- Osmotic diuresis results in magnesium loss
- Drugs may cause magnesium wasting

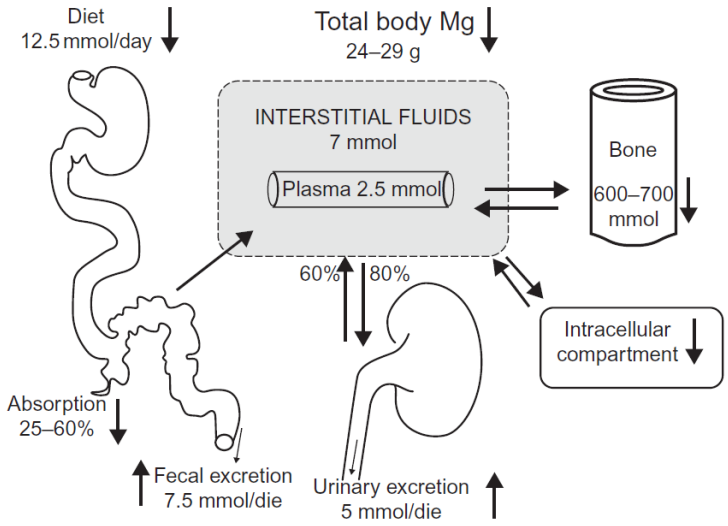

FIGURE 54.1 Mg homeostasis with age (arrows indicate possible sites of alteration with aging).

Several alterations of Mg metabolism have been associated with aging, including a reduction of Mg intake and intestinal absorption and an increase of Mg urinary and fecal excretion (Figure 54.1). The most common mechanisms that may cause Mg deficits with aging are summarized in Table 54.4 [3], which include primary Mg deficit (inadequate Mg nutrient intake, reduced efficiency of Mg absorption, and increased urinary excretion of Mg) and secondary Mg deficiency (associated with drug use or pathological conditions associated with aging).

MAGNESIUM AND COGNITIVE FUNCTION

Mg is necessary for brain function. Physiological concentrations of Mg are essential for synaptic conduction and are required for normal functioning of the nervous system. Mg exerts various actions on neuronal functions via different pathways. The concentration of Mg affects many biochemical mechanisms, which consist of *N*-methyl-D-aspartate (NMDA) receptor response to excitatory amino acids [5], inhibition of calcium channels, calcium influx, and glutamate release, and effects on the stability and viscosity of the cell membrane [1–3]. The toxic effects of calcium in excitable cells are influenced by intracellular levels of Mg [6]. Mg is a physiological calcium antagonist, and this action may contribute to its neuroprotective properties. In particular, since it is now clear that Mg ion modulates vascular tone by affecting calcium ion concentrations and its availability at critical sites, the level of Mg may play a crucial role in controlling cerebral vasomotor tone, i.e., a Mg deficit producing vasospasm while elevated Mg causes tone relaxation in cerebral arteries [7]. Thus, a low level of brain Mg may alter the transmission of impulses among the brain's neurons and may result in decreased brain efficiency and cognitive dysfunction. These mechanisms have important roles in chronic neuronal degeneration and subsequent development of dementia.

Metallic elements have been shown to play a role in the pathogenesis of AD [8]. Different metals may be involved in multiple aspects of the disease process, such as the regulation of the amyloid precursor protein (APP) gene expression,

TABLE 54.4 Main Mechanisms of Mg Deficit with Aging

Primary Mg Deficit
• Inadequate Mg dietary intake • Reduced efficiency of Mg absorption (associated with reduced vitamin D levels)? • Increased urinary excretion of Mg (associated with age-dependent reduction of kidney function and of Mg tubular reabsorption)
Secondary Mg Deficiency
• Associated with age-related diseases and comorbidities • Increased urinary Mg loss secondary to drugs (i.e., diuretics) frequently used in older persons

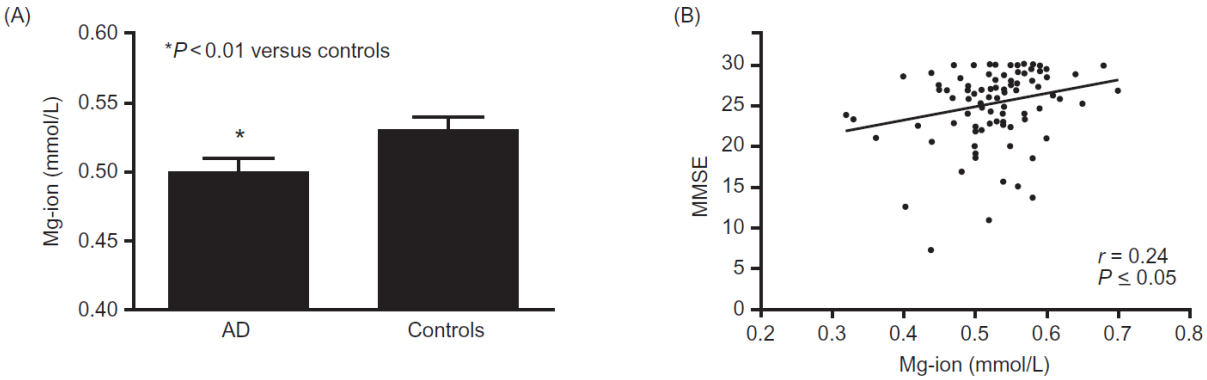

FIGURE 54.2 (A) Serum ionized magnesium levels (Mg-ion) in elderly subjects with Alzheimer's disease (AD), and in age-matched controls. (B) Relationship between serum ionized magnesium levels (Mg-ion) and cognitive function (MMSE).

and mRNA translation, the proteolytic processing of APP, the aggregation and degradation of amyloid-beta, and the formation of neurofibrillary tangles. The role of aluminum (Al) as a neurotoxic metal is well known, and numerous studies have revealed abnormal accumulation of Al within neurons derived from brain tissue containing neurofibrillary tangles obtained from autopsies of AD patients [9]. Heavy metals such as lead, mercury, and cadmium are also neurotoxic and associated with intellectual impairment. The possible relevance to AD is ascribed to the involvement in the formation of paired helical filaments (PHF), the aggregation and toxicity of amyloid-beta, and the generation of oxidative species [9].

The role of Mg in dementia and other degenerative disorders has been the focus of increased attention in recent years. A number of biochemical and physiological changes have been found to be associated with neural degeneration and cell death. There is evidence that a decrease in Mg may play an important role in acute neuronal death following central nervous system (CNS) trauma and ischemia and that Mg has protective properties in neural injury [10].

Several alterations of Mg metabolism have been found in AD patients. Previous studies have shown decreased serum Mg values in patients with severe AD [11]. We have described a reduction of the active ionized free Mg concentrations (Mg ion) in plasma obtained from AD patients [12]. Mg ion was significantly lower in the AD group versus age-matched older adults without AD (0.50 ± 0.01 mmol/L versus 0.53 ± 0.01 mmol/L; $P < 0.01$) (Figure 54.2A). For all subjects, Mg-ion levels were significantly and directly related to cognitive function (Mg-ion-MMSE, $r = 0.24$; $P < 0.05$, Figure 54.2B), suggesting that there is a correlation between Mg-ion levels in the serum of AD patients with the severity of the disease. Cilliler et al. [13] also suggested that there was a negative correlation between Mg levels in the serum of AD patients with the Global Deterioration Scale (GDS) and the Clinical Dementia Rating (CDR), further confirming a possible protective role of Mg, and/or a negative impact of Mg deficits on cognitive function. Mg has also been found to be lower in the brain tissue from autopsies of AD patients. Glick [14], re-examining data previously published by Perl and Broady [15] in the brain from autopsies of patients with AD, showed a significant decrease in the frequency of intracellular Mg deposits in neurones of AD as compared with control patients. Furthermore, a causal relationship between Mg levels in hippocampal neurons and impairment of learning was suggested. Landfield and Morgan [16] showed that elevating plasma Mg improves

hippocampal frequency potentiation and reversal learning in aged and young rats. Increasing brain Mg in rats also enhances short-term synaptic facilitation and long-term potentiation and improves learning and memory functions [17]. Mg deficiency in animals has been suggested to impair fear conditioning and emotional memory [18].

A role of Mg has been shown in the processing of the APP, the source of the neurotoxic amyloid-beta peptide involved in the pathogenesis of AD, possibly modulating the production of amyloidogenic or non-amyloidogenic products. Alpha secretases are a family of proteolytic enzymes that cleave APP in its transmembrane region. Specifically, alpha secretases cleave within the fragment that gives rise to the Alzheimer's disease-associated peptide amyloid-beta when APP is instead processed by beta secretase and gamma secretase. Thus, alpha-secretase cleavage precludes amyloid-beta formation and is considered to be part of the non-amyloidogenic pathway in APP processing. Yu et al. demonstrated that Mg modulates APP processing in a time- and dose-dependent manner. Extracellular Mg at high doses increases protective APP alpha-secretase release, while low Mg increases the secretion and accumulation of toxic amyloid-beta [19]. According to Yu et al., the mechanism by which varying Mg concentrations led to shifts between alpha- and beta-secretase cleavages of APP might be partially explained by the evidence that Mg at high doses promoted retention of APP on plasma membrane, whereas Mg at low doses reduced cell surface APP level. Moreover, the activity of Mg as an antagonist of the NMDA receptor may have a role in its protective effects on cognitive function; a chronic NMDA receptor activation has been shown to inhibit the alpha-secretase and APP cleavage, while promoting neuronal amyloid-beta production [20].

ALZHEIMER DISEASE, OXIDATIVE STRESS, AND MAGNESIUM

Aging and age-related degenerative diseases are characterized by a pro-oxidative, pro-inflammatory state that may contribute to their physiopathology, because of the deleterious damage of free radicals on cell constituents. The brain is an organ particularly likely to undergo oxidative damage. The cerebral metabolism requires high levels of energy, and it is closely dependent on aerobic conditions; it is also very rich in polyunsaturated fatty acids, easily oxidizable, and in transition metals, likely to facilitate the formation of radical OH. In addition, the brain is characterized by a low content of antioxidant systems compared to other tissues and organs in the body and is therefore particularly susceptible to oxidative damage. Thus, the alteration of oxidative metabolism present in old age might render the brain tissue more susceptible to damage caused by the accumulation of neurotoxic peptides such as amyloid-beta. Studies on postmortem brain tissue obtained from AD patients have shown alterations of several oxidative damage markers, including increases in lipid peroxidation, oxidative damage of proteins, and glyco-oxidation and a reduction of antioxidant enzyme systems. Thus, AD seems to be associated with an increased oxidative stress via several mechanisms: (a) an increased production of reactive oxygen metabolites; (b) a decline of the antioxidant systems and defense; and (c) a decreased efficiency in the repair of damaged molecules [21].

A large portion of the energy used for physiological functions in humans is produced by mitochondria. Mg in the mitochondria accounts for one-third of total cellular Mg, and it is present as a complex with ATP and as a component of membranes and nucleic acids. Mg is critical for basic mitochondrial functions, including ATP synthesis, electron transport chain complex subunits, and oxygen detoxification [3,22]. Mg deficiency is associated with increased oxidative stress and decreased antioxidant defense [3,22]. Mg deficiency has been associated with several metabolic diseases linked to oxidative stress and aging [23]. Several studies have shown convincingly that Mg deficiency results in increased production of oxygen-derived free radicals in various tissues, increased free-radical-elicited oxidative tissue damage, increased production of superoxide anion by inflammatory cells, decreased antioxidant enzyme expression and activity, decreased cellular and tissue antioxidant levels, and increased oxygen peroxide production [22–30]. Mg deficiency in rats causes decreased hepatic glutathione, superoxide dismutase, and vitamin E, together with increased lipid peroxidation and malondialdehyde (MDA) levels, secondary to upregulated nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity [31]. In stroke-prone spontaneously hypertensive rats, Mg deficiency results in marked increases in oxidative stress, superoxide accumulation, and mitogen-activated protein kinase (MAPK) activation [32]. Mg has antioxidant capacities and may prevent oxygen radical formation by scavenging free radicals and by inhibiting xanthine oxidase and NADPH oxidase [33]. Mg supplementation may reduce oxidative stress. In experimental diabetes, a decreased intracellular Mg level and increased Mg urinary excretion were associated with increased plasma MDA and decreased expression of hepatic superoxide dismutase and glutathione *S*-transferase, and all these effects were corrected by Mg supplementation [34].

NEUROPROTECTIVE ROLE OF MAGNESIUM

Thus, Mg deficits may cause an increase in oxidative stress, as well as an increase in amyloid-beta secretion and deposition and may determine a decrease in the neuronal activity. However, the mechanisms of the reported Mg deficits in AD patients need to be further elucidated. Mg levels are dependent on multiple factors, such as oral intake, hormonal changes,

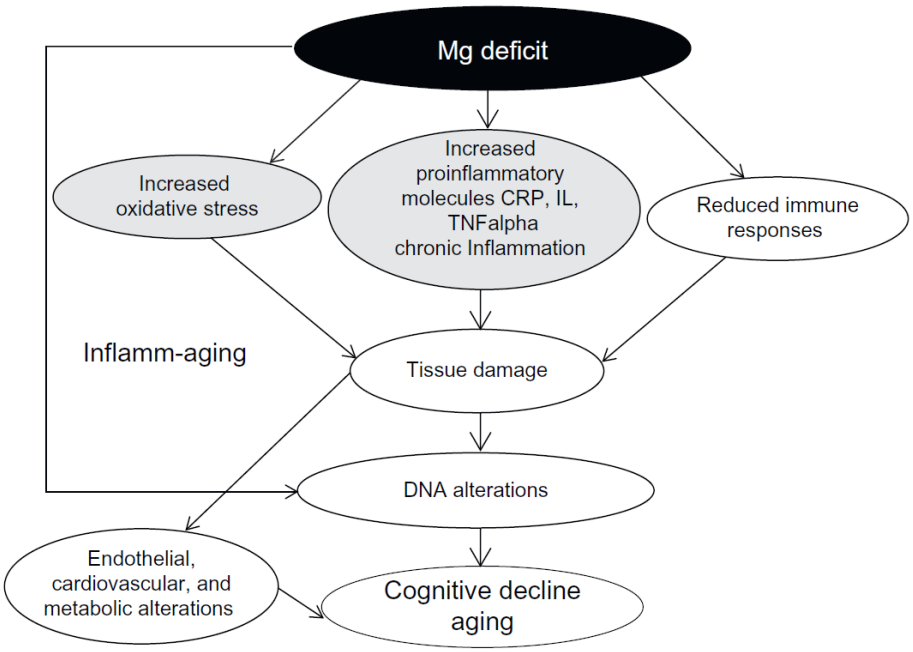

FIGURE 54.3 Overall hypothesis in which chronic Mg deficit has been proposed as one of the physiopathological links that may help to explain the interactions among inflammation, oxidative stress, and cognitive decline.

intracellular compartmentation, and protein binding. Dietary problems, which are common with aging and in particular in patients with AD, may be one of the factors facilitating Mg deficits. A protective role of Mg has been suggested for other neurodegenerative diseases, such as Parkinson's disease. Mg supplementation prevents the loss of dopaminergic neurons and ameliorates neurite pathology in a Parkinson's disease model, indicating a role for Mg in protection from degeneration of dopaminergic neurons in the substantia nigra [35]. Mg therapy has been suggested to prevent traumatic brain injury-induced hippocampal extracellular signal-regulated kinase (ERK) activation, neuronal loss, and cognitive dysfunction [36]. Therapeutic administration of Mg is still controversial regarding the treatment of AD. Mg supplementation has been shown to improve endothelial function in elderly diabetic patients [37] and may be of help in possible alterations of vasomotor tone in AD patients. Although there are no specific trials with Mg supplements in the prevention or therapy of cognitive disorders, interestingly, treatment of dementia patients with nutritional Mg support has been suggested to improve memory and other symptoms [38]. Given the prevalence of Mg inadequacy in the aging population, Mg supplementation may be of potential help in the prevention and treatment of AD. However, whether Mg supplementation may exert protective effects against AD remains to be further elucidated [39].

CONCLUSIONS

The consequences of Mg imbalance in elderly people related to defective membrane function, chronic inflammation, and increased oxidative stress may include an increased vulnerability to age-related diseases and age-related cognitive decline (Figures 54.3 and 54.4). The possible association of age-related Mg deficiency with AD is a working hypothesis that needs to be tested in future prospective studies. Mg participates in the biochemical mechanisms of neuronal properties and synaptic functions, which are involved in the pathophysiology of neurodegenerative diseases. Mg was demonstrated to modulate APP processing, and Mg levels were found to be decreased in various tissues of AD patients. Even if this needs to be proven by specific trials, it is likely that maintaining an optimal Mg status throughout life, and in particular in older persons, may help to prevent cognitive decline associated with aging.

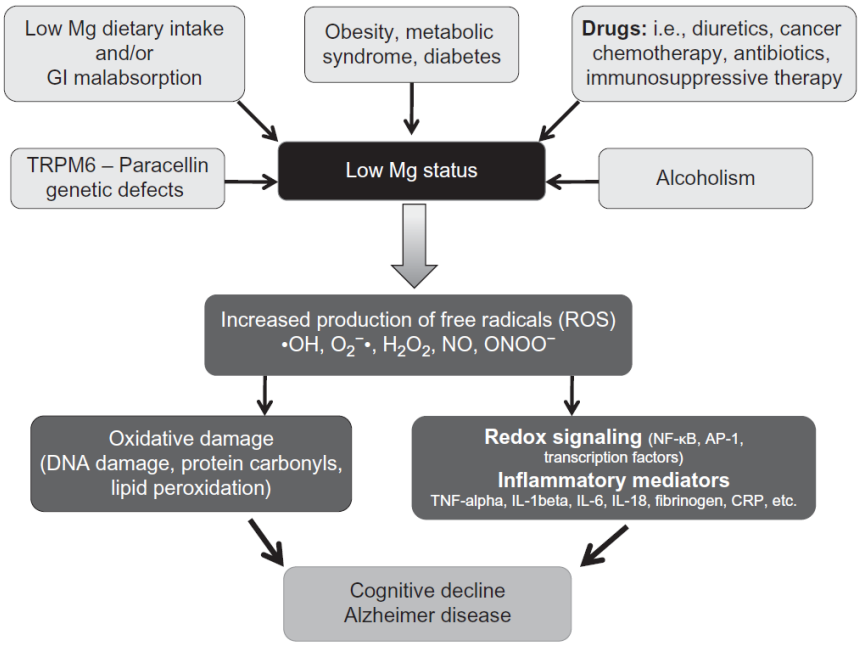

FIGURE 54.4 Low Mg status has different determinants that may converge in old age. Because Mg reduces the production of free radicals by the mitochondria as an antioxidant, its deficit may lead to the accumulation of oxidative damage. These events have been identified as "inflammaging," that is, the low-grade chronic inflammation frequently seen in old age, which is associated with cognitive decline and other age-related conditions.

SUMMARY POINTS

- Mg is a key intracellular cation because it is an essential cofactor in a wide variety of biological processes, including protein synthesis, nucleic acid synthesis and stability, neuromuscular excitability and conduction of neural impulses, stimulus-contraction coupling, muscle contraction, and acts as an antioxidant.
- Aging is frequently associated with Mg deficit due to dietary reduced intake and/or absorption, increased renal wasting and/or reduced tubular reabsorption, age-related diseases, and/or drugs, leading to increased oxidative stress and chronic inflammation.
- Mg affects many biochemical mechanisms vital for neuronal properties and synaptic plasticity, including the response of NMDA receptors to excitatory amino acids, stability, and viscosity of the cell membrane.
- Mg has a role in the processing of amyloid-beta precursor protein, which plays a central role in the pathogenesis of AD.
- Mg acts as a mild calcium antagonist and as an antioxidant against free-radical damage of the mitochondria. Chronic Mg deficiency results in excessive production of oxygen-derived free radicals and low-grade inflammation, also considered possible pathogenic factors in AD.
- Mg concentrations in plasma and in various tissues were found to be decreased in AD patients and negatively correlated with clinical deterioration.

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