

Importance and management of micronutrient deficiencies in patients with Alzheimer's disease

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Abstract: Alzheimer's disease (AD) is the most common form of dementia, and it generally affects the elderly. It has been suggested that diet is an intensively modifiable lifestyle factor that might reduce the risk of AD. Because epidemiological studies generally report the potential neuronal protective effects of various micronutrients, the aim of this study was to perform a literature review on the major nutrients that are related to AD, including selenium, vitamins C and E, transition metals, vitamin D, B-complex vitamins, and omega-3 fatty acids.

Keywords: Alzheimer's disease, nutritional deficiencies, diet, oxidative stress, lipid, vitamins

Introduction

Population aging is a worldwide phenomenon that results in changes in health profiles, including an increase in the predominance of chronic diseases. In addition, the prevalence of dementia is increasing; according to Ferri et al,¹ 4.6 million new cases arise every year, and if new prevention strategies are not implemented, the number of affected people will exceed 81 million by the year 2040.

Alzheimer's disease (AD) is the main cause of dementia in the elderly. The disease is clinically characterized by progressive and irreversible cognitive deficits and behavioral alterations that affect memory and learning ability, activities of daily living, and quality of life. The major risk factor for the development of AD is aging, although some genetic risk factors are also known. Approximately 1% of people aged 65–69 years, 3% of people aged 70–74 years, 6% of people aged 75–79 years, 12% of people aged 80–84 years, and 25% of people aged 85 and over will develop AD.² Cerebrovascular disease and a history of diabetes, hypertension, smoking, obesity, and elevated lipid levels have been found to increase the risk of AD. A healthy lifestyle is associated with lower rates of dementia; higher education, mentally stimulating activities, and involvement in mental, social, and productive activities play important roles as well.^{3,4} Because pharmacological treatments for AD are limited, there is a growing interest in understanding how diet could mitigate the risk and progression of AD. Associations between diet and cognitive decline are strongly suggested in numerous epidemiological studies and interventional trials, although it is difficult to establish whether diet is a primary factor. However, among modifiable risk factors, nutrition seems to be the most important factor because nutritional status might alter other risk factors.⁵

AD patients usually have insufficient levels of specific nutrients, and low intake of these nutrients is associated with an increased risk of developing AD. However, AD is associated with progressive changes in eating behaviors. The mesial temporal

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cortex, which is involved in memory and food intake control, is affected by dementia. Disturbances affecting this region involve serotonin, dopamine, and epinephrine neurotransmission, which in turn are involved in eating behavior regulation and could result in appetite loss and refusal to eat, decreasing food intake.^{6,7}

Epidemiological studies generally report the potential neuronal protective effects of various micronutrients, including B-complex vitamins, antioxidants, vitamin D, and polyunsaturated fatty acids. These nutrients are related to the stimulation of neural plasticity and to the reduction in ongoing neurodegenerative processes; they also show an ability to reduce the pathological burden in the brain.^{8,9} Therefore, the objective of this study was to perform a literature review on the major nutrients that are related to AD, focusing on the importance of their deficiencies in AD progression and on strategies for prevention and/or treatment of AD. This work addresses the main aspects concerning antioxidants, including selenium (Se) and vitamins C and E; transition metals such as zinc (Zn), iron (Fe) and copper (Cu); vitamin D; B-complex vitamins; and omega-3 fatty acids.

Antioxidants

Oxidative stress plays a central role in the initiation and progression of AD. The brain is particularly vulnerable to oxidative damage because of its elevated oxygen utilization rate; high content of polyunsaturated lipids that are susceptible to lipid peroxidation; accumulation of transition metals such as Fe, Cu, and Zn, which are capable of catalyzing the formation of reactive oxygen species (ROS); and relatively poor concentrations of antioxidants.^{10–12} Moreover, the aging process implies morphological and physiological changes in the brain, resulting in higher ROS production and a decrease in antioxidant capacity.^{12,13}

Amyloid beta-protein (A β) is the major amyloid protein in AD. This protein inhibits the electron transport chain in mitochondria, decreases the respiratory rate, induces the release of ROS and might also cause neurotoxicity through the direct production of ROS by its interaction with transition metals and lipid membranes.¹⁴

To combat the cytotoxic activities of ROS, cells are equipped with a variety of antioxidant defenses, including antioxidant enzymes such as catalase and glutathione peroxidase, as well as free-radical-scavenging chemicals such as ascorbate and vitamin E. Antioxidants can act by minimizing or even removing oxidants such as ROS and metal ions, or by interfering with the oxidation chain reactions and optimizing the cell's own antioxidant defenses.¹⁵

Selenium

Se is an important trace element for the body, and its essential nature is due to the necessity of selenocysteine incorporation in some selenoproteins. Among Se functions, its antioxidant role, played through selenoprotein P (SePP) and the enzymes glutathione peroxidase (GPx) and thioredoxin reductase, has been emphasized in previous studies.¹⁶

Studies that evaluate the relationship between Se levels and cognitive decline suggest that a lack of Se might increase the risk of dementia;^{17,18} however, the results of various studies are contradictory. Cardoso et al¹⁹ and Vural et al²⁰ verified that AD patients had lower Se levels than healthy elderly people, whereas Ceballos-Picot et al²¹ found an increase in plasma Se levels in AD patients compared to a control group. Moreover, Smorgon et al,²² when evaluating the association between trace elements and cognitive function decline in different groups, found a direct correlation between the plasma Se concentration and cognitive function. Compared to the control group, AD patients showed reduced Se plasma concentrations.

From an animal model, it has been observed that the Se supply to the brain depends on SePP. SePP is the major Se transporter and is responsible for up to 60% of the total serum Se concentration. The role of SePP as a transporter is related to its capacity to link to ten selenocysteine residues and to its extracellular location. Thus, Se enters the brain through an interaction between SePP and a receptor, after which time it is released intracellularly for the synthesis of selenoproteins.^{23,24}

It is believed that SePP synthesis occurs in the brain; SePP is then secreted into the cerebrospinal liquid, where it associates with neuronal cells or remains available for other tissues, acting as a selenium supply. Biosynthesis, cellular storage, and reuptake of SePP originates the “SePP cycle.” This process is consistent with the fact that SePP activity and expression are maintained in the brain even in situations of organic depletion once the Se status in the brain is not dependent on body Se levels. SePP also plays an antioxidant role, as it has the ability to reduce phospholipid hydroperoxides and to inhibit the oxidation of low-density lipoproteins.^{23,24}

Lu et al²⁵ and Miller et al²⁶ suggest that SePP levels tend to increase in aging and in AD patients. Bellinger et al²⁷ identified the presence of SePP aggregated to amyloid plaques and to neurofibrillary tangles, raising two hypotheses: SePP might act in a direct way as an antioxidant, or in an indirect way by transporting Se for the synthesis of other antioxidant selenoproteins. Accordingly, Takemoto et al²⁸ observed in vitro that neuronal cells that were exposed to the oxidant

effects of amyloid plaques were protected in the presence of SePP.

GPx constitutes a selenium-dependent five-enzyme family. These enzymes are expressed in neurons and glia cells, and their main function is the elimination of peroxides.^{23,29} GPx are involved in a sequence of reactions that aim to reduce hydrogen peroxides and organic hydroperoxides.^{30,31} These enzymes obtain electrons via glutathione, but differ from each other regarding their specificity to different substrates of hydroperoxides and their tissue distributions.³²

Some studies suggest that cognitive decline is associated with a decrease in GPx activity. Cardoso et al¹⁹ and Vural et al²⁰ observed lower activity of this enzyme family in AD patients compared to healthy individuals, while Parudariu et al³³ verified that dementia patients and patients with mild cognitive decline presented lower GPx1 activity.

Beef, chicken, fish, eggs, and wheat are considered good sources of Se. However, the amounts of Se in such foods reflect its concentration in the soil, so the same kind of food could present different Se concentrations depending on its origin.^{34,35} The Brazil nut ranks as the best Se source due to its high concentration; the levels of Se in Brazil nuts vary from 8 µg/g to 83 µg/g, and Se is highly bioavailable in this food.³⁵

Thomson et al³⁵ achieved an improvement in Se status in healthy individuals after supplementing them with two Brazil nuts daily for 12 weeks. Other studies have verified that the daily ingestion of one Brazil nut was effective in restoring Se status in dialysis patients, severely obese women, and the elderly.^{36–38}

Brazil nut consumption may also be effective in improving Se status in patients with AD, and this improvement could be an important therapeutic target regarding the maintenance of these patients' cognitive functions. Depending on the region where the nuts were grown, it is safe to recommend the intake of one to two nuts daily for the purpose of reaching adequate blood Se levels, unless the patient presents allergies.

Vitamins C and E

Vitamin E (tocopherols and tocotrienols) is the major membrane-bound fat-soluble antioxidant, and vitamin C (ascorbic acid) is an important water-soluble antioxidant that protects low-density lipoproteins from oxidation.³⁹ These vitamins act synergistically because oxidized α -tocopherol is reduced by ascorbate, leading to its regeneration.⁴⁰

In vitro studies suggest that antioxidants, including vitamins C and E, may prevent hyperphosphorylated tau protein dysfunction. Additionally, vitamin E has been related

to a reduced rate of neuronal death induced by A β protein in cultures of hippocampal and cortical cells.⁴¹

Studies have shown that vitamin E intake tends to be lower in AD patients,^{42,43} and the association between dietary vitamins C and E and dementia risk have yielded inconsistent results based on short-term and long-term follow-up periods. Morris et al⁴⁴ and Devore et al⁴⁵ associated a higher intake of vitamin E but not vitamin C with a lower long-term risk of dementia over a mean follow-up period of 2 years and 9.6 years, respectively. Luchsinger and Mayeux⁴⁶ found no relationship between the intake of vitamins C and E from food or supplements and the risk of developing AD during 4 years of follow-up time. In a cross-sectional study, Gu et al⁹ evaluated the association between nutrient intake and plasma A β levels in a cognitively healthy elderly population. Their data suggest that vitamins such as C, E, D, B12, and folic acid might have no association with A β -related mechanisms because the intake of these vitamins did not affect plasma A β levels. However, data from the Cache County Study have shown that the combined use of vitamin E and C supplements was associated with a reduced occurrence of AD. Interestingly, there was no reduction in AD risk with isolated vitamin E or C intake or with multivitamins, which may be justified by the dependence between these vitamins in scavenging ROS.⁴⁷ These observations were different from those reported in the Adult Changes in Thought study, which showed no effect of the supplemental use of vitamins E or C on reducing the risk of dementia or AD for over 5 years of follow-up time.⁴⁸

According to Brewer,⁴⁹ the controversial results found in various studies could be justified by incorrect dosage and timing, unbalanced monotherapy, or incorrect targets. The dosage should be evaluated to obtain a decreased plasma oxidative redox potential, and it is essential to associate water-soluble electron acceptors with vitamin E therapy to improve systemic ROS removal. Oxidative stress is one mechanism that is associated with AD pathogenesis, but other pathways should be targeted as well. Furthermore, AD can probably not be reversed by supplementation therapy, so AD prevention should be prioritized.

Moreover, an individual's early evaluation and the identification of prescribed medicines are fundamentally important to determine the presence of interactions that could interfere with nutrient bioavailability. The literature is not consistent in reporting the benefits of antioxidant supplementation (they do not establish a safe or effective dosage), and it is believed that this measure should not be recommended for the purpose of preventing or treating AD.⁵⁰ However, the intake of antioxidant-rich foods should be prioritized because they

contain important components and phytochemical substances that interact with each other, potentiating their beneficial effects.^{51,52} Furthermore, because the vitamin E found in supplements is usually synthetic and is composed of only one of eight natural isoforms (α -tocopherol), dietary sources of vitamin E should be used over supplements to provide different combinations of tocopherol and tocotrienol forms, which might play an important role in preventing AD.^{48,53}

Transition metals: zinc, iron, and copper

Zn is one of the most important minerals for human metabolism. The versatility of its physicochemical characteristics is the basis of its vast participation in the metabolism of carbohydrates, proteins, lipids, and nucleic acids. Zn also plays an important role in polynucleotide transcription and, consequently, in the control of gene expression and other fundamental biological mechanisms. Zn contributes to normal growth and development, membrane integrity, antioxidant defenses, immunity, appetite maintenance, scarring and night vision.⁵⁴ In a study involving the human genome database, it was estimated that approximately 10% of the human proteome codes for proteins that are potentially linked to Zn.⁵⁵ In the central nervous system, Fe is required as a cofactor for oxidative phosphorylation, neurotransmitter production, nitric oxide metabolism, and oxygen transport, and Cu is an essential cofactor for neurotransmitter synthesis and plays an important role in neuroprotection via the cytosolic Cu/Zn superoxide dismutase.⁵⁶

The brain controls the homeostasis of these metals as part of its physiology because those ions play important roles in neuronal activities. However, it is believed that alterations in metal metabolism at the cerebral level may be associated with AD. Those alterations probably participate in cascades of pathogenic events, which eventually cause clinical symptoms.⁵⁶ In cultured neurons, metals seem to mediate A β toxicity through the modulation of oxidative stress caused by that protein. A β has a strong affinity for Cu²⁺, Zn²⁺, and Fe³⁺, and is able to reduce Cu²⁺ to Cu⁺ and Fe³⁺ to Fe²⁺, producing free radicals that increase A β toxicity.⁵⁷

High levels of Cu can be found in the senile plaques of AD patients, and studies have shown that this metal mediates A β aggregation and increases this protein's oxidant capacity in an electron transfer reaction that reduces Cu²⁺ to Cu⁺.^{58,59} The A β precursor protein (APP) also has a high affinity for Cu²⁺, and higher Cu levels promote an increase in intracellular APP, which leads researchers to speculate that APP could act as a Cu transporter.⁶⁰ The involvement of Fe in the

formation of senile plaques resembles that of Cu. Finebrock et al⁵⁷ and Bolognin et al⁶¹ showed that in its free form, this mineral is capable of triggering A β aggregation, enhancing its neurotoxicity.

Researchers suggest that a change could occur in the transport and turnover of Cu in the presence of AD, which promotes an altered distribution of the metal among the various compartments and an accumulation in the central nervous system. Some studies have shown that the levels of free Cu (not bound to ceruloplasmin) are increased in the blood of AD patients and are negatively correlated with cognitive function, although the level of total Cu is not necessarily altered.^{62–64} Cu can be found in an organic form (bound to proteins) and in an inorganic form (as an unbound salt). These two forms differ regarding their sources, with the organic form found in foods, and the inorganic form found in water from Cu pipes and in most supplements. Regarding metabolism, the organic form is naturally and safely processed by the liver, and the inorganic form at least partially bypasses the liver and contributes immediately to the free Cu pool; it is also able to cross the blood–brain barrier easily.^{64,65} Thus, it is believed that the use of Cu piping could be a public health issue due to its relationship with a loss of cognitive function and worsening of AD.

Studies have shown that free extracellular Zn might increase A β adhesivity, interfering with its catabolism and inducing its deposition through structural destabilization and transformation.^{66–69} This action is related to the involvement of Zn in the synthesis and processing of APP. The synthesis of this protein is regulated by Zn-containing transcription factors.⁷⁰ Processing by the nonamyloidogenic pathway, which is catalyzed by one α -secretase and results in the formation of soluble APP, a neurotrophic factor,⁷¹ may be influenced by Zn because APP presents a binding site for this metal at the position where α -secretase catalyzes the processing of APP. It has recently been proposed that A β deposits promote Zn sequestration in vulnerable extraneuronal regions that are important for memory. This process depletes intraneuronal Zn concentrations and promotes microtubule destabilization via the reduction of electrostatic interactions or aberrant ligation between tubulin, as well as the formation of neurofibrillary tangles with consequent neuronal degeneration.⁷²

Despite the attention paid to Zn in AD, the role of food modification regarding this nutrient in the reduction of disease advancement is poorly understood. Although they did not find conclusive evidence that could guide dietary Zn modifications to reduce the risk of AD, Loeff et al⁷³ claim, in a systematic review, that reduced Zn concentrations in AD

patients might be related to disease risk. They suggest that a greater emphasis should be placed on an adequate supply of Zn to the elderly, either through increased consumption of Zn-containing food sources such as seafood, meat, nuts, and whole grains, or through supplementation in situations where food intake is insufficient, which is widely observed among AD patients. Before introducing Zn supplementation, a biochemical evaluation of Zn status is recommended. There is no consensus regarding the best biomarker for this analysis; however, plasma is a good option to verify a patient's Zn status. Once a deficiency is identified, Zn supplementation can be safely performed in the amounts recommended by the Institute of Medicine,⁷⁴ taking into account data from Lowe et al,⁷⁵ which show that every doubling of Zn intake leads to a 6% difference in the Zn serum or plasma concentration.

Vitamin D

Currently, vitamin D deficiency is widespread and prevalent in all population groups, with approximately 1 billion people classified as deficient (<20 ng/mL) or with insufficient concentrations of 25-hydroxyvitamin D (<30 ng/mL). It should be noted that a large proportion of the senile population suffers from this deficiency.^{76,77} In addition to rickets, vitamin D deficiency is a risk factor for bone disorders such as osteopenia, osteomalacia, and osteoporosis, which implies a greater risk of fractures in different age groups.^{78,79}

More recently, with the advancement of molecular methodologies, it has been observed that vitamin D might be metabolized in several other tissues, including the pancreas, prostate, breast, colon, kidneys, and macrophages, in addition to those previously known and implied in the control of bone homeostasis. Therefore, this vitamin deficiency could be related to other pathophysiological processes that are extremely relevant to public health.⁷⁶

Given the simultaneous prevalence of vitamin D and dementia in the elderly population, there has been a search for clarification about the possible role of this nutrient in the etiology of such diseases.⁸⁰ In addition to the aforementioned tissues, it has been reported that vitamin D presents a high binding affinity in several brain regions, including neurons, glial cells, macrophages, spinal cord, and the peripheral nervous system.⁸¹ The identification of vitamin D receptor expression and of 1- α -hydroxylase – the enzyme responsible for vitamin activation – in the human brain corroborates the importance of the vitamin as a neuroactive hormone with autocrine and paracrine functions, as well as the possibility of therapies for alterations that affect the brain.⁸²

Cross-sectional and longitudinal studies of the association between hypovitaminosis D and low dietary consumption of this nutrient have demonstrated important results regarding the cognitive performance of the elderly. With regard to vitamin D deficiency, Annweiler et al⁸³ verified that this deficiency, indicated by serum concentrations lower than 10 ng/mL, was associated with a worse cognitive decline profile in a cohort of French women aged 75 years or older when compared to women with a normal vitamin status (serum concentration higher than 10 ng/mL) and comparable age. The results remained the same after adjusting for several confounding variables. On the other hand, Slinin et al⁸⁴ found only a tendency toward an independent association between low serum concentrations of vitamin D (less than 20 ng/mL) and a risk of cognitive decline in a population of over 1600 North American men aged 65 years or older after a mean follow-up period of 4.6 years, but only when individuals were evaluated with a Modified Mini-Mental State Examination. Another cross-sectional study performed by Llewellyn et al⁸⁵ demonstrated that Italian individuals aged 65 years or older with vitamin D serum concentrations below 10 ng/mL and followed for 6 years presented a substantial relative risk of cognitive decline of 1.61 after adjusting for several variables (95% confidence interval [CI], 1.19–2.01; $P = 0.02$) compared to those with sufficient vitamin D serum concentrations (≥ 30 ng/mL) when the subjects were evaluated through the Mini Mental State Exam, and a relative risk of 1.32 (95% CI, 1.03–1.51; $P = 0.05$) when the subjects were evaluated through Trail-Making Test B. Breitling et al⁸⁶ verified that the cognitive performance (assessed through the Cognitive Telephone Screening Instrument) of a German elderly population that was followed for 5 years and adjusted for important confounding variables (age, educational level, body mass index, and season of the year) was significantly lower in women in the lowest quartile of vitamin D serum concentrations (odds ratio [OR]: 2.1, 95% CI, 0.4–3.9; $P = 0.018$); very similar results were found for the men in the population.

However, with regard to dietary vitamin D intake, a cross-sectional study with more than 5000 French elderly women verified that those women with inadequate weekly vitamin D dietary ingestion (<35 $\mu\text{g}/\text{week}$) presented a significantly decreased cognitive performance compared to those women with adequate dietary ingestion (≥ 35 $\mu\text{g}/\text{week}$) (OR = 1.30, 95% CI = 1.04–1.63, $P = 0.024$) after adjusting for several confounding factors.⁸⁷

Studies have speculated about two possible directions of the relationship between vitamin D concentration and

cognition. Despite the uncertainty about the causality of this association, it is suggested that cognitive function impairment promotes low vitamin dietary ingestion and/or impairs the individual's exposure to the sun, which would result in low vitamin serum concentrations. Nevertheless, given the results of these studies, it could be suggested that the association of hypovitaminosis D with diseases that promote alterations in cognitive performance, including AD, could be understood as a causal relationship in which vitamin D plays a neuroprotective role.⁷⁷

In a review of several studies, Kalueff and Tuohimaa⁸¹ indicate that vitamin D neuroprotective functions are related to factors such as a reduction in calcium toxicity, modulation of glutathione metabolism, direct antioxidant effects, reduction in nitric oxide synthesis, induction of neurotrophins and neuritogenesis, modulation of cytokine release, anti-ischemic actions, and neuronal protection against hormone-induced cell death. It has also been described that vitamin D stimulates clearance and A β phagocytosis by macrophages of AD patients and protects these immune cells against apoptosis by regulating both nongenomic (extranuclear protein functions) and genomic (gene expression) signaling.^{88,89} Attention has also been given to the actions of the klotho protein, which seems to regulate vitamin D concentrations in addition to interacting with this vitamin in the regulation of cerebral functions and the aging process.⁸¹

The results of studies aiming to evaluate the effects of vitamin D on cognition are controversial.^{90,91} There have been discussions about the methods used to evaluate cognition, the intervention time and, mainly, the dose and form of vitamin D used because the literature clearly shows that vitamin D3 (cholecalciferol) is more bioavailable than vitamin D2 (ergocalciferol).⁹¹ Vitamin D supplementation is advised to increase the levels of this vitamin and to maintain the 25-hydroxyvitamin D concentration between 30 ng/mL and 80 ng/mL.⁹² Studies show an increase in serum 25-hydroxyvitamin D concentration from 0.64 ng/mL to 0.79 ng/mL (1.6 to 1.97 nmol/L) per microgram of daily vitamin D3 intake. This information is important to guide the recommended supplementation, and from these data, it is suggested that vitamin D supplementation for the elderly with AD is preferably performed at doses between 800 IU and 4000 IU, which is the upper level set by the Institute of Medicine.⁹³ The consumption of supraphysiological doses does not promote a significant impact on overall cognitive performance.⁷⁷ There seems to be no benefit of exaggerated consumption of vitamin D supplements on cognitive performance, and the idea that hypercalcemia

induced by excessive vitamin D intake could increase the risk of dementia should also be taken into consideration.

B-complex vitamins

Among B-complex vitamins, niacin, thiamin, and vitamin B12 present well established relationships with the deterioration of mental status because all three vitamins are related to neurological syndromes.⁹⁴

Regarding vitamin B12 deficiency, 40% of patients develop neuropsychiatric syndromes, which are characterized by progressive and variable spinal cord, peripheral nerve, and brain damage. Initial sensory impairments occur, such as distal and symmetric paresthesia of the lower limbs, which are often associated with ataxia.⁹⁵ This deficiency is even more important in the elderly, who are more susceptible due to factors such as poor vitamin absorption from foods (chiefly due to gastric atrophy) and pernicious anemia, which is an autoimmune disease that is characterized by the destruction of the gastric mucosa. The elderly frequently suffer from this hypovitaminosis, and institutionalized and sick elderly patients can present a prevalence of 30%–40%, depending on the considered reference values and biomarkers.⁹⁶

Two important neurological alterations, Wernicke–Korsakoff syndrome and pellagra, are associated with thiamine and niacin deficiency, respectively. The first promotes damage to the central and peripheral nervous systems, with sight and muscular coordination problems, and subsequent memory loss, confabulations, and hallucinations. Pellagra is characterized by dementia, diarrhea, and dermatitis symptoms, in addition to alterations in the central nervous system, such as neurasthenia and psychosis symptoms including disorientation, memory loss, and confusion.⁹⁷

Although folic acid is not directly related to neurological disease, there is strong interest in this compound, as well as in vitamin B12, regarding dementia due to the fact that both nutrients are cofactors in homocysteine metabolism. Folic acid deficiency could reduce the concentration of acetylcholine (a deficient neurotransmitter in AD), or it could be related to a higher oxidative stress level.⁹⁴

Prospective observational studies have shown that homocysteine total plasma concentrations show a strong relationship to the risk of dementia and AD, and an increase of 5 μ mol/L in the homocysteine concentration increases the risk of AD by 40%, even after adjusting for variables such as age, gender, apolipoprotein E (ApoE) genotype and serum folate, vitamin B6, and vitamin B12 concentrations.⁹⁸

One study showed that in Italian individuals (4 years of follow-up), high homocysteine plasma concentrations

and reduced folic acid serum concentrations are independent predictors of dementia and AD. In individuals with hyperhomocysteinemia, the risk of developing dementia was 2.08 (95% CI 1.31–3.30, $P = 0.002$), and the risk of developing AD was 2.11 (95% CI 1.19–3.76, $P = 0.011$). Regarding serum folate levels, the risk of dementia and AD were 1.87 (95% CI 1.21–2.89, $P = 0.005$) and 1.98 (95% CI 1.15–3.40, $P = 0.014$), respectively, in individuals with reduced values.⁹⁹

Cognitive performance has been related to homocysteine total plasma concentrations. Elias et al¹⁰⁰ verified a significant inverse association between homocysteine levels and multiple cognitive abilities, such as abstract reasoning; new verbal learning and memory; verbal and visual memory; concentration, scanning, tracking, and executive performance; visual organization; and object naming and language, in individuals aged 60 or older but not in younger individuals.

High homocysteine concentrations are strongly associated with worse neurobehavioral performance in an analysis of more than 1000 patients aged between 50–70 years. On average, an increase in homocysteine levels from the 25th percentile to the 75th percentile was associated with neurobehavioral tests compatible with an increase in age of 4.2 years.¹⁰¹ On the other hand, there have been reports that high homocysteine levels are not associated with AD and cognitive decline.¹⁰²

Despite a number of relevant results, Morris et al⁹⁴ claim that the evidence related to associations of B-complex vitamins (mainly folate) with parameters of cognitive decline are weak, due chiefly to study limitations. However, the evidence related to homocysteine concentrations seem to be stronger, and there has been an effort to determine the mechanism of action of this substance in increased dementia and AD risks, as well as in a reduction in cognitive decline. It is speculated that cellular and vascular pathways are involved. Elevated total homocysteine levels are considered alteration markers in the one-carbon cycle, which is essential for adequate methylation in neurons. This effect occurs because homocysteine works as a fundamental intermediate of methionine metabolism via a methylation cycle that requires vitamin B12, folate, and vitamin B6, and generates an activated methyl group in S-adenosylmethionine. S-adenosylmethionine works as a methyl group donor in nucleic acid, phospholipid, protein, myelin, and catecholamine methylation reactions. Other possible mechanisms of action include the acceleration of aging through the shortening of telomere lengths; toxicity and neuronal dysfunction; calcium influx and ROS generation in hippocampal neurons; excitotoxic damage

by glutamatergic N-methyl-D-aspartate receptor activation through homocysteic acid; protein homocysteinylolation with consequent alterations in the function of Na⁺/K⁺/ATPase, and in the inhibition of its activity; and a direct interaction with A β , increasing its formation, and with Tau protein, promoting its hyperphosphorylation.¹⁰³

Considering its role in the reduction of homocysteine plasma levels, it is possible that folate, vitamin B12, and vitamin B6 supplementation could reduce the risk of dementia, allowing for healthy cerebral aging. However, some researchers are more cautious when addressing the possibility that folic acid supplementation might mask vitamin B12 deficiency or exacerbate neurodegenerative decline. Some studies on supplementation present conflicting results. Aisen et al¹⁰⁴ did not find positive results regarding a reduction in cognitive decline by supplementing individuals who presented mild to moderate AD with large amounts of B-complex vitamins (5 mg/day of folate, 25 mg/day of vitamin B6, and 1 mg/day of vitamin B12) for 18 months, and they verified a large number of adverse effects related to depression in the treated group. On the other hand, Smith et al¹⁰⁵ observed a significant reduction in the brain atrophy rate in elderly people with mild cognitive alterations who received supplementation with 0.8 mg/day of folic acid, 0.5 mg/day of vitamin B12, and 20 mg/day of vitamin B6 for 2 years.

According to Morris et al,⁹⁴ considering the scarce scientific literature on this topic, it would be safer to avoid folic acid supplementation in case there is no evidence of a clear deficiency, in addition to a continued monitoring of vitamin B12 deficiency. Seshadri¹⁰³ defends the need for thorough studies before confirming or refuting the idea that reductions in homocysteine concentrations (through lifestyle modifications or B-complex supplementation) might delay the beginning of cognitive performance decline or slow its progression. Seshadri¹⁰³ also claims that the existing evidence about homocysteine action as a risk factor for AD seems too appealing to be discarded.

Omega 3

Omega-3 long-chain polyunsaturated fatty acids, including α -linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA), are dietary fats that are incorporated into cell membranes and play a role in antiinflammatory processes and in the viscosity of cell membranes. ALA can only be obtained from the diet, while DHA and EPA can be synthesized in the body by the desaturation and elongation of ALA.¹⁰⁶ DHA is the most abundant lipid in the neuronal membrane, and EPA is involved in the modulation of mem-

brane fluidity, synaptic plasticity, and increase in the number and affinity of receptors. EPA is the substrate for the production of the antiinflammatory prostaglandin-3 and competes with arachidonic acid for incorporation into cell membrane phospholipids and for the active sites of cyclooxygenase enzymes.¹⁰⁷ On the other hand, although arachidonic acid plays an essential role in synaptic function, when present in high concentrations, it acts as a second messenger in some processes involving apoptosis and the production of inflammatory substances. Thus, an imbalance between omega-3 and omega-6 polyunsaturated fatty acids may result in an increased susceptibility to neuronal damage, as observed in AD.^{108–110} DHA and EPA are mainly found in foods such as fish oils and fatty fish, including salmon, tuna, and trout, whereas ALA is commonly found in vegetable oils such as soya, canola, and linseed oils, nuts, and in smaller quantities in seeds, vegetables, legumes, grains, and fruits.¹¹¹

In the majority of analyzed cohorts, the results show that fish consumption is associated with a lower risk of AD development, either due to the effects of DHA or of EPA, or because it is considered a healthy behavioral and eating pattern.¹¹²

As an observational study example, Barberger-Gateau et al¹¹³ evaluated a cohort ($n = 8085$) of patients aged 65 years or older with no dementia (The Three City Cohort Study). After a mean follow-up period of 3.48 years, they observed that weekly fish consumption presented an association with reduced AD risk (hazard ratio [HR] = 0.65, 95% CI = 0.43–0.994; $P = 0.047$), even after adjusting for ApoE genotype, body mass index (BMI), and diabetes. The frequent consumption of fish also presented an association with a reduced risk of dementia development, but only in ApoE $\epsilon 4$ noncarriers, and even when adjustments for BMI and diabetes were performed (HR = 0.60, 95% CI = 0.40–0.90; $P = 0.01$). The regular consumption of omega-3 fatty acid was marginally associated with a reduced risk of dementia occurrence after adjusting for ApoE genotype, BMI, and diabetes (HR = 0.46, 95% CI = 0.19–1.11; $P = 0.08$), and the regular consumption of omega-6-rich oils, unaccompanied by omega-3 and fish consumption, has shown an association with a considerably increased risk of dementia development in ApoE $\epsilon 4$ noncarriers (HR = 2.12, 95% CI = 1.30–3.46, $P = 0.003$).

In a cross-sectional study on the association between the ingestion of several nutrients and A β 40 and A β 42 plasma levels in a healthy elderly population (above age 65), Gu et al⁹ verified that the highest omega-3 intake level was associated with lower A β 40 and A β 42 concentrations, even after adjust-

ing for age, gender, ethnicity, educational level, caloric intake, ApoE genotype, and recruiting period.

Randomized, placebo-controlled clinical trials have been developed to verify the effects of supplementation with different concentrations of DHA and EPA on cognitive function in patients presenting mild cognitive deficiency or AD to different degrees. Overall, results have been subtle or absent.^{114–118} Among other factors, such unsatisfactory results might be attributed to the fact that almost none of these studies consider the ApoE genotype profile and, therefore, the genetic susceptibility for AD development.¹¹⁹

Reviews of studies of transgenic animal models have compiled a series of beneficial results in response to omega-3 consumption, mainly regarding synaptic alterations, A β accumulation, Tau protein alteration, and cognitive deficits. These models are important for the knowledge of the mechanisms of actions, including the following: positive regulation of neurotrophic factors, inhibition of the inflammatory cascade, reduction in oxidative damage (especially through an increase in glutathione reductase activity and reduction in oxidized protein accumulation, lipid peroxidation, and ROS levels), and actions on cellular membrane properties and cellular signaling pathways.^{112,120}

Given the importance of the aforementioned studies, Calon¹¹² highlights relevant key points that – in addition to the promising results shown – have been raised and must be carefully evaluated to avoid premature conclusions about the efficiency of omega-3 consumption. In the opinion of Calon¹¹² it is essential to verify whether advanced age or AD impairs the capacity of DHA to cross the blood–brain barrier and reach the brain tissues. The author also stresses the need to better define the therapeutic roles of DHA and EPA, specifying their relative contributions and their specific mechanisms of action. Finally, three aspects are emphasized: (1) the effects of omega-3 fatty acids are potentially related to a modification of disease potential, and for this reason, it is not expected that they present effects on late AD; (2) the consideration that AD is not a homogenous disease and might present itself in more than one form, meaning that each individual could respond differently to treatment; and (3) taking into account the high intragroup variability in the responses to a specific omega-3 fatty acid supplementation.

Strategies to prevent micronutrient deficiencies

Considering a pronounced population aging process and consequent increase in the prevalence of dementia, the search

for strategies to prevent or postpone the onset of diseases such as AD is necessary. Diet is an intensively modifiable lifestyle factor that is likely to work toward a reduction in the risk of developing AD. Faced with the results discussed in this review, it seems reasonable to affirm that individuals' nutritional status must be carefully considered upon the occurrence of disease and throughout one's entire life. Despite the necessity of additional studies, the adoption of healthy eating habits that allow the maintenance of blood levels of several micronutrients remains at the top of dietary recommendations.

On the other hand, it must be stressed that most studies have investigated nutrients in their isolated forms, and it is known that there is a great complexity in the human diet that is strongly influenced by synergy or antagonism among components.¹²¹ Therefore, some studies of whole foods and of dietary patterns have been performed. Dietary patterns that are predominantly composed of whole foods instead of refined foods, as well as the Mediterranean and Dietary Approaches to Stop Hypertension diets, have been associated with an improvement in cognitive performance and with a reduced risk of the development of mild cognitive impairment, of a progression from mild cognitive impairment to AD, and of the onset of AD itself.^{122–127} On the other hand, some studies report a failure of these dietary patterns to improve cognitive performance and reduce the risk of AD occurrence.^{128,129} Therefore, there is a consensus in the literature that at the present time, definitive dietary recommendations are not plausible. However, lifestyle changes, including greater consumption of fats derived from fish, vegetable oils, nonstarchy vegetables, and fruits with low glycemic indexes – in addition to reduced consumption of foods containing additional sugars and a moderate intake of alcoholic beverages – are recommended not only to reduce dementia risks, but also for a series of other diet-responsive conditions.¹³⁰

Furthermore, it is known that AD might relate to altered taste and the ability to chew and swallow, resulting in changes in dietary patterns, which often tend to acquire monotonous characteristics. As a consequence, ingested foods might not be sufficient to provide an individual's entire nutritional need, so supplementation becomes an important strategy to ensure an adequate nutritional supply. However, it is important to evaluate the patient's biochemical and clinical profile before starting supplementation. Moreover, it is suggested that the dosage used should comply with established recommendations to ensure patient safety.

Disclosure

The authors report no conflicts of interest in this work.

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