Nutritional aspects and their influences on the pathophysiology of Alzheimer's disease: A systematic review

Aspectos nutricionais e suas influências na fisiopatologia da doença de Alzheimer: *uma revisão sistemática*

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A B S T R A C T

The objective of this study was to conduct a review about the nutritional aspects and their influences on the pathophysiology of Alzheimer's disease. The review describes the pathophysiology of Alzheimer's disease, the generally indicated diets, and the nutritional factors that may aggravate the disease based on a literature review using the following keywords in English and Portuguese: "Alzheimer's disease", "physiopathology", "nutritional aspects", and "antioxidants". A total of 100 articles were found, 48 in *Lilacs* and 52 in *MedLine*, but only 54 articles were selected for the review. The use of antioxidants as free radical scavengers is generally indicated in diets for Alzheimer's patients. Studies also suggest that caffeine, vitamin B_{12}, and folic acid have neuroprotective effects. Cohort studies found that a high intake of saturated fatty acids and obesity increase the risk of Alzheimer's disease. People with Alzheimer's disease should avoid diets high in carbohydrates and saturated fats, and prefer foods high in antioxidants.

Keywords: Alzheimer disease; Antioxidants; Neurophysiology; Review literture as topic.

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R E S U M O

O objetivo do presente trabalho foi conduzir uma revisão sobre os aspectos nutricionais e suas influências na fisiopatologia da doença de Alzheimer. Descreveram-se a fisiopatologia da doença de Alzheimer, os alimentos em geral indicados e os fatores nutricionais que podem agravar a doença. Para tanto, foi realizada uma revisão da literatura usando as seguintes palavras-chave em inglês e em português: "doença de Alzheimer", "fisiopatologia", "aspectos nutricionais" e "antioxidantes". Um total de 100 artigos por meio da busca com as palavras-chave foram selecionados para o estudo nas bases de dados, estando 48 artigos disponíveis na base Lilacs e os outros 52, na base MedLine, no entanto, foram selecionados para a revisão 54 artigos. Com base na revisão, pode-se perceber que o emprego de substâncias antioxidantes como os sequestradores de radicais livres são alimentos, em geral, indicados para portadores da doença de Alzheimer. Estudos também sugerem efeito neuroprotetor da cafeína, vitamina B_{12} e o ácido fólico. Estudos de corte demonstram que uma alta ingestão calórica de ácidos graxos saturados e a obesidade aumentam o risco da doença de Alzheimer. Dessa forma, por meio deste estudo, foi possível perceber que os portadores da doença de Alzheimer devem evitar dietas ricas em carboidratos e ácidos graxos saturados e ingerir alimentos preferencialmente ricos em antioxidantes.

Palavras-chave: *Doença de Alzheimer; Antioxidantes; Neurofisiologia; Literatura de revisão como assunto.*

I N T R O D U C T I O N

Alzheimer's Disease (AD), characterized by the German neuropathologist Alois Alzheimer in 1907, is a progressive neurodegenerative and irreversible disease with insidious onset that entails memory loss and several cognitive disorders. Generally, late-onset AD occurs after age 65 years, and early-onset AD occurs before age 65 years and may be present in other family members. Clinically, early- and late-onset AD are the same and indistinguishable nosological unit[1].

In this context, the influence of nutritional aspects on the aging process and dementia has been studied because nutrition may protect against or delay age-related disorders and degenerative changes[2]. Elderly with dementia lose weight, and the possible explanations are many: medial temporal lobe atrophy and high energy expenditure, leading to muscle atrophy, loss of autonomy, functional dependency, risk of falling, pressure ulcers, and infections[3].

The data on nutrition for people with dementia in Brazil is scarce despite the importance of the subject for treating these individuals and improving their quality of life[4].

M E T H O D S

A literature review was conducted about the nutritional aspects and their influences on Alzheimer's disease pathophysiology. The review describes Alzheimer's disease pathophysiology, the generally indicated diet, the nutritional factors that can aggravate the disease, and the influence of high-carbohydrate diets, and discusses the nutritional aspects, their influence on AD pathophysiology, and the role of diets in delaying or preventing the main complications associated with this disease.

The review included complete articles, abstracts, case studies, and preclinical and clinical trials in Portuguese and English, published from 1992 to 2011, and listed in the databases *Lilacs* and *MedLine*. The following English and Portuguese keywords were used, respectively: "*Alzheimer's disease*", "*physiopathology*", "*nutritional aspects*", and "*antioxidants*"; "*doença de Alzheimer*", "*fisio-patologia*", "*aspectos nutricionais*", and "*antioxi-dantes*".

A total of 100 articles were found, 48 in *Lilacs* and 52 in *MedLine*, but only 54 articles met the inclusion criteria for the review.

The exclusion criteria were: articles published in Spanish, theses, dissertations, monographs, unavailable articles, and articles whose abstracts were not on the study subjects. Only the articles included in the review were fully read.

Alzheimer's disease pathophysiology

Over the course of evolution, different neurodegenerative mechanisms have prevailed in different brain regions, influenced by the patient's age and risk factors. The neural pathways of the cholinergic system and its connections are rather affected in AD. Brain changes characteristic of AD include senile plaques and neurofibrillary tangles. Senile plaques result from the abnormal Amyloid Precursor Protein (APP) metabolism, leading to the formation of amyloid beta peptide (Aβ) deposits; neurofibrillary tangles are formed when the neuronal cytoskeleton collapses due to tau protein hyperphosphorylation. At AD onset, these changes can already be seen in medial temporal lobe structures, including the hippocampus and the parahippocampal gyrus, considered essential structures for the memory process. As the disease progresses, the degenerative process spreads to the association neocortex, reaching brain areas responsible for other cognitive processes[5].

Aβ peptide neurotoxicity may stem from its contribution to oxidative damage by inducing lipid peroxidation, which generates a cascade of free radicals and cytosolic Reactive Oxygen Species (ROS) and leads to Adenosine Triphosphate (ATP) depletion and apoptosis[6-7]. Indeed, different brain areas present high lipid peroxidation, and the hippocampus and amygdala of affected patients present high activity of the antioxidant enzymes catalase, superoxide dismutase, glutathione peroxidase, and glutathione reductase[8-9]. Brain iron (Fe) is also high in Alzheimer's patients[10-11]. Given the pro-oxidant potential of this metal, higher brain iron levels may be related to higher oxidative damage. Iron oxidation-reduction (redox) reactions are essential for iron's cofactor functions in several enzymes, but these same

properties make free ferrous iron (Fe^{+2}) highly toxic because of its ability to generate free radicals. Free ferrous iron in the circulating blood binds strongly to Transferrin (Tf), hindering its power as a reducing agent and thereby preventing its interaction with H_2O_2, which would result in the formation of the harmful hydroxyl radical (Fenton's reaction), which could damage lipids, proteins, Deoxyribonucleic Acid (DNA), and carbohydrates[12].

Currently, oxidative stress has been pointed out as one of the main causes of neurodegenerative diseases, leading to a neuroinflammatory process. Free radicals are molecules that have an unpaired electron that can react with several cellular components, causing irreparable neuronal loss. Free radical action and production are highly influenced by diet. Thus, a high-antioxidant diet can promote longevity, decreasing the risk of several diseases[13].

Foods generally indicated in ad

Numerous studies have shown evidence that oxidative stress caused by oxygen free radicals can contribute to the pathogenesis of AD, which would justify the use of antioxidants[5]. Thus, the classic free radical scavenger alpha-tocopherol has been used with some success in AD treatment. Both alpha-tocopherol and ascorbic acid decrease the amount of free radicals present in the hippocampus and brain cortex, drawing considerable interest on these substances. Studies have shown that the long-term use of either or both antioxidants has slowed AD progression or reduced the number of new cases in individuals at risk of AD, such as smokers and individuals aged more than 65 years[14].

Studies about antioxidants pointed out a protective effect of mainly alpha-tocopherol, which is the main antioxidant vitamin transported in the bloodstream by the lipid portion of lipoprotein particles. Alpha-tocopherol, beta-carotene, and other natural antioxidants known as ubiquinones protect lipids from lipid peroxidation. Alpha-tocopherol intake in excess of the recommended levels can decrease the risk of cardiovascular diseases, improve immune

function, and modulate important age-related degenerative conditions[15-17]. Generally, foods such as whole grains, peanuts, nuts, hazelnuts, corn, soybean, and leaf vegetables, excellent sources of alpha-tocopherol, can be indicated to AD patients.

Ascorbic acid is easily absorbed by the small intestine by either a sodium-dependent active process or by passive diffusion[18]. It has been considered the most important and most potent dietary water-soluble antioxidant[19]. Ascorbic acid seems to protect against lipid peroxidation in two ways: first, directly, by eliminating peroxide radicals before they begin lipid peroxidation; and second, indirectly, by regenerating the active form of alpha-tocopherol and other antioxidants, such as β-carotene, flavonoids, and glutathione, enabling them to perform their antioxidant functions[20]. In the plasma ascorbic acid acts as a reducing agent, donating electrons to several reactive species and eliminating them before they can react with membranes and lipoproteins[21]. Thus, a diet with dietary sources of ascorbic acid, such as citrus fruits, red fruits, tomato, and broccoli would be beneficial, with no risk of overdosing[22].

Polyphenols are the most abundant dietary antioxidants. Daily consumption can reach 1 g, far exceeding all other phytochemicals classified as antioxidants[23]. The main classes of the nearly 4,000 known flavonoids are flavonols, catechins or flavones, anthocyanidins, and isoflavones[24]. Unlike ascorbic acid and alpha-tocopherol, which act in the aqueous medium and phospholipid layer, respectively, flavonoids occur in both phases[25]. Catechins, abundant in green tea and cocoa, are among the most potent antioxidant flavonoid polyphenols *in vitro*[26,27].

According to Ho *et al.*[28] moderate consumption of two unrelated red wines generated from different grape species, a Cabernet Sauvignon and a muscadine wine that are characterized by distinct component composition of polyphenolic compounds, significantly attenuated the development of AD brain pathology and memory deterioration in a transgenic AD rat model. This is due to neuronal preservation and brain circulation. Once again

polyphenols are the protective substances. Studies[29] have suggested that Alzheimer and Parkinson diseases can be related to deficiencies of vitamins, dietary elements (Cu, Fe, Li, Mg, Zn), and polyphenols[29].

Some recent epidemiologic studies reported that coffee/caffeine protect against the development of AD, regardless of other factors[30,31] but the mechanism involved is not totally clear. Nerve cell cultures suggest that adenosine A_2 receptor antagonism protects neurons against the neurotoxicity induced by β-amyloid protein[32,33]. Other studies found that 1.5 mg (equivalent to 500 mg in humans) of caffeine daily decreases the production of β-amyloid proteins in rats, protecting their cognition[34]. Besides caffeine, other antioxidants in coffee may have essential functions against this disease, decreasing oxidative stress in the cell by neutralizing free radicals[35-37].

Folic acid and vitamin B_{12} can also prevent changes in the Central Nervous System (CNS) of older people associated with mood disorders and dementias (including AD and vascular dementia)[38]. Vitamin B_{12} is not synthesized by animals or plants, only by some prokaryotes. Thus, humans cannot synthesize this vitamin and must obtain it from food[39].

Folic acid can be found in peanuts, hazelnuts, nuts, beans, liver, and leaf vegetables, such as spinach. On the other hand, the best dietary sources of vitamin B_{12} are animal-origin foods, such as liver and other meats, milk, and dairy products.

Nutritional factors that may worsen ad

Quality of life in old age is strongly associated with cognitive function, and cognitive function can be influenced by numerous factors. One of the most obvious but poorly recognized factor is nutrition. Like other organs, the brain is particularly sensitive to the action of nutrients. Furthermore, specific nutritional deficiencies as well as overeating have been associated with AD. Some authors have proposed that diet could be the main culprit. In 1997, William

Grant found correlations between AD prevalence and the amounts and kinds of foods consumed in different countries, finding positive associations between AD incidence and total calorie and total fat intakes[40,41]. Kalmijn *et al.*[42] found a correlation between fat intake and dementia in 5,386 participants from Rotterdam. These studies found a strong environmental component to AD and suggested that dietary changes can prevent it.

Cohort studies found that high intake of saturated fatty acids and obesity increase the risk of AD[42]. For example, the daily intake of the omega-6 fatty acid, linoleic acid, has increased dramatically due to the use of corn as cattle feed and vegetal fats in food products. Now linoleic acid intake exceeds alpha-linolenic acid (an omega-3 fatty acid) intake by a factor of 4-10, according to the composition of breast milk[43]. High fat intake, particularly omega-6 and saturated fatty acids, is associated with poor cognitive performance and a risk factor for AD[44-46].

In the early 1960s, Ancil Keys[47] strongly promoted the avoidance of dietary fats and cholesterol, and the use of cholesterol-lowering drugs over the decades saw an increase in AD prevalence[48]. Animals fed high-cholesterol diets show high Aâ production, while cholesterol-lowering drugs decrease Aβ levels[49-51]. However, cholesterol depletion also activates Aβ production, indicating that proper membrane function requires some cholesterol[52]. Thus, the development of late-onset AD is complex and supports the involvement of several pathways. These pathways can interact, triggering and/or accelerating the cascade of events[42].

High-carbohydrate diet

Studies have suggested that AD does not result from high-fat diets but from high-carbohydrate diets. This hypothesis is reinforced by the genetic association between AD and the Apolipoprotein Epsilon4 (ApoE4) allele, which plays a role in lipid processing and insulin/Insulin-like Growth Factor (IGF) signaling in aging[53]. Indeed, genetic apolipoprotein E polymorphisms that decrease cholesterol transport

across the blood-brain barrier are strongly associated with AD onset[42].

In Alzheimer disease etiology, high-carbohydrate diets are proposed as one of the main causes of AD by two basic mechanisms. The first one is the disturbance of lipid homeostasis in the CNS, mainly low supply of essential fatty acids. This compromises cell membrane integrity, reducing membrane protein function. The second is a mild, chronic elevation of insulin/IGF signaling, accelerating cell injury. These two mechanisms contribute to the two stages of the disease. Stage I begins when the altered lipid metabolism inhibits the function of membrane proteins, such as glucose transporters, leading to low glucose uptake and consequently, low metabolism in susceptible brain areas. At this stage, there are no evident clinical signs of dementia even though the disease has started. Stage II begins when excessive cell damage or loss of homeostatic mechanisms prevents the compensation of inhibited cell functions. At stage II, the levels of acetyl coenzyme A (acetyl-CoA) become critically low, affecting the production of several cell components, such as cholesterol and acetylcholine, and the clinical signs of dementia become evident. Cholesterol metabolism disorders cause large-scale and altered processing of APP (amyloid beta precursor protein), decreasing cellular traffic and promoting â-amyloid peptide (Aβ) generation. As the disease progresses, the lack of transport and neurotrophin receptors produce increasing amounts of Aβ that, ultimately, result in high cell death and the characteristic AD pathology[54]. Thus, it is best to reduce the intake of high-glycemic carbohydrates and increase the intake of fibers, proteins, and fats. Such diets seem to reduce the risk of AD[55].

C O N C L U S I O N

Alzheimer's disease is currently considered the "disease of the twenty-first century". Effective therapies for this disease are still unavailable, despite abundant research. This systematic review shows the importance of diet for AD patients. They clearly have

to avoid high-carbohydrate diets because these diets disturb lipid homeostasis in the CNS and increase insulin/IGF signaling. Furthermore, lower intake of saturated fats has been shown to prevent or delay disease onset significantly. According to recent studies, oxidative stress is also involved in the pathogenesis of Alzheimer's disease. Hence, antioxidants play an important role in human health. A high-antioxidant diet may protect against AD progression. However, AD remains a mystery and future studies are needed to address all the unanswered questions.

C O N T R I B U T O R S

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