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Nutrients and Alzheimer's Disease

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ABSTRACT

Alzheimer's disease is a type of dementia that causes neurodegeneration and memory loss that disrupts daily life. It is characterized by amyloid beta plaques and tau neurofibrillary tangles. Although there are medications to treat symptoms, Alzheimer's has no cure. However, several modifications like environment and lifestyle changes may reduce the progression of AD by reducing levels of oxidative stress. Oxidative stress is a factor that is heavily involved in the Alzheimer's pathway and results from an imbalance of reactive oxygen species. Therefore, this paper aims to highlight several beneficial diet changes that may improve the symptoms or slow the progression of AD.

Introduction

As of 2023, there are around 55 million worldwide cases of dementia, between 60 and 70% of which are Alzheimer's disease [1]. Alzheimer's disease is a type of dementia in which memory loss gradually impacts an individual's ability to carry out daily life [2]. The disease is characterized by specific proteins in the brain such as amyloid beta plaques and tau neurofibrillary tangles [3]. Amyloid plaques can interfere with cell signaling between synapses, and tau tangles disrupt signal and nutrient transfer along microtubules [4,5]. In Alzheimer's, dysfunction and disruption by aberrant proteins may cause neuronal death [6]. Over time, neuronal death spreads throughout the brain, leading to neurodegeneration [3].

Alzheimer's disease has no definite cure, although there are various medications to treat symptoms [4]. The FDA approved the drug, Lecanemab, which treats early Alzheimer's and is an antibody that targets amyloid beta plaques to help alleviate cognitive impairment [7]. However, the medication requires regular Magnetic resonance imaging (MRI) scans due to possible side effects of brain swelling and bleeding [4]. Another approved drug for moderate to severe Alzheimer's is memantine, an antagonistic drug that prevents disruption of synaptic transmission [8], although patients have not displayed effective responses [4]. Since medications have limited benefit, research is investigating alternative treatments such as lifestyle changes. For instance, diet modifications can reduce risk factors and alleviate disease progression, and certain diets may be beneficial for neurodegenerative diseases [5]. For example, the Mediterranean diet may improve cognitive function in those with Alzheimer's disease [6,9]. However, the processes by which these diets exert their beneficial effects are unknown. Therefore, in this review paper, we will highlight the mechanisms underlying diet that improve the symptoms or delay the progression of Alzheimer's disease.

Vitamins

Vitamin B6, B12, and B9 may improve Alzheimer's disease by lowering levels of homocysteine, a modifiable risk factor in vascular and neurodegenerative diseases [10,11]. High levels of homocysteine in blood, hyperhomocysteinemia, can result from vitamin B deficiencies. Homocysteine is a sulfur-containing amino acid formed as an intermediate in methionine metabolism [12]. Vitamin B9 known as folate, or its synthetic version folic acid, donates a methyl group to homocysteine to form methionine and S-adenosylmethionine (SAM), which is then converted to other intermediates, continuing the homocysteine-methionine cycle [13] [14]. Physiological levels of homocysteine are important because it is

an intermediate in methionine generation, an essential amino acid involved in regulating metabolic, immune, and digestive processes [15]. Methionine is also a precursor to glutathione, an antioxidant that protects neurons from oxidative stress [16]. A decrease in vitamin B decreases methyl group donors, and nutrient deficiency interrupts the homocysteine-methionine cycle and leads to homocysteine accumulation [17].

In general, high homocysteine levels are linked to brain atrophy and cognitive decline [18] [19,20]. Hyperhomocysteinemia may lead to the formation of amyloid plaques by hydrolysis of the amyloid precursor protein (APP), producing amyloid beta polypeptides, a crucial step in Alzheimer's development as those proteins can misfold and result in AD [21,22]. Several studies followed older individuals over time to measure their plasma homocysteine levels. These studies revealed that a 5 micromoles per liter increase of plasma homocysteine above physiological levels increased Alzheimer's risk by 12-40% [2321]. When taken together, these studies demonstrate that high homocysteine levels may be a risk factor for Alzheimer's disease. In addition, a meta-analysis study investigating the association between homocysteine, folate levels, and dementia concluded that compared to controls, dementia patients have higher homocysteine and lower folic acid levels [21], suggesting that homocysteine may contribute to dementia progression. A study of individuals with mild cognitive impairment investigated the effects of vitamin B6, B9, and B12 on cognitive impairment and found that patients with vitamin B supplementation had approximately 30% lower plasma homocysteine levels as compared to controls [19] showing that vitamin B supplementation may lower homocysteine. In addition, supplemented individuals had better outcomes on tests for global cognition, semantic, and episodic memory compared to controls. This shows a possible link between lower homocysteine levels, Vitamin B supplementation, and improvements in cognition. Vitamin B supplementation to reduce homocysteine levels may be a possible dietary change to alleviate Alzheimer's symptoms [19,20,24,25].

E vitamins are a group of eight compounds that are fat-soluble antioxidants found in cell membranes [26] and have been shown to have neuroprotective, hypocholesterolemic, and anti-inflammatory properties [2627,2829]. Vitamin E can improve cognitive impairment by decreasing oxidative stress [29]. Oxidative stress is an imbalance between reactive oxygen species (ROS), or free radicals, and the body's ability to remove them through antioxidants [30]. Different ROS such as hydrogen peroxide can be formed from various biological pathways, but ROS are mainly produced by the mitochondria electron transport chain, where some O_2 is reduced to superoxide anions O_2^- [31] [32]. ROS can damage cellular structures and DNA [3334,35]. Oxidative stress can lead to a major cause of neurodegeneration, lipid peroxidation, where ROS attacks lipids and causes phospholipid degeneration [36] [37]. Lipid peroxidation creates a lipid radical and an unstable lipid hydroperoxide that generates additional free radicals [3826]. The brain is lipid-rich, making it particularly vulnerable to oxidative stress [39]. Neurons are heavily affected because they are post-mitotic cells. In addition, the brain is mitochondria-rich, and its high metabolic rate, if unregulated, can potentially lead to ROS generation and increased oxidative stress [40]. In Alzheimer's, amyloid beta can induce oxidative stress by binding to redox-active metals such as copper and iron that can generate ROS and create plaques. Copper and iron are important cofactors for neurotransmitter synthesis, myelin production, and synaptic signaling [41]. These metal-amyloid complexes generate more ROS [41]. In turn, this increased oxidative stress can increase amyloid beta production.

Antioxidants can combat oxidative stress by donating an electron pair to neutralize a reactive oxygen species [42]. Vitamin E is a lipophilic antioxidant that scavenges free radicals to stop chain initiation, a process that generates more free radicals[27]. In a study investigating the relationship between oxidative stress and amyloid beta-induced apoptosis, researchers exposed cell cultures to amyloid beta fragments and reactive oxygen species such as hydrogen peroxide H_2O_2 [43]. They then added antioxidants such as alpha tocopherol, a form of vitamin E, to some cells [43]. The study found that oxidative stress induced by amyloid beta peptides increased H_2O_2 by 400%, ultimately showing that amyloid beta increases oxidative stress by activating stress-activating protein kinases [43]. They also found that the effect of oxidative stress, such as lipid peroxidation, was prevented by alpha tocopherol [43]. In addition, researchers studied whether different forms of vitamin E would protect against cognitive decline from Alzheimer's in individuals older than 65 years of age [44]. They found that combined intake of tocopherol forms was associated with a 26% reduction in risk per 5 mg/d increase in vitamin E intake [26,44]. This was consistent across factors such as sex, race, and age [44]. This suggests that supplementing a diet with vitamin E may prevent or slow cognitive decline and ultimately reduce the

risk for Alzheimer's. An analysis of nutrition in 521 Alzheimer's patients found that their blood plasma contained significantly lower vitamin E levels when compared to cognitively healthy people[45]. This could be due to Alzheimer's brains having increased oxidative stress, and as a result greater amounts of ROS. Vitamin E levels are lower in blood because antioxidants are being used up in combating excess free radicals [46]. A study investigated the effect of alpha-tocopherol, memantine, and both combined as treatments for mild to moderate Alzheimer's [47]. They found that the patients supplemented with 2000 IU/d of alpha tocopherol showed decreased functional and cognitive decline, with a delay in disease progression of 19% per year. However, both the memantine and memantine combined with alpha-tocopherol showed less effective results [47]. One possible reason for the decreased effectiveness may be that memantine is used to treat moderate to severe cases. These studies altogether suggest that vitamin E could be beneficial to Alzheimer's by slowing cognitive decline.

Vitamin D is a group of fat soluble vitamins that is known for regulating calcium homeostasis and bone structure, but is also associated with improving cardiovascular disease, cognitive impairment, and dementia [48]. It has two major forms, Vitamin D2 commonly found in food, and D3 which is mainly synthesized by skin exposure to sunlight [49]. In the body, it is considered inert until it undergoes a series of hydroxylation reactions, where hydroxyl (OH) groups are added to convert it into active form 25-Hydroxyvitamin D or $1,25(OH)_2D$ [49,50]. Vitamin D has regulatory effects on the brain through its Vitamin D receptors (VDR) [51]. VDR is in the hippocampus and prefrontal cortex, areas responsible for learning and memory. Additionally, VDR is most abundantly expressed in the substantia nigra, an area of the midbrain responsible for movement and reward functions. Researchers have found low vitamin D levels in patients with Parkinson's disease, a neurodegenerative disease that affects the substantia nigra. Vitamin D deficiency may be involved in multiple neurodegenerative diseases [52,5354].

A prospective study followed older individuals without dementia to determine whether vitamin D deficiency was associated with an all-cause dementia and Alzheimer's risk increase[55] . They found that people with a mild-moderate vitamin D deficiency had a 51% increased risk of dementia while severely vitamin D deficient individuals had a 122% increased risk [55]. The observed risk was similar between Alzheimer's and all-cause dementia[55]. Low levels of vitamin D are associated with Alzheimer's because vitamin D can regulate neurons through axon growth and enhances myelination[55,56]. Myelinated sheaths in the central nervous system decrease with age and is associated with Alzheimer's pathology [57]. Vitamin D may improve myelination by activating genes associated with myelin [58]. As a result, low vitamin D levels may contribute to Alzheimer's pathway. Several other studies have reported an association between low vitamin D3 levels and Alzheimer's and dementia [59,6061]. Another study investigated the effects of vitamin D on Alzheimer's pathology by feeding transgenic app/ps1 mice vitamin D-deficient diets for 13 weeks, and measuring their learning and memory [62]. They found that vitamin D deficiency increased ROS in vitamin D-deficient mice as opposed to controls. In turn, increased oxidative stress may suppress the activity of glutathione peroxidase 4 (GPx4), and the cystine/glutamate antiporter (xCT). GPx4 is an enzyme that protects cells from lipid peroxidation, and xCT regulates the exchange of extracellular cystine and intracellular glutamate [63,64]. Glutamate is a neurotransmitter in the central nervous system, although excessive glutamate transfer activity is associated with neurodegeneration in Alzheimer's [65 66]. A prospective study on individuals without dementia explored the relationship between vitamin D supplementation and dementia [67]. Researchers exposed some participants to vitamin D supplementation of three formulations: calcium–vitamin D, cholecalciferol, and ergocalciferol [67]. They found that people with vitamin D supplementation were associated with 40% less dementia incidence compared to non-supplemented people [67]. Vitamin D supplementation may be a potential treatment for slowing Alzheimer's symptoms and disease.

Antioxidants

Carotenoids are antioxidants and have neuroprotective properties such as being anti-inflammatory, and may prevent cognitive decline. Carotenoids are pigments contributing to plant photosynthesis; however, animals can't synthesize carotenoids and must gain them from food.[68]. In animals, carotenoids are important for being a precursor to vitamin A, which is important for vision and the immune system [68,69]. They also function in general as photo protectors and

antioxidants. While more than 600 carotenoids have been identified, research mainly focuses on beta carotene, alpha-carotene, beta-cryptoxanthin, lutein, and zeaxanthin. Beta carotene can be converted to vitamin A, and lutein is a macular eye pigment group of carotenoids found in the eye that protect the retina [7071,72 71].

A study investigated whether Alzheimer's brains had lower levels of carotenoids than healthy elderly brains [73]. Researchers analyzed and compared amounts of different carotenoids in the brains, and found that healthy brains had 1.5 times more lutein and 2 times more zeaxanthin than Alzheimer's brains [73]. Decreased carotenoid levels would be reduced amounts of antioxidants, and increased oxidative stress and lipid peroxidation. People with higher amounts of lutein and zeaxanthin in their diets had up to 50% decreased risk of Alzheimer's [73]. Carotenoid supplementation may reduce Alzheimer's disease risk and clinical progression. A study tested the effects of supplementing older people with lutein/zeaxanthin to see if carotenoid supplementation affected cognitive function [74]. Lutein and zeaxanthin are isomers, meaning they have identical chemical formulas but differing structures and different functions. Lutein is more commonly found in fruits and vegetables compared to zeaxanthin [75]. The study found that supplementing 10 mg of lutein and 2 mg of zeaxanthin for a year led to a statistically significant increase in cognitive attention and flexibility when compared to controls [74]. A similar study evaluated the association between carotenoids and Alzheimer's risk. They found that increased intake of total carotenoids was associated with a 48% decrease in Alzheimer's. This suggests that carotenoids may be beneficial for decreasing Alzheimer's risk.

More than 8000 polyphenolic compounds have been discovered, but they are divided into two main classes, flavonoids and phenolic acids [76]. Polyphenols protect plants from ultraviolet damage, pathogens, and when consumed by humans may protect against cancer, diabetes, cardiovascular and neurodegenerative disease [77]. Polyphenols act as antioxidants because their phenolic groups can accept an electron and stabilize oxidative chain reactions, and as a result reduce oxidative stress [76,77]. Polyphenols are one of the major compounds present in tea. Different teas contain varying amounts of polyphenols due to their fermentation and preparation process. Black tea most contains the flavonoids theaflavins and thearubigins, while green tea is especially rich in catechins. The main catechins in green tea are epigallocatechin gallate (EGCG), epigallocatechin (EGC), epicatechin, and epicatechin-3-gallate [78]. Catechins can have antioxidant properties by chelating metal ions such as Fe^{2+} and Cu^{2+}. Iron and copper are involved in the Alzheimer's pathway, as their binding to amyloid beta can induce oxidative stress. Catechins can prevent the generation of hydroxyl radical OH and other free radicals formed by the Fenton and Haber Weiss reactions by chelating metal ions [79–81 82]. Chelation binds metal ions to a ligand through a coordination bond [83]. Catechins can act as antioxidants by reducing excess iron and copper, and decreasing ROS generation. A study investigated whether prolonged green tea consumption affected oxidative stress as a result of aging [84]. Researchers fed some mice green tea, and measured amounts of protein carbonyls, a biomarker of oxidative stress. They found that chronic green tea consumption decreased protein carbonyls when compared to controls. In addition, they observed lipid peroxidation by measuring amounts of malondialdehyde, a biomarker derived from peroxidation of polyunsaturated fatty acids [84,85]. They found that as mice aged, malondialdehyde levels increased by 70%, but green tea-treated mice had lower levels than controls. Another study fed Alzheimer's-like mice EGCG specifically, to determine whether EGCG was beneficial for Alzheimer's disease [86]. They found that oral EGCG treatment improved expression of synaptic proteins, increased anti-inflammatory cytokines, and alleviated microglia activation compared to controls. Alzheimer's exhibits synaptic damage and brain inflammation is heavily involved in disease progression [86,87]. Microglia are the brain's primary immune cells. Increased anti-inflammatory cytokines and decreased microglia activation is associated with less inflammation. Catechins may prevent the generation of free radicals and decrease oxidative stress.

A prospective cohort study of Japanese people aged 65 years or older investigated whether consumption of green tea was associated with dementia risk. They found that green tea consumption is significantly associated with a lower dementia risk [88]. However, not all types of tea have the same impact. A study investigated the effects of green, red, and black tea on mice to discover whether there were neuroprotective benefits [88,89]. They found that while green tea prevented oxidative stress and lipid peroxidation, there was no significant improvement with red and black tea [88]. This could be because green tea has the highest EGCG concentration, with EGCG comprising up to 80% of green tea

polyphenols [90]. Polyphenols, especially catechins in green tea, may prevent the generation of free radicals and decrease oxidative stress to improve Alzheimer's.

Discussion

Specific vitamins and antioxidants may alleviate Alzheimer's symptoms and slow clinical progression, such as the vitamins B, E, and D. The brain is vulnerable to oxidative stress, but antioxidants can help regulate oxidative stress by neutralizing ROS. Vitamin B supplementation helps by regulating homocysteine, an intermediate in methionine metabolism. Vitamin E is also an antioxidant, and neutralizes ROS. Vitamin E supplementation has been shown to decrease lipid peroxidation and oxidative stress. Vitamin D is known for regulating calcium homeostasis, as well as neuron growth through increasing myelination. Vitamin D deficiency has been associated with increased Alzheimer's risk. In addition to vitamins, this review also focused on antioxidants such as carotenoids and polyphenols. Supplementation of carotenoids and polyphenols were shown to decrease Alzheimer's risk and clinical progression.

Although this review researched a wide variety of vitamins and antioxidants, there are still many others that could potentially benefit Alzheimer's patients. Vitamins B6, B9, and B12 were the main focus of supplementation to regulate homocysteine levels. There are also different forms of Vitamin E, but this study mainly focused on the effects of alpha-tocopherol. In addition, there are more than 600 carotenoids and 8000 polyphenols discovered, but this study focused on lutein, zeaxanthin, and the catechin EGCG [76]. However, these vitamins and antioxidants may not benefit people equally. For example, Vitamin E reduced lipid peroxidation and amyloid beta in Alzheimer's like mice with moderate progression, but had no significant effect on mice with severe cases. Vitamin E is effective for mild and moderate stages of Alzheimer's disease, however, it may be ineffective for severe disease stages and its benefits will vary among patients. [91]. Similarly, Vitamin D supplementation may have a stronger benefit in females than males, possibly because of estrogen levels [67]. Regarding polyphenols, not all teas are as beneficial to Alzheimer's, since red and black tea were shown to have no significant improvement on oxidative stress [88,89]. Studies have shown that people may need to drink between 5 to 6 cups a day to experience the benefit [92]. While these nutrients may not be effective for some individuals, many individuals experience an improvement in symptom burden. Therefore, vitamins and polyphenols may be an effective adjunctive therapy for patients with Alzheimer's disease.

Specific diets high in the vitamins and antioxidants discussed in this review may be a possible lifestyle change in protecting against Alzheimer's. Vitamins B6, B9, and B12 are found in fish, meat, poultry, and dairy products. While B12 is not commonly found in plants, B6 and B9 are also present in starchy or dark green leafy vegetables [93–95]. Vitamin E's alpha-tocopherol is prevalent in nuts, seeds, and vegetable oils [96]. While vitamin D is also obtained through sun exposure, it can be found in fatty fish [97]. Carotenoids can be found in brightly colored or leafy green fruits and vegetables [98]. Polyphenols can be found in berries, nuts, and like this review discussed, tea [99]. Researchers have found the Mediterranean diet to reduce Alzheimer's risk, as the diet contains adequate amounts of the vitamins and antioxidants discussed in the review paper [99–101]. The mediterranean diet is a primarily plant-based diet with lower amounts of meat, fish, and dairy consumption [99102]. Olive oil and nuts contain various polyphenols, whereas vegetables and meat contain vitamins discussed in the review [103]. In comparison, the Western diet is characterized by high consumption of red meat, processed desserts, refined oils, and low intake of fruit and vegetables [103–105]. These foods do not offer adequate amounts of nutrients, and imbalance of nutrition can lead to diseases such as cardiovascular disease, inflammation, and increased risk for neurodegenerative diseases [106]. Consuming foods or adhering to diets containing supplemented amounts of these nutrients, such as vitamins and antioxidants, may help alleviate Alzheimer's symptoms and progression.

Conclusion

Alzheimer's disease is characterized by amyloid beta plaques and tau neurofibrillary tangles. Oxidative stress can increase the diseases' clinical progression, but supplementation with vitamins B, E, and D as well as antioxidants such as carotenoids and polyphenols may decrease oxidative stress and disease risk. Diets that contain high amounts of these specific nutrients may be beneficial to Alzheimer's, although these nutrients may not benefit all patients equally. Therefore, future research should further investigate the relationship between nutrients and Alzheimer's disease.

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