The Role of Nutrition in Preventing Alzheimer’s Disease and Other Dementias: A Literature Review

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Abstract

**Objective:** The objective of this literature review is to examine the most common forms of dementia that affect adults. The paper will also explain what research suggests are the most prevalent causes or predisposing factors. The key points that will be focused on are the different nutritional and lifestyle changes that can be made in order to prevent or help slow down the process of cognitive decline.

**Data Collection:** The research articles referenced in this paper were obtained by using PubMed and Google Scholar. These are both sites that access many different forms of literature (articles, books, abstracts, etc.) concerning any area of research. PubMed provided over 1300 articles concerning dementia and nutrition.

**Data Synthesis:** Different researchers used different methods in order to determine the effectiveness of their treatment. Some use a variety of cognitive test to measure the intellectual ability of the patient both before and after their prescribed protocol. Others used blood testing administered both before and after to check for levels of certain chemicals, vitamins, fats, and cholesterol.

**Conclusions:** All of the research also suggests that a number of different ways can help decrease this neuroinflammation. Several methods suggest that there are certain items that should be decreased in the diet. For example, exposure to iron, copper, and methyl mercury should be watched for in the patient’s lifestyle. Several antioxidants such as vitamin E, vitamin C, and S-adenosylmethionine can be used to help induce neuroprotective effects. Reducing fat and cholesterol are also helpful. The main objectives in preventing or slowing down this disease are to reduce harmful oxidative reactions and the amyloid beta plaques that get deposited in the brain.

**Key Words:** Alzheimer’s, nutrition, dementia, cognitive decline, lifestyle
Introduction

The Alzheimer’s Society defines dementia as a set of symptoms including loss of memory, mood changes, and problems with communication and reasoning that progressively get worse. The most prevalent dementia, as well as the most well-known among the general population, is Alzheimer’s disease (AD). This is a disease that affects an estimated 5.4 million people and costs $183 billion per year to treat. This is approximately 60-70% of all dementia cases and affects people after 65 years of age. The trademark neuropathologic features of Alzheimer’s are the neurofibrillary tangles and the beta amyloid plaque formation in the brain. Schaeffer believes that,

“Neurofibrillary tangles contain hyperphosphorylated and aggregated forms of Tau, a microtubule-associated protein that normally promotes the assembly and stability of microtubules in neuronal cells. Abnormally hyperphosphorylated Tau in AD brain accumulates in neurons into paired helical filaments, which in turn aggregate into neurofibrillary tangles leading to neuronal death. Therefore, the neuro-pathological hallmarks of AD induce progressive neuronal dysfunction and degeneration, resulting in severe brain atrophy and decline of memory and other cognitive functions.”

Adults in later stages of dementia most times put their trust in their friends and family to take care of them as they cannot perform general everyday tasks on their own. This puts stress on both the patient and the caregiver due to the 7 stages of cognitive
decline that a patient goes through. There are no known cures or preventative measures for dementia. However, there has been extensive research done to see if there are nutritional and lifestyle modifications to help slow the decline.

Discussion

Possible Causes: Dementias such as Alzheimer’s are believed to be caused mainly by oxidative stress placed on the cells in the body. In 2010, Kell proposed that this oxidative stress can be promoted by increased radical production from the beta-amyloid proteins in the brain binding iron\(^1\). A more detailed explanation is required in order to understand exactly how this process takes place. Iron is categorized as a transition metal. Quite simply, what this means is that there are different valencies, or forms in which iron can occur. In chemical reactions in the body, iron (Fe) acts as a catalyst. This iron catalyst helps to change the rate at which any reaction occurs. Iron is involved in many enzymatic reactions, most significantly redox reactions. These reactions are typically specific because all six ligand binding sites are safely bound. It is imperative that there is a description of a “safe” bind. The catalytic site contains an architecture that is specific to certain ligands. When these bonds are not the exact match, an unsafe or improper bond forms, and the result is a ferrous form of iron (Fe II). The Fenton reaction takes hydrogen peroxides or other peroxidases and react them with ferrous iron. This is where the damaging hydroxyl radicals originate. There is another reaction, the Haber-Weiss reaction, that combines superoxides with ferric iron (Fe III), thereby
producing more ferrous iron (Fe II). This Fe II further fuels the Fenton reaction, thus generating a greater abundance of hydroxyl radicals which contribute to the oxidative stress levels\(^1\).

A report from Atamna gives a more detailed report of specifically how the iron binding affects the brain. Beta-amyloids in the human brain have two iron binding sites that can very tightly bind the heme portion of iron. This beta-heme complex formation produces a high peroxidase activity due to heme depletion. The neurotoxic effect leads to susceptibility of Alzheimer’s disease\(^2\).

This theory of oxidative stress is supported in research done by Adibhatia. The body has an innate ability to detoxify itself, but when reactive oxygen species (ROS) are produced in excess, oxidative stress occurs. The mitochondrial respiratory chain, specifically the oxidative phosphorylation process of this chain, is responsible for producing ROS. This occurs when ROS such as superoxide anion radicals, hydrogen peroxide, and hydroxyl radicals combine with reactive nitrogen species. According to Adibhatia, excess production “can damage all components of the cell, including proteins, carbohydrates, nucleic acids, and lipids, leading to progressive decline in physiological function and ultimately cell death.”\(^8\) The same research also suggests that cell membranes play a crucial role in neurodegenerative diseases. These cell membranes are made of cholesterols, fatty acids, and phospholipids. Altered lipid metabolism and
neurosteroid synthesis can lead to injuries in the central nervous system. This research also states that,

“In AD brains, a general trend was observed towards decreased levels of all steroids, with significantly lower amounts of pregnenolone and dehydroepiandrosterone. These lower levels correlated with increased amounts of β-amyloid peptides and phosphorylated tau proteins. It is not known whether these neurosteroid deficiencies contribute to or result from AD pathology, but since many neurosteroids have neuroprotective actions, their lower levels may contribute to Aβ neurotoxicity.”

The cholesterol in the membrane also controls the amyloid protein precursor compartmentation. Kalman believes that “The amyloid precursor protein molecule could be present either in-, or outside of the membrane rafts. Any kind of process, which alters the compartmentation preference of the amyloid precursor protein molecule, by transferring it to the membrane rafts, favors beta- and gamma-secretase cleavage, and should be recognized as an amyloidogenic process.” This means that amyloid protein precursors are turned into their harmful cytotoxic counterparts because the lipid metabolism is faulty. Beta amyloid specific metabolism occurs when the cholesterol levels in the membrane are raised resulting in deposition of the amyloid precursor protein.
Methyl mercury has also been proved to increase neuronal death due to the effect that it has on brain cells, especially on astrocytes. Astrocytes play a very important part in the glutamate to glutamine conversion process. Neurotransmitters release glutamate, and it is taken up by the astrocytes. There it is converted to glutamine and released back into the intracellular space where it is used to synthesize new neurotransmitters. During the research conducted by Yin and his colleagues, when astrocytes are exposed to significant concentrations of methyl mercury, there is an increase that occurs in the levels of F2-IsoPs. This lipid peroxidation biomarker, F2-IsoPs, is indicative that there is an increase in oxidative injury to the cells. Yin also remarked that the significant level needed to cause such an increase is 5 μM of methyl mercury. Methyl mercury is a substance that is environmental in nature. The most common place to find methyl mercury is in the waterways. Here, inorganic mercury is methylated to methyl mercury. The seafood chain then becomes a site for the accumulation of this compound. People whose diet consists of large amounts of fish are at higher risk for methyl mercury contamination according to Aschner. Another proposed theory for contributions to Alzheimer’s and other types of dementias is due to apoptosis, or cell death. Lan suggests that this cell death is due to a folate deficiency in the population. Folate has long been known to contribute to good neural health. It is very important, because when there is not an adequate amount present, the one-carbon metabolism
process is disturbed. A disruption in this chain leads to an increase of the cytotoxic amino acid homocysteine, which leads to an increased breakage of the DNA strands\textsuperscript{5}.  

Another theory that researchers report is that copper toxicity can lead to Alzheimer’s disease. The beta amyloid plaques that form in the brain of an Alzheimer’s patient bind copper\textsuperscript{6}. Neurofibrillary tangles which are also present in the diseased brain are made of tau proteins and also have any affinity to bind copper. Homocysteine, the cytotoxic amino acid mentioned earlier, can also interact with the copper molecule. However, it should be clarified that there are two types of copper in the human bloodstream. One form is bound to ceruloplasmin and is a so-called “safe” copper. The other is referred to as “free” copper. It constitutes 5-15\% of the copper population, and it is readily available for exchange as it is only loosely bound to albumin. According to Brewer, Alzheimer’s patients have elevated serum levels of free copper\textsuperscript{6}. The element enters the human body by consumption of drinking water. The Environmental Protection Agency allows 1.3 parts per million of copper to be present in the drinking water. Unfortunately, the small amount of 0.12 parts per million is the minimal amount necessary to add to the formation of beta amyloid plaques in the brain. Another entrance route of copper is in the form of a multi-vitamin mineral pill that many people take as part of their routine supplementation. These forms of copper are inorganic, and therefore bypass the liver and take a direct route to the bloodstream. Copper in the diet is bound in an organic, thus being processed through the liver and not turning into free
copper. Brewer also supports his hypothesis by looking at the timeframe in which our country has been plagued by Alzheimer’s disease. This disease has only been noticed for the past 100 years. He believes that the invention and utilization of copper plumbing has a very strong correlation to the disease. Prior to 100 years ago, homes in America did not have copper plumbing, nor were there reported cases of this dementia. Japan, which is a very wealthy country, currently does not endorse the use of copper plumbing in their country. Not surprisingly, they have a very insignificant number of Alzheimer’s cases. In contrast, members of the Japanese community that have migrated to the state of Hawaii have reported more cases than those still in Japan. There is also evidence to show that underdeveloped countries have none to minimal reports due to their inability to avoid plumbing, especially that which is made of copper⁶.

**Possible Preventative Measures:** Most of society first goes to a medical doctor when diagnosed with a disease and takes their prescribed medications to help treat the symptoms of any disease that they have. There are several natural modifications that can be done to either prevent the disease or to slow the progression of the disease. Polidori reviewed recommendations made by the Third Canadian consensus Conference on Diagnosis and Treatment of Dementia that stated that by reducing the systolic blood pressure to 140 mmHg and lower in individuals over 60 years old will reduce dementia risks.
Soybean isoflavones (SIF) are another natural way to help decrease the risk of the disease of dementia. These soybean isoflavones appear to exhibit antioxidant activity and modulate the enzymatic antioxidant defense system. Ma suggests that the best way to administer these SIFs is to do so pre-intragastrically. This ensures that concentrations are increased in both the serum and brain tissues. This inevitably decreases formation of the harmful beta amyloid plaques\textsuperscript{10}.

Ramesh did research on the impact of diet on Alzheimer’s disease and whether or not it has a beneficial effect. Some protective items were found to be antioxidants, fish, methionine-rich proteins, and vitamins. Some items that Ramesh suggests to avoid due to their deleterious effects are saturated fatty acids, excess alcohol, and high calories diets. One of the first and seemingly easiest things to do is to implement a reduced calorie diet. This has been proven to modulate neuroinflammation and oxidative stress thereby reducing production of reactive oxygen species. Brain-derived neurotrophic factor (BDNF) is a neurotrophic factor that is expressed more highly as a result of a reduced calorie diet. This BDNF protects neurons against oxidative and metabolic insults and is also known to stimulate neurogenesis. Memory and learning functions are increased due to the production of this factor. Unfortunately it is decreased in Alzheimer’s disease. One should keep in mind that the exact way that a reduced calorie diet has these effects is not entirely understood. According to Ramesh’s hypothesis, “It is postulated that CR increases synaptic plasticity, anti-inflammatory
mechanisms and inducing neuroprotective factors. CR was shown to protect the age-related loss of neurons in AD. They also observed that CR could reduce the enlargement of ventricles, caspase activation, and astrogliosis. From the above findings it indicated that CR could increase neurogenesis.” It is imperative to state that this diet is most productive when introduced at a younger age. If introduced after the patient has already been diagnosed with the disease, it can either have a diminished effect, or no effect at all.$^{12}$.

One of the genetic risk factors for developing Alzheimer’s disease is the ApoE-ε4 allele. ApoE is a factor that helps moderate the transport of lipid in blood, brain and cerebrospinal fluid.$^{12}$ More specifically, it serves as a ligand for low density lipoprotein (LDL) receptors and the cholesterol and fat that are associated with them.$^{13}$ Based on the studies of Lopez-Miranda for the Journal of Lipid Research, individuals that are carriers of this ApoE-ε4 generally exhibit lower levels of the LDL cholesterols. If levels are elevated, this can be correlated with a diet that has been high in saturated fats and cholesterol.$^{13}$ The researchers recruited subjects at three different sites for their study. They pre-determined diets and the amount of time that the test subjects would remain on that diet. At least one meal each day was eaten at the test site. All other meals were prepared at the site and given to individuals to be taken home. The two types of diets were fundamentally high fat versus low fat. The test subjects in the group were split into carriers and non-carriers of the ApoE-ε4 allele. After all the research had been
conducted, “analysis supports the concept that ApoE-ε4 allele is associated with an increased LDL cholesterol response to dietary manipulation.”\textsuperscript{13} It was also discovered, that after a low fat diet, the males LDL cholesterol lowered twice as much as the women’s.

Mediterranean diet as a healthy eating model has been widely recognized with reducing the risk for cardiovascular mortality and cancer incidence and mortality. More recent studies have examined the effect that this diet may have on brain tissue and how that affects cognitive decline. Feart has proposed that the Mediterranean diet “has the special feature to combine several foods and nutrients already separately proposed as potential protective factors against cognitive dysfunctions.”\textsuperscript{14} There are several different variations of this diet depending on the specific region of the country in which one is located. This particular research group focused on the country of Greece. The traditional diet in Greece is, “characterized by abundant plant foods consumption in the form of fruits, vegetables, breads, other forms of cereals, potatoes, beans, nuts and seeds; fresh fruit as the typical dessert; olive oil as the main source of monounsaturated fat; dairy products as principally cheese and yogurt; a low to moderate consumption of fish depending on the proximity of the sea; a low to moderate consumption of poultry; fewer than four eggs consumed per week; low amount of red meat and wine consumed in low to moderate amounts, normally during meals.” Feart looked at a pool of 2258 that were on the diet and followed them for four years. Out of this number, only 262 of
the subjects developed Alzheimer’s disease. The results also indicated that, “Higher adherence to the Mediterranean diet was significantly associated with lower risk for development of AD, even after adjustment for age, sex, ethnicity, education, ApoE genotype, caloric intake, smoking, comorbidity index and body mass index.”

There were also cognitive ability tests conducted. These tests were the Mini-Mental State Examination (MMSE), Isaacs Set Test (IST), Benton Visual Retention Test (BVRT) and Free and Cued Selective Reminding Test (FCSRT) assessing respectively, global cognitive function, semantic verbal fluency, visual memory and verbal episodic memory. The findings were that when a subject adhered more strictly to the diet, their scores on these same tests in later years were not lowered as much as the subjects who were not adhering to the diet. Diet followers also remained more dementia free over time, and their cognitive abilities and episodic memories remained more intact.

It has already been discussed that one of the believed major causes of dementias including Alzheimer’s disease is the production of free radicals and other reactive oxygen species (ROS). Antioxidants are very important to include in one’s diet and supplementation. There are a variety of antioxidants, and they all seem to serve as free radical scavengers. One supplement that has undergone research on its relation to the disease is vitamin E. When the levels of vitamin E in non-dementia patients are compared to that of the diseased patients, it is shown that diseased patients have much
lower levels of about 18.65 mmol/L versus about 30 mmol/L in the other subjects.

Another study showed that supplementation with 500 IU of vitamin E and 1-2% of the diet containing strawberries and spinach, could protect against cognitive decline prior to developing it. If this diet was administered after cognitive decline had already begun, it had no effect\(^\text{12}\). Kontush and Schekatolina conducted a placebo trial where they administered 2000 IU of vitamin E per day over a period of 2 years to patients who had already been diagnosed with Alzheimer’s disease. The results were that about 53% of the patients had their functional deterioration decelerated\(^\text{15}\). Kontush did additional research on this supplementation theory and found that vitamin E taken in conjunction with vitamin C produced an even greater effect on slowing down cognitive decline\(^\text{16}\).

The dosage that was used was 400 IU of vitamin E and 1000 mg of vitamin C. When used in conjunction, the vitamins increased their CSF and plasma concentrations, and they were able to decrease the lipoprotein oxidizability in the brain. Vitamin E alone did not decrease the susceptibility of CSF and plasma lipoproteins to in vitro oxidation. The research of Zandi confirms the above statements. It showed that the combination of vitamins E and C reduced both the prevalence and incidence of Alzheimer’s. However, the supplements alone provided no protective effect\(^\text{17}\).

It has been shown that cardiovascular disease, atherosclerosis, and abnormalities in the cerebral microvasculature can lead to cerebral infarcts, which can thereby lead to increased susceptibility to Alzheimer’s disease. Based on this, Clarke chose to review the
relationship between the blood serum levels of homocysteine, vitamin B12, and folate and the occurrence of Alzheimer’s. Nonfasting blood samples were taken to chart baseline levels of each chemical. Radioimmunoassay established the levels of B12 while microbiological assays the folate levels. High-performance liquid chromatography with fluorescence detection determined the homocysteine levels. The mean serum homocysteine levels at the first visit were significantly higher in patients with clinically diagnosed and histologically confirmed AD than in controls. These levels were also directly associated with age, male sex, smoking, and creatinine levels. It was inversely associated with folate levels. AD patients in the study demonstrated decreased levels of serum folate and vitamin B12. These statistics are important based on the following research. Chang shows that, “atrophy of the cerebral cortex, dementia, cerebrovascular diseases, and specific domains of cognitive functioning such as episodic recall and recognition” are present due to low serum folate levels. Intelligence, memory, attention, problem solving abilities, and fine motor coordination were assessed using a battery of different cognitive tests. These tests were completed on the same day that blood samples were taken. Chang used Spearman’s correlation analysis to relate the testing scores to blood serum levels of folate and vitamin B12. The results showed that, among other B vitamins, folate status as assessed by folate concentrations in the plasma and red blood cells was significantly correlated with test scores for several domains of cognitive function. Plasma folate was significantly correlated
with total intelligence quotient scores, while red cell folate was correlated with the scores for memory, fine motor coordination, and problem solving ability.”

Folate deficiency, by hindering the synthesis of DNA and protein synthesis for neuronal and glial growth and proliferation during critical points, can detrimentally influence neurotransmission and memory function. Folate is also involved in maintaining adequate methionine pools for the synthesis of S-adenosylmethionine (SAMe).

Transmethylation reactions involving nucleic acids, proteins, phospholipids, amines and other neurotransmitters require the SAMe molecule. With decreased SAMe concentrations, neural function is impeded by negatively affecting methylation of cellular DNA. In more generalized terms, the supplementation of these vitamins is very important in the diet to help facilitate all the required reactions in the brain that keep the tissue healthy. Chang states, “It may be difficult to apply what we found in our study directly to general public, however, there is growing evidence supporting the view that good nutritional status of folate and other B vitamins is an important determinant for cognitive function.”

Conclusions: Based all the research that has been presented, it is very safe to say that researchers believe that one of the most prevalent causes of Alzheimer’s is the presence of reactive oxygen species and their harmful effects on neural tissue. All of the research also suggests that a number of different ways to help decrease this neuroinflammation. Several methods suggest that there are certain items that should be decreased in the
diet. For example, exposure to iron, copper, and methyl mercury should be watched for in the patient’s lifestyle. Another important factor that appears to be consistent across several researchers is reducing the levels of fat and cholesterol in the patient’s diet. Besides cutting out things, there are also things that can be added. Several antioxidants such as vitamin E, vitamin C, and S-adenosylmethionine can be used to help induce neuroprotective effects. Overall, while there is no cure for Alzheimer’s disease and other dementias, there are many things that can be done to lower the risks of acquiring it or to slow the progress of the disease if already diagnosed.
References


