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## Diet and Alzheimer's Disease: What the Evidence Shows

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### Introduction

Our understanding of dietary influences on Alzheimer's disease is in its infancy, and the number of epidemiologic studies examining promising associations is limited. Thus, at this time, we cannot say with certainty that any particular nutritional component causes or prevents Alzheimer's disease. With that caveat, much of the evidence from early studies in many ways reflects a pattern of dietary associations very similar to more established dietary risk factors for cardiovascular diseases, such as heart disease. Thus, patients who adopt these dietary practices will reduce their risk for heart disease and *may* also curtail their risk of developing Alzheimer's disease.

### Antioxidant Nutrients

Perhaps the best evidence of disease prevention involves the antioxidant nutrients, vitamins E and C. The neuropathologic features of Alzheimer's disease include amyloid beta (A-beta) plaques, an abnormal accumulation of A-beta protein outside neuronal cells, and neurofibrillary tangles within the cells. Numerous animal and laboratory studies have shown that Alzheimer's disease involves oxidative and inflammatory processes, although it is not known whether these processes are a cause or effect of the disease or both. The ultimate result, however, is disruption of neuronal cell functioning and signaling, leading to neuronal cell death.

The brain is a site of high metabolic activity that generates free radical molecules, oxygen molecules with unpaired electrons that are highly reactive and thus toxic to cell tissue. Infection, cell injury, and environmental toxins, such as smoking and pollution, also generate free radical molecules. The body possesses natural defense mechanisms to combat oxidative stress, including antioxidant proteins and nutrients. Vitamin E is a potent chain-breaking antioxidant that resides within cell membranes, where it can neutralize free radicals as they are generated. Vitamin E also has anti-inflammatory properties. Vitamin C, a less potent antioxidant than vitamin E, circulates within the plasma and retains the additional function of restoring vitamin E to its antioxidant capacity.

Animal and laboratory studies demonstrate that the antioxidant nutrients, and vitamin E in particular, protect the brain from damage due to oxidative and inflammatory mechanisms.<sup>[1,2]</sup> Rodents fed antioxidant-supplemented diets had superior learning acquisition and memory retention compared with rodents on control diets. At death, the brains of the antioxidant-fed rodents exhibited less neuronal cell loss and less evidence of oxidative damage and inflammation.<sup>[3,4]</sup>

The available evidence from human studies is limited and not altogether consistent. Two prospective studies, 1 of Chicago, Illinois, residents<sup>[5]</sup> and 1 in Rotterdam, The Netherlands,<sup>[6]</sup>

found a lower risk of Alzheimer's disease with a higher food intake of vitamin E. However, another prospective study conducted in New York found no association.<sup>[7]</sup> Vitamin E intake in the New York study may have been too low to provide a neuroprotective benefit; the median of 7 IU/d for persons in the top third of intake was comparable to the lowest intake levels in the Chicago and Rotterdam studies.

Of the 3 trials, only the Rotterdam study found a reduced risk of Alzheimer's disease with high food intake of vitamin C. However, the Chicago study found that participants with the highest food intake of vitamin C were more than twice as likely to have a history of stroke or hypertension, and these persons may have increased their fruit consumption as a recent preventive measure, thus obscuring a potential protective association with Alzheimer's disease.

### **Supplements vs Dietary Vitamins**

In none of the 3 prospective studies was vitamin E and vitamin C *supplement* use associated with less risk of Alzheimer's disease. Two other prospective studies<sup>[8,9]</sup> examined vitamin supplement use in relation to Alzheimer's disease, and only 1 of these<sup>[8]</sup> found evidence of reduced risk. There are several plausible explanations for the absence of association with vitamin E supplements. Vitamin E supplements have traditionally contained only alpha-tocopherol, the most biologically active form of vitamin E; however, gamma-tocopherol is the more abundant form in the US diet. Whereas alpha-tocopherol is the more potent antioxidant, gamma-tocopherol also has anti-inflammatory properties.<sup>[10]</sup> Recent studies indicate that the combined intake of the 8 different tocopherol forms reduces oxidative stress and inflammation to a greater degree than alpha-tocopherol alone.<sup>[11]</sup>

Another explanation for the absence of association with vitamin E supplements is that food intake may be a better indicator of long-term exposure to vitamin E. In addition, the study findings could be biased if many study participants initiated vitamin supplement use because of developing problems in cognition.

In summary, the strongest evidence for antioxidant protection against Alzheimer's disease rests with high food intake of vitamin E. The richest food sources of vitamin E include vegetable oils, margarine, nuts (especially almonds), and seeds (especially sunflower seeds). Moderate amounts of vitamin E are found in whole grains, egg yolk, and a limited number of vegetables (eg, collard greens) and fruits (eg, avocados, apples, melon).

### **Dietary Fat Composition**

Another promising area of study involves the effect of dietary fat composition on the risk of Alzheimer's disease. The composition of fat in the diet is known to affect blood cholesterol levels. In metabolic studies, diets with a high ratio of saturated fat to polyunsaturated or monounsaturated fats resulted in a poor blood cholesterol profile, characterized by high levels of low-density lipoprotein and low levels of high-density lipoprotein cholesterol.<sup>[12]</sup> Consumption of transunsaturated fat, obtained from partially hydrogenated vegetable oils in commercially baked products, is particularly hypercholesterolemic.<sup>[13]</sup>

Although the biochemical mechanism is not yet identified, cholesterol appears to be an important component in Alzheimer's disease and is involved in both the generation and deposition of A-beta.<sup>[14]</sup> One of the more important genetic risk factors for Alzheimer's disease, the apolipoprotein E-<sub>4</sub> allele (APOE-<sub>4</sub>), is the principal cholesterol transport in the brain.

Several lines of evidence support the theory that an elevated blood cholesterol level is related to the development of Alzheimer's disease. In experimental models, animals fed high-fat and high-cholesterol diets exhibited impaired learning and memory performance compared with animals on control diets and also demonstrated more A-beta deposition in the brain, greater loss of neurons, and other Alzheimer's disease-related neuropathology.<sup>[15,16]</sup> One study of 444 Finnish men found that an elevated blood cholesterol level (> 6.5 mmol/L) in midlife was associated with 3 times the

risk of developing Alzheimer's disease in late life.<sup>[17]</sup>

Two recent studies of patients who had been prescribed statin drugs found a significantly lower risk of Alzheimer's disease compared with similar patients who were not prescribed these medications.<sup>[18,19]</sup> Whether the observed reduction in Alzheimer's disease resulted from cholesterol lowering or some other property of these medications remains to be seen as the findings of related studies emerge.

The 3 prospective dietary studies conducted in Chicago,<sup>[20]</sup> New York,<sup>[21]</sup> and Rotterdam<sup>[22]</sup> also examined the relation of dietary fat intake to the development of Alzheimer's disease. The Chicago study reported the strongest evidence of an association. High intake of saturated fat doubled the risk of Alzheimer's disease, and even moderate intake of trans fat increased the risk by 2 to 3 times.<sup>[20]</sup> By contrast, higher intake of both polyunsaturated and monounsaturated fats was associated with lower risk of developing Alzheimer's disease.

The New York study found evidence of a greater 4-year risk of Alzheimer's disease for those with higher intakes of total fat and saturated fat but no evidence of an association with the intake of polyunsaturated fat.<sup>[21]</sup> Investigators for the Rotterdam study also found an increased risk of disease with higher intakes of total fat, saturated fat, and cholesterol after 2 years of follow-up,<sup>[22]</sup> but none of the dietary fats was associated with Alzheimer's disease after 6 years of follow-up.<sup>[23]</sup> Further study will be required to understand the inconsistent findings across studies and to determine whether the composition of fat in the diet is causally related to risk of Alzheimer's disease.

### **Fish and n-3 Fatty Acids**

Long-chain n-3 fatty acids, a type of polyunsaturated fat consumed almost exclusively from fish, may also hold promise for the prevention of Alzheimer's disease. One of the n-3 polyunsaturated fatty acids, docosahexaenoic acid (DHA, 22:6n-3), is the primary component of membrane phospholipids in the brain and is particularly abundant in the more metabolically active areas. DHA is directly available in fish, but smaller amounts can be synthesized endogenously from its precursor n-3 fatty acids, alpha-linolenic acid (18:3n-3) and eicosapentaenoic acid (EPA, 20:5n-3). EPA is also consumed directly from fish, but alpha-linolenic acid is obtained from vegetable oils and nuts.

The n-3 polyunsaturated fatty acids have antiaggregatory, antithrombotic, and anti-inflammatory properties. Much of the evidence of the neuroprotective effects of the n-3 fatty acids stems from investigations of their importance as essential dietary components in early brain development. In animal models, rodents fed diets enriched with n-3 fatty acids performed better in learning and memory tasks compared with rodents fed control diets.<sup>[24-26]</sup> A number of studies have found that the n-3 fatty acid diet resulted in better regulation of neuronal membrane excitability,<sup>[27]</sup> improved capacity for neuronal transmission,<sup>[28]</sup> and reduced oxidative damage.<sup>[29]</sup>

Several case-control studies reported lower biochemical levels of n-3 fatty acids in the plasma<sup>[30]</sup> and brain tissue<sup>[31]</sup> of patients with Alzheimer's disease compared with controls. One fish meal a week was associated with a 60% reduction in the risk of developing Alzheimer's disease in both the Rotterdam and Chicago studies.<sup>[9,32]</sup> The Chicago study also examined risk of disease according to intake of the n-3 fatty acids. Higher total intake of the n-3 fatty acids was significantly associated with a lower risk for Alzheimer's disease. DHA provided the strongest association, EPA was not associated, and alpha-linolenic acid was associated with lower risk only among persons with the APOE-<sub>4</sub> allele. The Rotterdam study did not find an association between total intake of n-3 fatty acids and risk of Alzheimer's disease.<sup>[10]</sup>

Although these studies show promise that dietary intake of fish and n-3 fatty acids may protect against Alzheimer's disease, more research needs to be done before we can attribute the findings of these few studies to a causal association.

Thus far, no human study has indicated that taking a fish oil capsule is associated with less risk of developing the disease, although several clinical trials are currently in progress to examine the therapeutic effect in patients with Alzheimer's disease.

## **Dietary Recommendations for Patients**

Physicians who may want to recommend dietary habits to their patients should take heed that the best evidence for nutritional prevention of Alzheimer's disease is through foods rather than vitamin supplements. Many of the foods that are good sources of vitamin E are also rich in n-3 fatty acids and unhydrogenated, unsaturated fats -- the dietary components with the most convincing evidence of neuroprotection to date. Among these foods are oil-based salad dressings, nuts, seeds, fish, mayonnaise, and eggs. Patients should limit their intake of foods that are high in saturated and transunsaturated fats, such as red meats, butter, ice cream, commercially baked products, and some margarines that contain partially hydrogenated oils.

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