Vitamin E and Alzheimer Disease

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Introduction

Recently, there has been growing interest in the use of vitamins for the treatment of various health conditions. One study has estimated that 35–54% of older Canadians take some form of vitamin or mineral supplement.1 Oxidative stress has been theorized to be an important contributor to select conditions, particularly those involving the cardiovascular and central nervous systems. Vitamin E is the only fat-soluble, chain-breaking antioxidant found in biological membranes4 and, therefore, has been investigated for its use in the treatment of ischemic cardiovascular disease in recent landmark studies such as the Heart Outcome Evaluation Study (HOPE)2 and Heart Protection Study (HPS).3

How Does Vitamin E Work?

Vitamin E is a generic term for chemical derivatives of tocopherol and tocotrienol.5 There are eight naturally occurring forms, but only α-tocopherol is found in human plasma, has the highest bioactivity and is the form used for medicinal purposes. α-tocopherol is found naturally in vegetable oils, almonds, sunflower seeds, walnuts, sweet potato, liver, wheat germ and egg yolk.6 Synthetic forms are available as vitamin capsules and in fortified foods. The synthetic version is less potent than is naturally occurring Vitamin E, due to its complex molecular stereochemistry.7 The naturally occurring compound is denoted as d-α-tocopherol or RRR-α-tocopherol and the synthetic compound is all-rac-α-tocopherol. The synthetic compound’s relative biological activity is 0.75 that of the naturally occurring Vitamin E. International Units (IU) are being replaced by mg equivalents as the favoured unit of Vitamin E activity. IU was based on the activity of 1 mg of a synthetic DL-α-tocopherol acetate. The conversion to pure RRR-α-tocopherol is 1.49 IU/mg.

Several studies4,9 have demonstrated that Vitamin E acts primarily as a non-specific, chain-breaking antioxidant that prevents the propagation of free radical reactions by trapping the radicals and forming non-radical products. α-tocopherol also appears to have several secondary functions, including: inhibition of protein kinase C activity in smooth muscle cells, human platelets, and monocytes; enriching endothelial cells thereby down-regulating adhesion molecules and decreasing the adhesion of blood cells to the endothelium; and, enhancing the release of prostacyclin by upregulating the expression of cytosolic phospholipase A2 and cyclooxygenase-1.5

Vitamin E and Alzheimer Disease

The studies on the relationship between Vitamin E and AD suggest that free radical damage plays a role in the degeneration and death of neurons in AD.10 Aging, itself a major risk factor for AD, is associated with an accumulation of reactive oxygen species that leads to damage of cell nuclei, mitochondrial DNA, membranes and cytoplasmic proteins. Neurons are particularly vulnerable to free radical damage because of their high oxygen consumption, high membrane content of polyunsaturated fatty acids and the relative lack of antioxidant enzymes.11 The oxidative stress hypothesis for AD is supported by studies of brains from patients with AD, which show damage associated with free radicals: protein oxidation, DNA oxidation, lipid peroxidation and evidence of advanced glycosylation end-products.12 AD brains have increased levels of trace elements (iron, copper, zinc and aluminium), which have a catalytic effect on free radical production.

Excessive levels of β-Amyloid are present in AD brains. The oxidative process leads to the aggregation of β-amyloid and causes the formation of β-amyloid peptides in a free radical form.12 Vitamin E has been shown to prevent the deleterious effects of amyloid β peptide toxicity in vitro.5 The ε4 allele of apolipoprotein E is associated with AD. Studies have found that the level of lipoperoxidation is higher in patients with the ε4 allele.12 Vitamin E inhibits lipid peroxidation, possibly preventing damage to the polyunsaturated fatty acids essential to cell membrane integrity.

Animal studies have found that Vitamin E improves the cognitive function of aged rats and provides protection against the effects of brain ischemia and certain neurotoxins.13 Vitamin E slows the cerebral deterioration seen in transgenic mice with overexpression of amyloid precursor protein.10 Bourdel-Marchasson et al.16 suggest that antioxidants are metabolically consumed when there is an excessive production of free radicals. They found lower plasma concentrations of α-tocopherol in normally nourished patients with AD when compared to controls. Other studies have found no difference or even higher levels of α-tocopherol in AD patients.10 Lower plasma levels of α-tocopherol have been associated with impaired cognitive function in the old and very old.15 The cross-sectional Austrian Stroke Prevention study16 found a positive correlation between plasma α-tocopherol levels and cognitive function in a non-demented population. There are conflicting data regarding the levels of Vitamin E in the cerebrospinal fluid (CSF) of AD patients.13

Morris et al.17 conducted a prospective observational study of the relationship between vitamin E and C supplementation and the risk of AD. They followed 633 elderly subjects for four years and found a lower incidence of AD in patients using high doses of Vitamin C and E. This antioxidant combination dramatically lowered the risk of vascular (OR 0.12, 95% CI 0.02-0.88) and mixed dementia (OR 0.31, 95% CI 0.11-0.89), but not AD in a cohort study utilizing the Honolulu-Asia Aging database.18
Vitamin E and AD

Statistical significance was not reached with Vitamin E alone (OR 0.84). Use of either Vitamin C or E was associated with better cognitive performance among the non-demented (OR 1.25, 95% CI 1.04-1.50). The authors hypothesized that the antioxidants may limit the extent of neuronal injury after an ischemic event rather than preventing the event.

A Cochrane review of Vitamin E for AD found only one randomized, controlled, double-blind, multicentre trial for analysis. This study, by Sano et al., followed 341 patients with moderately severe AD for two years. The patients were randomized to one of four arms: selegiline 10 mg/d, synthetic α-tocopherol 1000 IU BID, a combination of both, or placebo. The primary outcome was time to occurrence of one of the following: death, institutionalization, loss of two out of three basic activities of daily living (as measured by part 2 of the Blessed Dementia Rating Scale) or severe dementia (defined as a Clinical Dementia Rating score of 3). Secondary outcomes included scores on ADAS-Cog, MMSE, Blessed Dementia Scale, Dependence Scale and the Behavior Rating Scale. At baseline, the MMSE score was higher in the placebo group. The MMSE score was predictive of primary outcome (p<0.001). The unadjusted analysis found no statistically significant differences among the four groups. When the analysis was adjusted for baseline MMSE, there was a significant delay to the occurrence of the primary outcomes in the vitamin E and selegiline groups as compared to the placebo group. The median time was 670 days (p=0.001) for the α-tocopherol group, 655 days (p=0.012) for the selegiline group, 585 days (p=0.049) for the combination group and 440 days for the placebo group. The authors concluded that selegiline or α-tocopherol slowed the progression of AD in patients with moderately severe disease. No statistically significant benefit was found on the cognitive endpoints. While the frequencies of a dental event, fall, or syncope were significantly higher with active treatment, after correction for multiple comparisons there were no statistically significant differences among the groups in adverse events.

There were many subsequent comments about this study. Some questioned

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### THE ROLE OF VITAMIN E IN PREVENTING FREE RADICAL DAMAGE

1. An oxygen radical removes an allylic hydrogen from a polyunsaturated fatty acid, resulting in a highly reactive alkylperoxyl radical.

   Alkylperoxyl radicals can directly damage membrane lipids. Their breakdown products can lyse membranes. As well, proteins and nucleic acids can be directly damaged by alkyl peroxyl radicals or they can be attacked by their dismutation products.

2. Vitamin E is fat soluble and acts as an antioxidant in the lipid part of cells. It donates one of its hydrogen atoms to the alkylperoxyl radical, which then becomes stable and unreactive. Vitamin E forms a stable phenoxyl radical.

3. The vitamin E radical lacks the energy to cause damage but will react with Vitamin C in the blood to regenerate the vitamin E. The vitamin C radical (monodehydroascorbate) is then reduced back to ascorbate or undergoes dismutation, producing dehydroascorbate and ascorbate.
Vitamin E and AD

the validity of using survival analysis while others criticized the use of the Cox proportional hazards model in the analysis since it was not initially the stated plan. The difference in the baseline MMSE score of 2.0 (placebo 13.3 and Vitamin E 11.3) was statistically significant (p=0.015). The Cochrane review\textsuperscript{13} used a different method of analysis but also arrived at the same conclusion as the authors. This suggested that the study data were robust with regards to the benefit of Vitamin E. It was concluded that there was insufficient evidence of efficacy of Vitamin E to recommend its use in the treatment of people with AD but that further study was warranted.

A recent randomized, double blind trial\textsuperscript{20} found no improvements in the P300 component of cognitive-event related potentials or on neuropsychological testing in patients treated with Vitamin E (2000 IU / d). There is at least one ongoing study that should shed some light on the utility of Vitamin E. The Alzheimer’s Disease Cooperative Study is conducting a randomized, double blind, placebo controlled study evaluating the efficacy and safety of synthetic Vitamin E (2000 IU / d) or donepezil (10 mg/d) in delaying clinical progression from mild cognitive impairment to AD.\textsuperscript{21} Enrollment of 720 patients with mild cognitive impairment was achieved in 2001 and the study should be completed by 2004.

Safety Profile

Although the data on benefit is not clear-cut, many elderly people take vitamin E supplements. In a convenience sample of 128 community-dwelling Canadians, over the age of 55, McKenziel found that 45 (48.9%) were using a vitamin E supplement. Fortunately, there is a relative lack of side effects. In human trials no or few side effects have been found with doses between 600–1200 IU / d.\textsuperscript{10} Gastrointestinal symptoms (indigestion, diarrhea, and cramps) were noted in trials using 3000–3200 IU / d. However, most studies lasted only weeks to months and long-term effects are unknown. Hemorrhagic stroke is the most important consideration. The unexpected finding of an increase in mortality, in male smokers taking 50 µg / d of Vitamin E, from hemorrhagic stroke in the ATBC study is preliminary but warrants further investigation.\textsuperscript{5} This was not observed in other larger trials where higher doses of Vitamin E were often combined with antiplatelet agents. Hemorrhage has been found in animal studies only with very high doses of vitamin E. This hemorrhaging was reversed by administration of vitamin K, suggesting that Vitamin E may prolong prothrombin time via Vitamin K-dependent carboxylase inhibition.\textsuperscript{23} In vitro studies have also found that vitamin E inhibits platelet aggregation and adhesion. There are no human studies demonstrating a risk for hemorrhage with high doses of vitamin E in healthy individuals. However, there are data showing that individuals deficient in vitamin K or who are on anticoagulants have an increased risk of a worsening coagulation profile with Vitamin E and, therefore, require careful monitoring.\textsuperscript{22}

A randomized, double blind, placebo controlled trial found that Vitamin E may accelerate the progression of disease in retinitis pigmentosa by interfering with Vitamin A absorption.\textsuperscript{5} However, another study found that Vitamin E halted the progression of retinitis pigmentosa as well as some of the neurological changes in patients with Friedrich-like ataxia.\textsuperscript{4} Further study is needed in this area. A comprehensive listing of the reported side effects of vitamin E is provided by Meyers\textit{ et al.}\textsuperscript{23} A number of these adverse effects (i.e., vasculopathic hepatotoxic effects, necrotizing enterocolitis and sepsis) have only been found in neonates while others have not been observed in the larger controlled trials. In Table 1 we list the adverse effects of vitamin E, which appear to be most commonly reported in adults.

Drug interactions are rare with vitamin E. A recent trial\textsuperscript{24} demonstrated that antioxidants have a blunting effect on lipid-lowering agents. The study randomized 160 patients to one of four groups: 1) simvastatin and niacin (S-N); 2) S-N + antioxidant cocktail (S-N-A); 3) antioxidant cocktail alone or 4) placebo. The antioxidant cocktail was comprised of
Vitamin E and AD

β-carotene 12.5 mg BID, Vitamin C 500 mg BID, Vitamin E 400 IU BID, and selenium 50 µg BID. Results display a significant blunting effect of the apolipoprotein A1 and high density lipoprotein-2c response with the S-N-A group compared to the S-N group. These results are important considering the number of patients taking both antioxidants and lipid-lowering agents. As previously stated, patients on anticoagulants need careful monitoring of their coagulation status especially at the onset of taking high doses of Vitamin E supplements. Table 1 lists the most potentially important adverse drug interactions of vitamin E.

Current Guidelines

The Canadian Consensus Conference on Dementia stated that although Vitamin E is relatively safe, there was insufficient evidence to recommend it for the treatment of AD. There was a dissenting opinion from the Canadian Consensus Conference Management of Dementing Disorders. Conclusion

The antioxidant effect of vitamin E may play a protective role against oxidative stress and slow the progression of AD, but the current evidence is inconclusive. Although data from animal and observational studies are highly suggestive, there is a lack of convincing evidence from multiple randomized-controlled trials to solidify the hypothesis. Vitamin E is relatively safe; however, careful monitoring is required for patients with a Vitamin K deficiency, on anticoagulants or taking lipid-lowering agents. If used for AD, a dose of 2000 IU /d would be suggested since this dose appears safe and a lower dose has not been studied for the treatment of AD. New data will hopefully aid in clarifying the utility of Vitamin E for AD.

References