

Vitamin E and Alzheimer disease: the basis for additional clinical trials¹⁻³

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ABSTRACT Many lines of evidence suggest that oxidative stress is important in the pathogenesis of Alzheimer disease. In particular, β -amyloid, which is found abundantly in the brains of Alzheimer disease patients, is toxic in neuronal cell cultures through a mechanism involving free radicals. Vitamin E prevents the oxidative damage induced by β -amyloid in cell culture and delays memory deficits in animal models. A placebo-controlled, clinical trial of vitamin E in patients with moderately advanced Alzheimer disease was conducted by the Alzheimer's Disease Cooperative Study. Subjects in the vitamin E group were treated with 2000 IU (1342 α -tocopherol equivalents) vitamin E/d. The results indicated that vitamin E may slow functional deterioration leading to nursing home placement. A new clinical trial is planned that will examine whether vitamin E can delay or prevent a clinical diagnosis of Alzheimer disease in elderly persons with mild cognitive impairment. *Am J Clin Nutr* 2000;71(suppl):630S-6S.

KEY WORDS Alzheimer disease, vitamin E, oxidative stress, free radicals, β -amyloid, clinical trials, mild cognitive impairment, Alzheimer's Disease Cooperative Study, elderly

INTRODUCTION

The purpose of this article is to summarize the rationale for conducting further clinical trials to assess whether vitamin E supplementation can slow or prevent Alzheimer disease (AD). AD is a neurodegenerative disorder associated with aging and characterized by progressive memory loss and cognitive deterioration. Pathologic examination of the brains of AD patients reveals generalized atrophy, neuritic plaques (dystrophic axons and dendrites surrounding an amyloid core), and neurofibrillary tangles (paired helical filaments). Oxidative stress, which occurs when there is an imbalance between antioxidants and reactive oxygen species within a cell, may lead to permanent cellular damage. The first indication that oxidative stress may be important in the pathogenesis of AD was the observation that aging itself is associated with increased free radical formation and the fact that the prevalence of AD increases markedly after the age of 65 y (1). Although other risk factors for AD have been identified, the increased incidence of AD with advancing age is a universal characteristic, even with genetic forms of the disease.

A commonly held hypothesis regarding the development of AD is that it is due to altered processing of the amyloid precursor

protein (APP), which leads to excessive β -amyloid formation or aggregation (2). Several genes are known to cause AD in a small percentage of patients. All these genes (ie, the APP gene on chromosome 21, the presenilin 1 gene on chromosome 14, and the presenilin 2 gene on chromosome 1) are associated with an increase in β -amyloid formation. The apolipoprotein (apo) E-4 genotype is a significant risk factor for AD. Similar to the other genes that cause AD, the *APOE*E4* allele is associated with increased amyloid deposition. A proposed mechanism of β -amyloid toxicity is that it induces free radicals, which disrupt cellular lipid, protein, and DNA.

In addition to β -amyloid, several other processes may also induce oxidative stress in AD. Activated microglial cells found in association with neuritic plaques may release cytokines, prooxidants, and free radicals (3). Energy deprivation from impaired glucose utilization or defects of oxidative metabolism may result in increased free radical production (4). Destabilization of the neuronal cytoskeleton may lead to dying back of axons and loss of trophic factor stimulation (5). The absence of trophic factor stimulation may lead to cell death through a mechanism involving free radicals (6). Ultimately, several etiologic hypotheses related to β -amyloid, cytoskeletal destabilization, energy failure, or toxic inflammatory responses may all converge in a common final pathway involving free radicals.

Clinical trials and epidemiologic studies suggest that several agents may help prevent the development of AD or slow further deterioration. These agents include vitamin E, selegiline, estrogen, and antiinflammatory drugs. Although these agents differ structurally and are from variable drug classes, one property they share is the ability to protect against free radical-mediated cellular injury either directly or indirectly.

EVIDENCE OF OXIDATIVE DAMAGE TO THE BRAIN IN ALZHEIMER DISEASE

The polyunsaturated fatty acids of membrane lipids are prime targets for reactive oxygen species and peroxide radicals. The

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²Supported by the National Institutes of Health (grant U01-AG10483).

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central nervous system is particularly vulnerable to lipid peroxidation because of its high lipid content and unusually high proportion of polyunsaturated fatty acids (7). In AD patients, concentrations of malondialdehyde, a measure of lipid peroxidation, are elevated (8, 9). Lipid peroxidation may promote the formation of additional reactive oxygen species and enhance protein and DNA oxidative damage. Studies in which spin trapping techniques were used showed oxidative damage to proteins (10). Other studies showed a 50% increase in oxidative damage to nuclear DNA and a 3-fold increase in oxidative damage to mitochondrial DNA in the cerebral cortex of AD patients as measured by 8-hydroxy-2-deoxyguanosine concentrations (11). The activity of heme oxygenase (decyclizing) (EC 1.14.99.3), an enzyme induced by oxidative stress, is also elevated in the brain of AD patients (12).

Neurons in particular are sites of extensive damage not only by reactive oxygen species but also by reactive nitrogen species. Nitrotyrosine is present in both neurons that contain neurofibrillary tangles (13) and those that do not (14). Nitrotyrosine can be produced by the effects of peroxynitrite on tyrosine. Peroxynitrite itself is a product of superoxide ions and nitric oxide, the latter being an important neurotransmitter and, like superoxide ions, a product formed in abundance at sites of inflammatory-immune activation. Alternatively, peroxidases (15), including leukocyte myeloperoxidase (16), can nitrate proteins, presumably by reacting with the nitrite ion, a product of nitric oxide bioactivity. Myeloperoxidase has been shown to be present at sites of other degenerative neurologic diseases accompanied by activation of the inflammatory and immune systems (17). Nitration of protein tyrosine moieties renders proteins dysfunctional, thereby contributing to early neuronal cell death. Neurons stain positive to antibodies to heme oxygenase-1 and malondialdehyde (18–20). Additionally, neurons bearing neurofibrillary tangles stain positive to antibodies to advanced-glycation end products (20) and protein carbonyls (21). Neurofibrillary tangles also stain positive to antibodies to superoxide dismutase and catalase, enzymes that protect against oxidative stress (22, 23).

SOURCES OF INCREASED OXIDATIVE STRESS IN ALZHEIMER DISEASE

Deposition of β -amyloid is a constant feature in the brains of AD patients. β -Amyloid is derived from APP, a widely expressed membrane glycoprotein. APP may be processed by a nonamyloidogenic pathway involving a protease known as α -secretase or by the activity of 2 other proteases, β -secretase and γ -secretase. Activity of the latter enzymes results in the formation of β -amyloid. The α -secretase cleavage product, sAPP α , has neuroprotective and neurotrophic functions. After β -amyloid is cleaved from APP, it may self-assemble into insoluble fibrils and form plaques. Fibrillar aggregates of β -amyloid are the primary component of neuritic plaques and the fibrillar form of β -amyloid is thought to be toxic (24, 25). β -Amyloid may lead directly to increased free radical formation (26–28) and is toxic in several cell culture systems. β -Amyloid can also stimulate inflammatory cells (microglia) to produce prooxidant species, including reactive nitrogen intermediates (3, 29).

Oxidative phosphorylation is impaired in AD. There is a selective deficiency of cytochrome oxidase, a major component of the respiratory chain, in both platelets and postmortem brain tissue of AD patients (30–33). Mutations in 2 mitochondrial

genes that encode for cytochrome oxidase were found to occur with higher frequency in AD patients than in cognitively normal control subjects. In one experiment, the mutant mitochondrial DNA from AD patients was transferred to cell lines (cybrids) from which the native mitochondrial DNA had been removed. The ensuing cell lines had reduced cytochrome oxidase activity and increased free radical production (34).

Iron can promote the formation of hydroxyl radicals from hydrogen peroxide and several studies have suggested that iron-handling mechanisms are altered in AD (35–37). APP can reduce Cu^{2+} to Cu^+ , which can then contribute to oxidative damage by reacting with hydrogen peroxide to generate hydroxyl radicals (38). Abnormal processing of APP may lead to copper-mediated free radical damage.

Mechanisms to counter the effects of oxidative stress may be altered in AD (23, 39–41). Higher concentrations of glutathione in the hippocampus and higher activity of glucose-6-phosphate dehydrogenase, catalase, and superoxide dismutase in some brain regions of AD patients than in control subjects suggest a compensatory enzyme response after oxidative damage (8, 40). Additionally, the activities of erythrocyte Cu/Zn superoxide dismutase and catalase are significantly increased in the plasma of AD patients (42).

Some reports also indicate that vitamin E status is altered in AD. One group found increased concentrations of vitamin E in the brains of AD patients, suggesting a possible compensatory response to oxidative damage (40), whereas another group found no significant difference between AD patients and control subjects (43). Other studies reported a decrease in plasma concentrations of vitamin E in AD patients (41, 44, 45). It is possible that even marginal vitamin E deficiency increases susceptibility to oxidative stress.

Together, the preceding data suggest that there is increased free radical production and an elevated, but inadequate, compensatory antioxidant response in the brain of AD patients. Ultimately, the oxidative stress proves excessive and results in the observed extensive oxidative damage.

RATIONALE FOR THE USE OF VITAMIN E IN ALZHEIMER DISEASE

Vitamin E is a generic term for a group of naturally occurring tocopherol and tocotrienol derivatives with biologic activity similar to that of α -tocopherol. The natural isomer, *RRR*- α -tocopherol, has the highest bioactivity. The biological activity of 1 mg synthetic *all-rac*- α -tocopheryl acetate is defined as the equivalent of 1 IU vitamin E. One milligram *RRR*- α -tocopherol has a biopotency equivalent to 1.49 IU. The absorption of vitamin E is facilitated by the digestion of dietary fat. In the blood, vitamin E is transported in association with lipoproteins, primarily LDL and HDL. Vitamin E is an essential nutrient in humans. It functions as a natural antioxidant, scavenging free radicals in cell membranes and protecting unsaturated fatty acids from lipid peroxidation. Normal plasma concentrations of vitamin E in humans range from 11.6 to 30.8 $\mu\text{mol/L}$ (46).

As noted in the previous section, β -amyloid can induce cytotoxicity through a mechanism involving oxidative stress and hydrogen peroxide. Vitamin E can block hydrogen peroxide production and the resulting cytotoxicity (28). Vitamin E reduces β -amyloid-induced cell death in rat hippocampal cell cultures (47) and PC12 cells (48) and attenuates excitatory amino acid-induced toxicity in neuroblastoma cells (49).



Neurofibrillary tangles are made up of paired helical filaments composed of a modified form of the microtubule-associated protein tau. Tau within paired helical filaments is characterized by a high level of phosphorylation and glycation (50, 51). The effects of glycation, oxidation, and free radical formation promote the irreversible cross-linking of proteins such as tau and β -amyloid. Antioxidants may be able to prevent this cross-linking (52). Similarly, under oxidant conditions, cysteine residues may facilitate paired helical filament formation by forming a cystine between 2 tau molecules (53). Antioxidants may also inhibit tau cross-linking by preventing the formation of cystine bonds.

Vitamin E concentrations in the brain can be increased by dietary supplementation, as shown by animal experiments. Pillai et al (54) found that dogs treated for 2 y with a vitamin E-supplemented diet had twice the brain concentrations of vitamin E as dogs fed a standard diet. Monji et al (55) found that vitamin E supplementation increased the concentration of vitamin E in rat hippocampus by 50–70%. Other groups found an approximate increase of 50% in vitamin E concentrations in the brains of rats fed a supplemented diet (56, 57).

Furthermore, vitamin E and other antioxidants effectively improve cognitive performance in aged animals and prevent oxidative damage in animal models of AD. Carney et al (58) showed that old gerbils chronically treated with a free radical scavenger (*N-tert-butyl- α -phenylnitron*) have decreased concentrations of oxidized protein in their brains and make fewer errors on tests of memory than untreated animals. Similarly, Socci et al (59) found that aged rats treated with antioxidants, including vitamin E, have greater memory retention than do placebo-treated rats. In another study, vitamin E supplementation was shown to protect against the deterioration in passive avoidance response seen with aging in rats (60). Vitamin E also protects against impaired water maze performance resulting from treatment with a neurotoxin (AF64A) that induces oxidative stress in cholinergic neurons (61). Additionally, dietary vitamin E supplementation reduces lipofuscin accumulation in the brains of middle-aged rats (55) and protects against lipid peroxidation (56). In gerbils, vitamin E prevents ischemic damage to neurons of the hippocampus (62). In transgenic mice expressing human variants of APP, vitamin E delays neurologic deterioration (63).

The Alzheimer's Disease Cooperative Study recently completed a multicenter clinical trial of vitamin E and selegiline supplementation of patients with moderate AD (64). Selegiline is a monoamine oxidase B inhibitor with antioxidant properties, at least in some experimental model systems (65). The primary objective of this study was to determine whether vitamin E or selegiline could slow functional decline. A total of 341 patients with moderately severe disease were enrolled in a double-blind, placebo-controlled, parallel-group, factorial design, multicenter trial. Patients were randomly assigned to receive either vitamin E [2000 IU/d, or 1342 α -tocopherol equivalents (α -TE)/d], selegiline (10 mg/d), both selegiline and vitamin E, or placebo. The primary outcome measure was the time to reach any one of the following endpoints: institutionalization, loss of basic activities of daily living (BADL) as measured by part 2 of the Blessed Dementia Rating Scale (66), severe dementia as defined by a clinical dementia rating of 3 (67), or death. The time to reach an endpoint in each treatment group was compared with the placebo group in an intent-to-treat analysis by using the Cox proportional hazard model.

The risk of reaching the primary outcome was significantly reduced by vitamin E treatment ($P < 0.001$), selegiline treatment ($P < 0.01$), and combined treatment ($P < 0.05$). There was no evidence of additional improvement with combined treatment over each treatment alone. The effect of vitamin E on each of the individual endpoints making up the primary outcome measure was also examined. Compared with the placebo group, the vitamin E group had a favorable hazard ratio and a prolonged time to event for all endpoints.

The study was designed such that there was sufficient power to detect a significant treatment effect only on the primary outcome (time to the first unfavorable endpoint). However, in addition to the significant effects of vitamin E on the primary outcome measure, the comparison of vitamin E with placebo showed a significant treatment effect for delay in institutionalization and a nearly significant effect for delay in the onset of severe dementia. Although significant benefits of vitamin E treatment compared with placebo were found with functional assessments, no significant benefit was shown with cognitive tests. This inability to find a cognitive benefit may have been related to the advanced nature of the disease at the time of study entry and the relatively long, 2-y period of follow up. A large proportion of subjects were unable to complete cognitive testing at the end of 2 y and many had behavioral or functional impairments that might have made it difficult to assess cognition accurately.

The results of this clinical trial indicate that treatment with vitamin E delays the time to important functional endpoints and suggest that vitamin E may slow disease progression in patients with moderately severe AD. The results also highlight the need to determine whether vitamin E might similarly delay symptomatic progression in patients with milder AD, particularly on cognitive measures, and whether it may prevent dementia in elderly individuals who are minimally or not yet cognitively impaired.

DOSING OF VITAMIN E

Given the possibility that vitamin E may be beneficial in preventing or slowing AD, a critical issue to resolve is the optimal dose of vitamin E required for this purpose. A 2000-IU (1342- α -TE) dose was administered in the Alzheimer's Disease Cooperative Study and in the DATATOP (Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism) clinical trial (68) and was found to be safe in both studies. In 5 other placebo-controlled, double-blind studies (69–73) in which doses of 600–2000 mg vitamin E were administered, no or few specific side effects were observed. In the few clinical studies in which doses higher than this were examined [3000–3200 IU (2013–2147 α -TE)], gastrointestinal complaints (eg, indigestion, gastric distress, severe cramps, and persistent diarrhea) that either necessitated withdrawal of subjects from the study or reduction of the dose administered were noted in up to as many as 25% of cases (74–77). No data are available from controlled trials in which the safety of vitamin E was evaluated at doses of 3000–3200 IU (2013–2147 α -TE) for periods exceeding a few months.

In 2 studies assessing the relations between dose and plasma concentrations (74, 76), no significant difference in plasma vitamin E concentrations was found for doses ranging from 1600 to 3200 IU (1074–2147 α -TE). Pappert et al (74) found that supplementation with 1600 or 3200 IU (1074 or 2147 α -TE) resulted in a three- to fourfold increase in plasma vitamin E concentrations over control values. A similar increase was found in the



Alzheimer's Disease Cooperative Study with 2000 IU (1342 α -TE) vitamin E/d. Experimental work in animals indicates that dietary supplementation with vitamin E increases vitamin E concentrations in the brain by \approx 30–60% of the elevation observed in plasma (55–57). Increases in brain concentrations of 50–100% can be achieved with dietary supplementation (54–57). By extrapolating the results of these animal studies by using plasma concentrations measured in humans receiving \approx 2000 IU (\approx 1342 α -TE) vitamin E/d, it seems possible that a threefold increase in the plasma concentration of vitamin E might result in a \geq 50% increase in the brain concentration of vitamin E in AD patients.

CONSIDERATIONS REGARDING AN ALZHEIMER DISEASE PREVENTION TRIAL

AD is likely similar to other chronic diseases such as atherosclerotic heart disease and cancer that have long preclinical periods during which it may be possible to prevent disease symptoms (1). The first pathophysiologic changes of AD are probably triggered in the decades before the onset of clinical symptoms through genetic, traumatic, anoxic, and possibly other events. Aging, with its associated increase in oxidative stress, may promote the disease process. Eventually, when the pathologic changes are severe enough, clinical symptoms appear. Implicit in this model is the notion that as AD evolves, pathologic changes occur that become fixed. If this model is correct, effective interventions to slow the disease at its earliest clinical stage may prove more valuable than the current, symptomatic treatment approach with acetylcholinesterase inhibitors.

One population in whom testing of potential disease-modifying agents might be most fitting is persons with mild cognitive impairment (MCI). Such individuals have minor cognitive deficits insufficient for meeting the current standard clinical criteria for AD (78). Pathologically, these persons are frequently in the incipient stages of AD, although this is not always the case. Although persons with MCI are at increased risk of developing clinically recognized AD, continued follow-up is usually necessary to determine whether they will continue to manifest cognitive decline or remain stable. This group of subjects is a particularly efficient and cost-effective cohort to target for prevention trials because they constitute a group in whom AD will be diagnosed at a much higher rate than in healthy elderly with no cognitive impairment. A primary prevention study in healthy elderly is expensive and time consuming, requiring thousands of patients. The Women's Health Initiative is currently performing such a study with use of estrogen as a potential preventive agent (79). The study design calls for 39 clinical centers across the United States to recruit \approx 8300 women aged 65–79 y with normal cognition over a 2-y period. Participants will be followed annually for 6–9 y to record the development of dementia. In contrast, a clinical trial to prevent dementia in persons with MCI is estimated to require only 3 y of follow-up with as few as 200–250 subjects per treatment.

A memory deficit is frequently the most prominent feature of MCI. Several investigators have followed persons with MCI to determine whether they are more likely to develop AD over time than persons with normal cognition. Rubin et al (80) followed 16 subjects with a clinical dementia rating of 0.5 (questionable dementia) for \leq 84 mo. Over this time span, 11 persons were shown to have AD on postmortem exam or progressed to a more severe clinical dementia rating. These observations suggest that persons with a clinical dementia rating of 0.5 frequently have

incipient AD. Other investigators observed similar findings. Flicker et al (81) found that patients diagnosed with MCI [with a score of 3 on the Global Deterioration Scale (82)] also had a high likelihood of subsequently developing dementia. Bowen et al (83) reported the rate of conversion to a diagnosis of dementia in 21 patients with isolated memory loss who were followed prospectively. About 48% of subjects developed dementia in a period just exceeding 3 y.

As part of a community registry, 67 persons with MCI were identified and followed longitudinally at the Mayo Clinic Alzheimer's Disease Center (84). The patients were evaluated every 12–18 mo, with follow-up data available for many individuals for \leq 54 mo. At 3 y, \approx 44% of the subjects initially classified as having MCI had dementia. The time required before AD was clinically diagnosed in persons with MCI was also estimated in an analysis conducted by the Alzheimer's Disease Cooperative Study of data collected from its member sites (85). Seventeen centers contributed data with follow-up information on 687 persons: 375 women (55%) and 312 men (45%) with a mean age of 72 y at the time of presentation. The estimated cumulative incidences of AD from the pooled data were 31% at 2 y and 44% at 3 y.

Masur et al (86) found delayed recall to be the best predictor of subsequent dementia in nondemented elderly patients. Tierney et al (87) studied a group of 123 memory-impaired patients longitudinally for 2 y with a research battery of neuropsychologic tests. They similarly found delayed recall to be the best predictor of AD. These studies suggest that delayed recall performance at the time of initial presentation may be a useful predictor of AD.

The presence of the *APOE*E4* allele also appears to increase the risk of developing AD in elderly persons with MCI (84, 87). Assessing *APOE* genotype in therapeutic studies is important for another reason as well; Poirier et al (88) showed that patients without an *APOE*E4* allele are more likely to have a good response to the cholinesterase inhibitor tacrine than patients having the allele. Because *APOE*E4* status may be an important predictor of AD or treatment response to specific agents, stratification of subjects according to the presence or absence of this allele in future studies of persons with MCI appears desirable. Stratification should help to prevent potential imbalances in *APOE*E4* status among treatment groups.

CURRENT PLANS FOR A NEW TRIAL OF VITAMIN E IN ELDERLY PERSONS WITH MILD COGNITIVE IMPAIRMENT

The Alzheimer's Disease Cooperative Study has planned a multicenter, randomized, double-blind, placebo-controlled, parallel-group clinical trial in patients with MCI to determine whether daily vitamin E ingestion can prevent or delay a clinical diagnosis of AD. Plans call for at least 2 treatments: 1) a pharmacologic dose of vitamin E [2000 IU (1342 α -TE)] plus a standard multivitamin and 2) placebo (vitamin E) plus a standard multivitamin. Persons with MCI will be recruited and followed for 3 y; clinical evaluations will be made at 6-mo intervals. The primary study endpoint will be conversion to probable or possible AD according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (89). These criteria are internationally recognized and an accepted standard for the diagnosis of AD. Previous studies showed high interrater agreement and reliability for these criteria (90, 91). It



is expected that $\geq 45\%$ of subjects in the placebo group will convert to AD. Persons who develop AD will be given the option of taking a medication approved by the Food and Drug Administration for the treatment of AD (Aricept; Eisai Inc, Teaneck, NJ) at the time AD is diagnosed. The trial will have $> 80\%$ power to detect a one-third reduction in the rate of conversion to AD in the group receiving high-dose vitamin E compared with placebo. Several important secondary outcome measures will be made to corroborate the primary outcome measure and provide a greater depth of understanding of the trial results. These secondary outcome measures include the Clinical Dementia Rating Scale (66), the Global Deterioration Scale (82), the Mini-Mental State Exam (92), the Alzheimer's Disease Cooperative Study Activities of Daily Living Scale (93), and a standardized neuropsychologic test battery.

The major criteria required for a diagnosis of MCI in the planned Alzheimer's Disease Cooperative Study clinical trial are a history of memory complaints; abnormal memory function not explained by other neurologic, psychiatric, or systemic disorders; and evidence of otherwise normal general cognitive function. At the time of screening, the clinician will elicit a medical history from the patient and an informant. The informant should corroborate a history of memory impairment. Abnormal memory function will be further documented by requiring trial entrants to perform below an education-adjusted score on the Logical Memory II component (delayed paragraph recall) of the revised Wechsler Memory Scale (94). Preliminary findings by the Alzheimer's Disease Cooperative Study and others indicate that this additional criterion should increase the efficiency of the study design by more accurately predicting those subjects with MCI who will develop AD. To be included in the trial, subjects must score ≥ 24 on the Mini-Mental State Exam and the clinician must certify that the subject has generally normal cognitive function beyond impairment in memory. Additionally, subjects may not have a clinical dementia rating > 0.5 (questionable dementia) at the time of entry. Individuals with a history of an elevated prothrombin time or blood coagulation defects secondary to liver disease, vitamin K malabsorption, or anticoagulant use are excluded because of possible deleterious effects of vitamin E on blood clotting in this subgroup.

A select number of oxidative markers will be measured during the study. The purpose of collecting these measurements is to determine whether oxidative status at the time of entry predicts subsequent AD, correlates with clinical outcomes, or is influenced by vitamin E treatment. Assessment of oxidative status will include measurement of plasma concentrations of α -tocopherol (vitamin E) and coenzyme Q as well as other markers.

CONCLUSIONS

The preclinical evidence supporting the use of antioxidants to prevent or slow AD is strong. There is clear evidence for increased oxidative damage in the brain of AD patients and numerous potential sources of excess free radicals that may contribute to this damage. Experiments performed in cell culture and in animals indicate that vitamin E and other antioxidants can prevent free radical-mediated cell death and diminish cognitive deterioration. Vitamin E has an excellent safety record. The results of the previous Alzheimer's Disease Cooperative Study clinical trial in patients with moderate AD suggest that vitamin E delays functional deterioration. These findings suggest that the rationale for another clinical trial now exists to determine

whether vitamin E can prevent the development of dementia in elderly individuals with MCI.

Since this manuscript was submitted, the Alzheimer's Disease Cooperative Study has initiated a multicenter, clinical trial of vitamin E in elderly persons with MCI. The trial has 3 treatment groups and is comparing vitamin E, Aricept, and placebo to determine whether either active treatment is more effective than placebo in preventing or delaying a diagnosis of Alzheimer disease. More information about the trial can be obtained from the author or from the Alzheimer's Disease Cooperative Study World Wide Web site at <http://www.memorystudy.org>. 

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