Review Article

Vitamin E family: Role in the pathogenesis and treatment of Alzheimer's disease

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Abstract

Introduction: Vitamin E family, composed by tocopherols and tocotrienols, is a group of compounds with neuroprotective properties. The exact role in the pathogenesis and the benefit of vitamin E as treatment for Alzheimer's disease (AD) are still under debate.
Methods: A literature search in PubMed, Medline, and Cochrane databases has been carried out. All types of studies, from bench and animal models to clinical, were included.
Results: High plasma vitamin E levels are associated with better cognitive performance, even if clear evidence of their ability to prevent or delay cognitive decline in AD is still lacking. Each vitamin E form is functionally unique and shows specific biological functions. Tocotrienols seem to have superior antioxidant and anti-inflammatory properties compared with tocopherols.
Discussion: The benefit of vitamin E as a treatment for AD is still under debate, mainly because of the inconsistent findings from observational studies and the methodological limitations of clinical trials.
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Keywords: Vitamin E; Alzheimer's disease; Mild cognitive impairment; Aging; Cognition; Supplementation; Treatment; Antioxidant

1. Introduction

In 1922, Evans and Bishop [1] first described a "substance X," lately defined as vitamin E, as a crucial factor for fertility and reproduction in female rats. Thus, vitamin E was scientifically named as tocopherol from the Greek word *tokos* meaning childbirth, *phero* meaning to bring forth, and *ol* ending to indicate the alcohol properties. Since its discovery, vitamin E has been extensively studied to better understand its role in different pathophysiological conditions [2–4]. Most of the data, so far available, are mainly focused on vitamin E lipid-soluble antioxidant activity, thanks to its ability to quench or neutralize excess radicals [5]. However, vitamin E, including eight compounds, claims also several biological roles unrelated to antioxidant properties, being regulators of gene expression and signal transduction and modulators of cell functions via interaction with specific membrane domains. Thus, the vitamin E family has many and complex biological activities and pleiotropic effects [6–10].

The introduction of the free radical theory to explain the pathophysiology of brain aging and neurodegenerative diseases, such as Alzheimer's disease (AD), has propelled a great interest in this vitamin. The theory posits that reactive oxygen species (ROS) and reactive nitrogen species (RNS) are responsible for oxidative and/or nitrosative modifications of several biological molecules and that accumulation of free radical–mediated damage to neuronal components, along with other age-related changes, is one of the main causes of neurodegeneration [11]. As a result, preventing or minimizing oxidative and/or nitrosative stress may counteract the molecular basis of pathological brain aging and subsequent neurodegeneration leading to brain damage, suggesting that vitamin E might be an important preventive and therapeutic strategy.

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In this review, we will consider the existing literature regarding the biological properties of vitamin E and the potential therapeutic and/or preventive role that this natural dietary factor plays in AD.

2. Methods

A literature search in PubMed, Medline, and Cochrane [12] databases of articles published with the medical subject heading keywords "Vitamin E," "Vitamin E and Alzheimer's Disease," "Vitamin E and cognition," "Vitamin E, cognition and aging," "Vitamin E, cognition and AD," and "Vitamin E trial" has been carried out. The keywords were used in all possible combinations to retrieve the maximal number of articles. All types of studies, from bench and animal models to clinical, were included.

3. Results

3.1. Vitamin E family: Metabolism and biological properties

The term "vitamin E" refers to a family of eight naturally occurring homologues that are synthesized by plants from homogentisic acid. It includes four tocopherols and four tocotrienols. Tocopherols and tocotrienols are subdivided into α, β, γ, and δ forms based on the methyl and hydroxyl substitution in their phenolic rings. α-Tocopherol is the most abundant form found in nature and, at present, the most widely studied [13]. The prevalent sources of vitamin E are vegetable oils, nuts, and seeds, containing all four tocopherol and tocotrienol congeners (α, β, γ, and δ) in different proportions. Common food sources of α-tocopherol are almonds, avocados, hazelnuts, peanuts, and sunflower seeds; of β-tocopherol oregano and poppy seeds; of γ-tocopherol pecans, pistachios, sesame seeds, and walnuts; and of δ-tocopherol edamame and raspberries. Tocotrienols are differentiated from tocopherols by the degree of saturation at the side chains having three double bonds at carbons 3, 7, and 11, whereas tocopherols possess saturated phytyl side chains. Tocotrienols prevail in rice bran, barley, oats, and palm oil [13]. Other sources of tocotrienols include grape fruit seed oil, oats, hazelnuts, maize, olive oil, Buckthorn berry, rye, flax seed oil, poppy seed oil, and sunflower oil.

Plasma concentration of vitamin E depends on absorption, tissue delivery, and excretion rate. Because all forms of vitamin E are lipid soluble, they are easily absorbed from the intestinal lumen after dietary intake via micelles created by biliary and pancreatic secretions. Vitamin E is then incorporated into chylomicrons and secreted into the circulation where, transported by various lipoproteins, it reaches the liver. Unlike tocopherols, which were distributed equally in all the lipoprotein fractions, tocotrienols are mainly detected in the high-density lipoprotein cholesterol. The estimated α-tocopherol half-life in plasma of healthy individuals ranges from 48 to 60 hours, which is much longer than the half-life of γ-tocopherol (roughly 15 hours). These kinetic data underscore the interesting concept that whereas α-tocopherol levels are maintained, the other forms of vitamin E are removed quite rapidly. Thus, α-tocopherol is regarded as the predominant form to be accumulated in tissues, where other vitamin E congeners are quickly metabolized to carboxychromanols, hydroxycarboxychromanol, and carboxyethylhydroxychroman (for tocotrienols) derivatives. Although the pharmacokinetics of tocotrienols are distinctly different from tocopherols, biodistribution study showed considerable accumulation of tocotrienols in peripheral tissues, such as bones, brain, lung, muscle, and skin. Vitamin E supplements mostly contain α-tocopherol, for which the current recommended dietary allowance is 15 mg/day. A tolerable upper intake level (UL) for any form of supplemental α-tocopherol has been established by the Food and Nutrition Board of the Institute of Medicine to avoid potential side effects. Specifically, the UL of 1000 mg/day of α-tocopherol in any supplemental form corresponds to the highest dose unlikely to result in hemorrhage in almost all adults. The safe dose of various tocotrienols for human consumption is estimated to be 200–1000 mg/day. Because of possible interference, it is recommended for tocotrienols to be taken approximately 6 hours apart from tocopherol-containing supplements [14].

All forms of vitamin E meet the chemical definition of an antioxidant moiety: "chain-breaking free radical scavenger," as demonstrated in conventional in vitro systems. Oxidative stress, defined as the imbalance between generation of reactive species and antioxidant defense, leads to damage of DNA and of proteins and lipids and it is thought to be involved in the pathogenesis of AD [15–17]. Vitamin E is widely accepted as one of the most potent antioxidant in nature, but hints for this function in vivo are scarce. The antioxidant property is related to the hydroxyl group of the aromatic ring of tocochromanols, which donates hydrogen to neutralize free radicals, such as ROS. The antioxidant activity of α, β, and γ isoforms of both tocopherol and tocotrienol is similar, except the δ isoform that has weaker activity [18,19]. Underscoring the importance of viewing vitamin E as a family is the evidence that γ-tocopherol and tocotrienols claim functions different from those of α-tocopherol. In fact, γ-tocopherol appears to be more efficient compared with α-tocopherol in increasing superoxide dismutase activity in plasma and in tissues [20]. Importantly, many studies have demonstrated the superiority of α tocotrienol over α-tocopherol in neutralizing the peroxyl radicals and lipid peroxidation, as shown in rat liver, whereas γ-tocotrienol elicited stronger protective effect against oxidative damage in brain mitochondria (reviewed in Brigelius-Flohé [18]). Being the main lipid-soluble antioxidant, vitamin E has a prominent role in protecting cellular membranes, which could be crucial in mitochondria, the main source and elective target of free radicals. Whether the antioxidant potential of vitamin E family is used in vivo for protection against oxidative damage is still an open question. In fact,

currently available markers of oxidative damage appear unable to disclose the antioxidant effects of tocopherols in vivo.

However, vitamin E biological activity is not limited to antioxidant properties. In fact, vitamin E forms are involved in the regulation of inflammatory response, modulation of cellular signaling, membrane-bound enzymes, gene expression, cell proliferation, and several molecular pathways (reviewed in Brigelius-Flohé [18]). For example, α-tocopherol inhibits the activation of the protein kinase C by preventing its phosphorylation and its localization to the membrane. α-Tocopherol was shown to enhance the protein phosphatase 2A (PP2A) activity, an enzyme that is implicated in AD pathophysiology [21]. Vitamin E regulates the expression of specific genes not only related to oxidative stress but also involved in cholesterol homeostasis, inflammatory pathways, and cellular trafficking, including of synaptic vesicular transport and neurotransmitter release. Genes found to be regulated by α-tocopherol include those encoding proteins involved in apoptosis (CD95L and Bcl2-L1), cell cycle regulation (p27, cyclin D1, and cyclin E), cell adhesion (E-selectin, L-selectin, ICAM-1, VCAM-1, and integrins), cell growth (CTGF), extracellular matrix formation and/or degradation (glycoprotein IIb, MMP-1, and MMP-19), lipoprotein receptors (CD36, SR-BI, SR-AI/II, and LDL receptor),

inflammation (IL-1β, IL-2, IL-4, and TGF-β), transcriptional control (PPARγ), metabolism (CYP3A4, HMG-CoA reductase, and γ-glutamylcysteine synthetase), and other processes (leptin and β-secretase in neurons) [22]. Each vitamin E form is functionally unique and shows specific biological functions as summarized in Table 1. In summary, tocotrienols seem to have superior antioxidant and anti-inflammatory properties over α-tocopherol, and the potential neuroprotective role of vitamin E family can be explained by biological properties other than the antioxidant activity.

3.2. AD pathogenesis: A role for vitamin E

AD is a neurodegenerative disorder associated with aging and characterized by progressive memory loss and cognitive deterioration. Among the hypothetical mechanisms involved in the cognitive decline and AD pathogenesis, are the increased oxidative stress and inflammation that may ultimately lead to neuronal death. The polyunsaturated fatty acids of membrane lipids are the main targets for ROS and peroxide radicals, which make the brain particularly vulnerable to oxidative damage. In patients with AD, concentrations of malondialdehyde, a measure of lipid peroxidation, are indeed significantly elevated [23]. Moreover, neurons are sites of

Table 1
Biological properties of tocopherols and tocotrienols

Vitamin E forms	Biological properties (putative mechanisms)

Tocopherols	• All forms
	  - Antioxidant (increase in the activity of antioxidant enzymes and quenching and scavenging of free radicals)
	• α-Tocopherol
	  - Anti-inflammatory activity (IL-6, CRP, and VEGF reduction)
	  - Modulation of cell proliferation and differentiation (PKC inhibition, MAP kinase, and PI3 kinase activation)
	  - Regulation of bone remodeling
	  - Neuroprotective (PP2A modulation)
	• γ-Tocopherol
	  - Anti-inflammatory activity (modulation of cytokines expression: IL-6, CRP, and VEGF reduction)
	  - Anti-neoplastic activity (modulation of signal transduction, apoptosis, and cell proliferation)
	• δ-Tocopherol
	  - Antineoplastic activity (modulation of signal transduction, apoptosis, and cell proliferation)

Tocotrienols	• All forms
	  - Antioxidant (increase in the activity of antioxidant enzymes and quenching and scavenging of free radicals)
	  - Cholesterol-lowering activities (inhibition of HMG-CoA reductase activity)
	  - Anti-inflammatory activity (suppression of NF-κB, TNF-α, IL-1, IL-6, IL-8, iNOS, and Cox2)
	  - Antineoplastic activity (activation of caspases)
	• α-Tocotrienol
	  - Immunostimulatory (induction of antibody and IFN-γ, IL-4, and IL-1β production)
	  - Antineoplastic activity (suppression of HMGR activity and inhibition of angiogenesis)
	  - Neuroprotective (inhibition of PP 60 [c-Src] kinase activity, phosphorylation of Erk, and inhibition of 12-lipoxygenase activity)
	• γ-Tocotrienol
	  - Antineoplastic activity (inhibition of NF-κB, TGF-β, and P38 signalling pathways; induction and potentiation of apoptosis; downregulation of Bcl-2 and cyclin D; suppression of HMGR activity; and inhibition of cell proliferation through cell cycle arrest)
	  - Neuroprotective (inhibition of 12-lipoxygenase activity)
	• δ-Tocotrienol
	  - Anti-neoplastic activity (induction and potentiation of apoptosis and inhibition of cell proliferation through cell cycle arrest)
	  - Immunostimulatory (suppression of TNF-α)

Abbreviations: CRP, C-reactive protein; HMG-Co A, hydroxy-methylglutaryl coenzyme A; HMGR, hydroxy-methylglutaryl reductase; IL, interleukin; INF, interferon; Inos, inducible nitric oxide synthase; MAP, mitogen activated protein; NF-κb, nuclear factor kappa-light-chain-enhancer of activated B cells; PI3, phosphoinositide 3; PKC, protein kinase C; PP2A, protein phosphatase 2A; TGF, tumor growth factor; TNF α, tumor necrosis factor α; VEGF, vascular endothelial growth factor.

extensive damage not only by ROS but also by RNS. Deposition of amyloid β (Aβ) is a constant feature in the brains of patients with AD, which leads directly to increased free radical formation and indirectly stimulating inflammatory cells (microglia) to produce prooxidant species, including reactive nitrogen intermediates. Some studies also indicate that vitamin E status is altered in AD where an increased concentrations of vitamin E in the brains and decrease in plasma of AD patients have been observed, suggesting a possible compensatory response to oxidative damage [24]. Although it remains an open question what initiates and propagates oxidative stress in AD, multiple antioxidant strategies have been tried in recent decades to assess potential beneficial effects against AD onset and/or progression. Vitamin E is able to decrease lipid peroxidation susceptibility by 60% in AD patients compared with controls [25]. Postmortem analysis of cerebrospinal fluid also reveals that α-tocopherol levels positively correlate with perceptual speed and AD pathology in patients [26]. Application of vitamin E in rat neuronal cultures prevents Aβ-associated ROS from forming and decreases oxidative stress markers [27].

The inflammatory pathways also seem to be involved in AD pathogenesis [28], and some vitamin E forms exhibit strong anti-inflammatory properties. Increased levels of proinflammatory cytokines (such as IL-1, IL-6, and TNF-α) have been detected in brain tissue and cerebrospinal fluid of patients with AD. Both TNFα and IL-1 can then increase expression of amyloid precursor protein and Aβ peptide [28]. Thus, it is reasonable to hypothesize that anti-inflammatory agents, including vitamin E, might reduce the probability of developing AD or slow its progression.

Modulation of cellular signaling can also be relevant for neuroprotection. Interestingly, studies conducted in rats demonstrated that in the hippocampus, vitamin E deprivation is associated with the expression of a number of genes linked to the onset and progression of AD. These genes were then identified as important regulators of hormone metabolism, apoptosis, growth factors, neurotransmission, and Aβ metabolism [29]. Concordantly, further studies showed that low α-tocopherol levels in the brain induce downregulation of genes involved in myelination and synaptogenesis, neuronal vesicle transport, and glial functions [30]. A more recent study, based on both in vitro and in vivo experiments, using animal models mimicking the human vitamin E deficiencies, confirmed a mechanism by which vitamin E protects against the formation of hyperphosphorylated tau, a well-established biomarker of AD through the inhibition of p38MAPK, whose activity is essential for phosphorylation of neuronal tau molecules [31].

Indeed, vitamin E and related tocopherols and tocotrienols inhibit several AD-relevant enzymes, which include COX2, implicated in neuroinflammation, oxidative damage, and the development of AD pathology [32–34]. Moreover, vitamin E activates PP2A, a phosphatase that plays a significant role in tau homeostasis and has been shown to be downregulated in human AD brains [21]. Thus, vitamin E, combining all the described activities, may exert preventive and therapeutic effects in AD pathogenesis.

3.3. Vitamin E, cognitive performance, and AD: The evidence from observational studies

Several studies investigated the association between vitamin E serum levels and cognitive performance (Table 2). The importance of adequate nutrition in support of healthy brain function was first described in the 1980s, when it was demonstrated as a direct link between nutritional status and cognitive performances. In old age subjects (over 60 years), a positive relationship between cognitive performance and plasma nutrient concentrations (including folate, vitamin B12, and vitamin C) was found [35]. Later, a study involving a multiethnic population in the United States showed that memory performances were linked to vitamin E and not to vitamin C and β-carotene. Precisely, poor memory performance was consistently evident when low plasma levels of vitamin E were detected [36]. Further evidence emphasize the positive role of vitamin E in brain healthy function, when high levels of α-tocopherol have been found in plasma of cognitively normal centenarians [37,38], what suggests the beneficial property of vitamin E on cognition. Finally, another evidence of a positive association between vitamin E status and cognitive function was found in a small study including cognitively healthy elderly subjects. Subjects with vitamin E intakes less than 50% of the recommended daily intake showed worse cognitive performances compared with subjects with a higher intake [39]. In general, no consistent results from supplements intake were found, whereas many studies on intake from food showed reduced risk of cognitive decline and/or AD.

Based on these strong evidences, several studies evaluated the association between vitamin E and AD. A study by Engelhart et al. [40] showed a lower risk of developing AD in individuals consuming food with a high content of vitamin E and C (vitamin E >15 mg/day) and followed for a period of 6 years. Dietary intake was assessed by means of a validated semiquantitative food frequency questionnaire. A further study conducted in Italy and involving 1033 elderly subjects supported the notion that higher vitamin E plasma levels might provide significant protection against cognitive impairment and dementia [41]. Ravaglia et al. [42] measured baseline plasma tocopherols and their oxidation markers in 761 elderly Italian subjects from a population-based cohort and demonstrated that plasma concentrations of some non-α-tocopherol forms of vitamin E are associated with cognitive impairment in elderly people. The preventive effect of vitamin E with respect to developing AD symptoms was confirmed in a more recent study on cognitively healthy subjects [43]. In this study, Mangialasche et al. [43] investigated the association between plasma levels of all eight forms of vitamin E family and incidence of AD among oldest-old individuals (over 80 years) followed up to

Table 2
Vitamin E, cognitive function, and AD: an overview of observational studies

Study	Population	Vitamin E measure	Results
Perkins et al. (1999)	4809 Non-Hispanic White, non-Hispanic Black, and Mexican-American elderly	Plasma α-tocopherol	Decreasing serum levels of vitamin E were consistently associated with increasing levels of poor memory after adjustment for multiple covariates
Kłapcińska et al. (2000)	Sixteen centenarians (1 male and 15 female subjects aged 101–105 years) living in the Upper Silesia district (Poland)	Plasma α-tocopherol	In comparison with young healthy female adults, the centenarians had significantly higher red blood cell glutathione reductase and catalase activities and higher, although insignificantly, serum vitamin E level
Ortega et al. (2002)	A group of 34 men and 86 women, aged 65–91 years, cognitively healthy	Plasma α-tocopherol	This study shows a relationship between vitamin E status and cognitive function
Engelhart et al. (2002)	A total of 5395 participants who, at baseline, were aged at least 55 years, free of dementia, noninstitutionalized, and had reliable dietary assessment	Plasma α-tocopherol	After a mean follow-up of 6 years, high dietary intake of vitamin E may lower the risk of AD
Cherubini et al. (2005)	A population-based cohort study conducted in Italy. A total of 1033 participants aged at least 65 years	Plasma α-tocopherol	This study supports the notion that higher vitamin E plasma levels might provide significant protection against cognitive impairment and dementia in elderly subjects
Ravaglia et al. (2008)	761 Elderly Italian subjects from a population-based cohort assessed in 1999–2000 for MCI and dementia	Plasma α, β, γ, δ-tocopherol, α-TQ, and 5NGT	Plasma concentrations of some non-α-tocopherol forms of vitamin E are associated with cognitive impairment in elderly people
Mangialasche et al. (2010)	A dementia-free sample of 232 subjects aged 80+ years, derived from the Kungsholmen Project, followed for 6 years	α, β, γ, δ-tocopherol, α, β, γ, δ-tocotrienol, α-TQ, and 5NGT in plasma	High plasma levels of vitamin E are associated with a reduced risk of AD in advanced age. The neuroprotective effect of vitamin E seems to be related to the combination of different forms, rather than to α-tocopherol alone
Mangialasche et al. (2012)	168 AD cases, 166 MCI, and 187 cognitively normal people from the longitudinal multicenter AddNeuroMed study	α, β, γ, δ-tocopherol, α, β, γ, δ-tocotrienol, α-TQ, and 5NGT in plasma	Low plasma tocopherols and tocotrienols levels are associated with increased odds of MCI and AD
Mangialasche et al. (2013)	81 Patients with AD, 86 with MCI, and 86 control individuals were enrolled from the longitudinal multicentre AddNeuroMed study	α, β, γ, δ-tocopherol, α, β, γ, δ-tocotrienol, α-TQ, and 5NGT in plasma	Plasma levels of tocopherols and tocotrienols together with automated MRI measures can help to differentiate AD and MCI patients from control subjects and to prospectively predict MCI conversion into AD
Mangialasche et al. (2013)	Sample of 140 noncognitively impaired elderly subjects derived from the CAIDE study and followed up for 8 years	α, β, γ, δ-tocopherol, α, β, γ, δ-tocotrienol, α-TQ, and 5NGT in plasma	Elevated levels of tocopherol and tocotrienol forms are associated with reduced risk of cognitive impairment in older adults

Abbreviations: AD, Alzheimer's disease; CAIDE, Cardiovascular Risk Factors, Aging, and Dementia; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; α-TQ, α-tocopherylquinone; 5NGT, 5-nitro-γ-tocopherol.

6 years. Results demonstrated that subjects with the highest levels of total tocopherols, total tocotrienols, or total vitamin E had a reduced risk of developing AD in comparison with those with lower levels. Most importantly, this study suggested that the neuroprotective effect of vitamin E was related to the combination of the different forms, rather than to α-tocopherol alone. The same research group reported similar observations with a study showing that low plasma tocopherols and tocotrienols were associated with increased odds of MCI and AD diagnosis, in a European multicenter study gathering 521 individuals [44]. With a more recent study, it has been demonstrated that plasma levels of tocopherols and tocotrienols together with automated magnetic resonance imaging measures can help to differentiate AD and MCI patients from cognitively healthy subjects and to prospectively predict MCI conversion into AD [45]. Indeed, elevated levels of tocopherol and tocotrie-

nol forms were found to be associated with a reduced risk of cognitive impairment in a cohort of older adults derived from the Cardiovascular Risk Factors, Aging, and Dementia study and followed up for 8 years [46].

3.4. Vitamin E, cognitive decline, and AD: The evidence from population-base prospective studies

The relationship of vitamin E dietary or supplemental intake with the risk of cognitive decline and AD has been investigated also in different population-base prospective studies, including self-selected vitamin supplementation and randomized placebo-controlled studies (Table 3). After dietary supplementation (including vitamins C, E, and thiamine), La Rue et al. [47] described a positive association between nutritional status and cognitive performance in an elderly (aged 66–90 years) sample of community residents.

Table 3
Vitamin E, cognitive function, and AD: an overview of population-base prospective studies

Study	Population and follow-up	Outcome	Vitamin E source	Results
Self-selected vitamin supplements				
La Rue et al. (1997)	137 Elderly (aged 66–90 years) community residents followed for 6 years	Cognition	Dietary supplementation	Use of self-selected vitamin supplements is associated with better performance
Morris et al. (2002)	2889 Community residents, aged 65–102 years followed for 3 years	Cognition	Dietary and supplements	Vitamin E intake, from foods or supplements, is associated with less cognitive decline with age
Grodstein et al. (2003)	14,968 Community-dwelling women who participated in the Nurses' Health Study followed for 15 years	Cognition	Supplements	The use of specific vitamin E supplements is related to modest cognitive benefits in older women
Zandi et al. (2004)	3227 Elderly (65 years or older) residents of Cache County	AD	Supplements	Use of vitamin E and vitamin C supplements in combination is associated with reduced prevalence and incidence of AD
Randomized controlled studies				
Sano et al. (1997)	Double-blind, placebo-controlled, randomized, multicenter trial in 341 patients with AD followed for 2 years	AD	Supplementation (α-tocopherol 2000 IU a day)	In patients with moderately severe impairment from AD, treatment with α-tocopherol slows the progression of disease
Petersen et al. (2005)	A double-blind study, including 769 subjects with the amnestic subtype of MCI followed for 3 years. Subjects were randomly assigned to receive vitamin E daily, donepezil daily, or placebo	AD	Supplementation (2000 IU of α-tocopherol daily)	Vitamin E has no benefit in patients with MCI
Kang et al. (2006)	6377 Women 65 years or older from the Women's Health Study and followed for 10 years	Cognition	Supplementation (600 IU α-tocopherol acetate, on alternate days)	Long-term use of vitamin E supplements do not provide cognitive benefits among generally healthy older women
Lloret et al. (2009)	57 AD patients were recruited and divided in 2 groups: placebo or treated with vitamin E per day for 6 months	Cognition AD	Supplementation (800 IU of α-tocopherol per day)	Vitamin E lowers oxidative stress in some AD patients and maintains cognitive status; however, in those in which vitamin E does not prevent oxidative stress, it is detrimental in terms of cognition
Dysken et al. (2014)	Double-blind, placebo-controlled, parallel groups, randomized clinical trial involving 613 patients with mild to moderate AD followed for 5 years	Functional status	Supplementation (2000 IU of α-tocopherol daily)	Vitamin E supplementation results in slower functional decline

Abbreviations: AD, Alzheimer's disease; MCI, mild cognitive impairment.

Morris et al. [48] monitored the cognitive changes of a large number of healthy people (aged 65–102 years) over a period of 3 years in the presence of high and low antioxidant consumption. Diet was assessed using a modified Harvard self-administered food frequency questionnaire that measured usual consumption during the past year of several food items and vitamin supplements. Results revealed a reduced cognitive decline per year in individuals with higher vitamin E intake (obtained by diet and from supplements) compared with subjects with low vitamin E intake [48]. In a larger study, Grodstein et al. [49] analyzed the cognitive performances of women aged 70–79 years after vitamin E and C supplementation for 15 years. Daily doses of vitamin E were determined by using the ranges reported from administrated questionnaires. They defined a very high dose of vitamin E as ≥600 mg. Results showed that users of supplements had significantly better cognitive performances than nonusers and that in the long-term users (>10 years), the effect of consuming vitamin E and C was equivalent, in cognitive performances, to being 1.5 years younger. Importantly, although the intake of vitamins E and C alone showed little evidence of improving the cognitive capacities of users, their combination was necessary to obtain significant effects [49]. In fact, vitamins C and E support each other's antioxidant function. Whereas vitamin E acts as an antioxidant and requires regeneration after it "heals" free radical damage before it can function properly again, the vitamin C, working as a potent reducing agent, is able to restore vitamin E's antioxidant function so that it can continue to fight tissue damage. Indeed, another study further supported that the use of vitamins E and C supplements in combination is associated with reduced prevalence and incidence of AD among elderly subjects [50].

Taken together, these studies demonstrate that consumption of vitamin E is linked to improved cognitive performance in humans. In light to such evidences, clinical trials

examined the efficacy of vitamin E supplementation to treat patients with AD. One of the first randomized controlled trials (RCTs) treated patients suffering from severe AD with selegiline and vitamin E (α-tocopherol 1000 IU twice per day) for 2 years [51]. Vitamin E supplementation significantly delayed decline in daily life activities and reduced needs for care. However, no improvements on cognitive test scores were observed in this study, maybe because of the relatively advanced severity of AD in this population. The results associated with vitamin E supplementation in patients with severe AD prompted investigating if similar effects that are even more beneficial could also be obtained in early stages of AD or, better, in prodromic phase such as mild cognitive impairment (MCI). To this purpose, Petersen et al. [52] enrolled subjects with amnestic MCI from the Alzheimer's Disease Cooperative Study, who was treated with 2000 IU/day of vitamin E or placebo for 3 years. This study failed to demonstrate any significant difference in the progression from MCI to AD after vitamin E supplementation. No unexpected side effects were observed after vitamin E treatment. A substudy of the Women's Health Study, a double-blinded, placebo-controlled, randomized trial of vitamin E supplementation with a 10-year duration that aimed at evaluating the cognitive performance of a large number of elderly healthy women randomized to receive vitamin E (α-tocopherol acetate) 600 IU every other day with a follow-up period of 4 years, showed that compared with the placebo group, the vitamin E group did not have a lower risk of substantial cognitive decline [53]. However, this study showed fewer adverse cognitive changes when the vitamin E group was compared with the placebo group with dietary intake of vitamin E below the median of 6.1 mg/day. Interestingly, beneficial effects (measured by the absence of cognitive decline over time) after vitamin E supplementation were observed in another AD cohort [54]. Importantly, in this case, the cognitive performance of the participants was constant over time (and even slightly improved) only when the vitamin E antioxidant activity was confirmed to be effective, by measuring blood oxidized glutathione (GSSG). Conversely, deleterious effects (pronounced loss of cognitive abilities) were present when no enhanced antioxidant levels were detected [54]. These results prompted authors to introduce the novel concept of stratifying AD patients into vitamin E respondents and non-respondents, based on measures of plasma GSSG, the oxidized form of the common antioxidant glutathione (GSH). This study highlights the anti-oxidative properties of vitamin E as a possible mechanism of action against AD pathology.

Indeed, the Trial of Vitamin E and Memantine in Alzheimer's Disease has been designed to assess, after 5 years, the efficacy of α-tocopherol or memantine or their combination versus placebo in delaying clinical progression of AD in patients already taking an acetylcholinesterase inhibitor [55]. This study included old age subjects with mild-to-moderate AD. The authors found that 2000 IU/day of α-tocopherol significantly delayed the functional decline and decreased the caregiver burden, confirming data generated in the study of Sano et al. [51] on severe AD patients. Serum concentration of vitamin E at baseline was measured before randomization and in annual assessments. Cut points of 1.3-fold or greater increases in α-tocopherol were associated with a good level of medication adherence. In addition, favorable effects (but not statistically significant) were associated with α-tocopherol treatment when cognitive functions such as memory and language were considered and also the time necessary for the caregivers to assist the patients.

4. Discussion

4.1. Why vitamin E therapy failed for the treatment of AD?

Despite many individuals take daily vitamin E supplements with the assumption that they may maintain a good brain health, the role of vitamin E in prevention and treatment of AD is still unclear and under debate. Two meta-analyses published in 2005 [56] and in 2007 [57], reporting increased mortality in subjects taking high dose of vitamin E, questioned its protective role. However, the meta-analysis published by Miller et al. [56] demonstrated that only the smaller trials showed either an increase or a decrease in all-cause mortality and that the overall effect was near to zero. Thus, the difficulty in performing precise and uniform studies accounts for these conflicting results. On the other hand, several considerations arise from the fact that vitamin E therapy is ineffective for some or outright detrimental for others. The data on randomized therapy are very limited and depend on small patient cohorts. For example, in the study by Lloret et al. [54], the sample size was very small, vitamin E supplementation included 800 IU/day, as opposed to 2000 IU/day in the other studies, and the supplementation period was 6 months, whereas in other studies, supplements were given for approximately 2 to 3 years.

Moreover, the two positive studies, by Dysken et al. [55] and Sano et al. [51], have weaknesses that should be considered. In the first one, vitamin E was beneficial only in patients not receiving memantine therapy compared with those receiving memantine and a convincing rationale was lacking. In the second one, there were large differences in baseline MMSE values between patients receiving placebo and those receiving vitamin E or selegiline. Consequently, also selegiline, which is not considered to enhance cognitive deficits, resulted beneficial. However, an important parameter that can influence the outcomes of such studies relates to the form of administered vitamin E. In these cases, the same form of vitamin E (DL-α-tocopherol) was used, and in both, the α-tocopherol status of the subjects was measured in serum. This uniformity contributes to an easy comparison of the two studies. This information, however, was not reported in the other reports reviewed, even when the

measurement of the vitamin E levels would have been useful for a comprehensive understanding of the proposed results.

Another factor complicating direct comparison of the outcomes on human data is the baseline level of vitamin E. Several epidemiological studies indicate that vitamin E from food sources is more effective at preventing age-related neurodegenerative disorders than supplementation [58]. This idea is supported by the fact that vitamin E from food sources usually comprises all tocopherols and tocotrienols, whose properties and possible functions are different [59]. Although α-tocopherol is the most abundant and bioavailable form of vitamin E in human tissues, it was demonstrated that tocotrienols may be more potent radical scavengers than α-tocopherol under specific experimental conditions [58,60,61]. Taken together, differences between RCTs and observational studies could be because of the varying chemical forms present in the supplements and in food and their bioavailability. In addition, the combination of nutrients from food, as seen in observational studies, may have interactive and synergic effects on health. Such beneficial effects may be masked or mitigated in supplementation trials [62].

4.2. Conclusions and future directions

About 100 years since the discovery of vitamin E, its functional roles in the brain still require investigations. More specifically, in spite of the strong biological plausibility of a possible neuroprotective activity, the role of the different forms of vitamin E family in protecting from AD is still unclear. In recent years, the isolation and identification of various forms of tocopherols and tocotrienols and the consideration of vitamin E as a family have been strongly impacted in the effort to establish biological effects behind the primary role as an antioxidant. Most studies have focused on α-tocopherol, and few studies have examined all eight natural vitamin E forms in relation to cognitive decline and/or AD.

Experiments with vitamin E in vitro and in animal models support the role of this molecule in mitigating the effects of AD pathology. Most of the human observational epidemiological studies in general are consistent with the hypothesis that there is an inverse correlation between vitamin E levels and/or intake and decline in cognitive functions and risk to develop dementia. In sharp contrast, randomized clinical trials with vitamin E apparently do not fully support this evidence. More research aimed at defining the uses and the dosage of different tocopherols and tocotrienols in prospective interventional studies is warranted for conclusive results.

Acknowledgments

RESEARCH IN CONTEXT

1. Systematic review: A literature search in PubMed, Medline, and Cochrane databases of all articles published with the medical subject heading keywords "Vitamin E," "Vitamin E and Alzheimer's Disease," "Vitamin E and cognition," "Vitamin E, cognition and aging," and "Vitamin E, cognition and AD" has been carried out. The keywords were used in all possible combinations to retrieve the maximal number of articles. All types of study designs were included.

2. Interpretation: The exact role in pathogenesis and the benefit of vitamin E as treatment for Alzheimer's disease (AD) is still under debate. In this review, we focus on the most important studies that have contributed to clarifying such aspects.

3. Future directions: More research aimed at defining the use and the dosage of different tocopherols and tocotrienols in prospective interventional studies is warranted to better clarify the role of vitamin E family in prevention and treatment of AD.

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