

# Vitamin E in ataxia and neurodegenerative diseases: A review\*

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## ABSTRACT

Vitamin E is one of the most important lipid-soluble antioxidants. It is essential for the neurological function but its role in the central nervous system has not fully been elucidated. It is known that tocopherol acts in protecting cell membranes from oxidative damage and it can act as an anti-inflammatory agent, which may also be neuroprotective, as well as regulating specific enzymes. There is growing evidence that oxidative stress plays a key role in the pathophysiology of several neurodegenerative disorders. These diseases are defined by the progressive loss of specific neuronal cell populations and are associated with protein aggregates. We reviewed some aspects related to the role of antioxidant properties of Vitamin E in preventing and/or curing neurodegenerative disorders such as the Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, ataxia, tardive dyskinesia and Huntington's disease.

**Keywords:** Vitamin E; Neurodegenerative Diseases; Ataxia with Vitamin E Deficiency

## 1. INTRODUCTION

Vitamin E is the major chain-breaking antioxidant in body tissues and is the first line of defense against lipid peroxidation, protecting cell membranes from free radical attacks through its free radical quenching activity.

It protects polyunsaturated fats in cell membranes that are important for membrane structure and function. Increased intake of Vitamin E enhances immune response.

And, Vitamin E regulates platelet aggregation by inhibiting the platelet cyclooxygenase activity and thus decreases the prostaglandin production. It also has a role in

the regulation of protein kinase C activation.

## 2. PHYSIOLOGY

Vitamin E is an essential fat-soluble Vitamin. Recently, the National Academy of Sciences defined Vitamin E as the 2R stereoisomers of alpha-tocopherol. However, past classifications of Vitamin E included a group of eight compounds—alpha-, beta-, gamma- and delta-tocopherols and tocotrienols. The naturally occurring d-alpha-tocopherol has the highest biological activity [1].

The ability of an individual to absorb Vitamin E is dependent on the ability to absorb fat. Vitamin E is absorbed passively into the lymphatic system from the small intestine and enters the blood as a component of the chylomicrons [2]. The majority of Vitamin E in plasma is in the low-density lipoproteins. Alpha-tocopherol is the major tocopherol in adult plasma and accounts for approximately 87% of the total tocopherol concentration.

There is a positive association between serum lipid levels and tocopherol levels [3]. Vitamin E concentrations in body tissues vary considerably. Adipose tissue and adrenal glands have the highest levels. It is found primarily in mitochondria. It is thought to play a role there in either stabilizing ubiquinone, or in helping ubiquinone transfer electrons. The elimination of this end product is primarily through the feces but a small fraction is removed by urine (<1%). Vitamin E levels in plasma range from 0.5 - 1.6 mg/dl in normal populations. Vitamin E does not have a specific carrier protein in the bloodstream but it is transferred by hepatic and lymphatic mechanisms. Additionally, Vitamin E is the most effective lipid-soluble antioxidant, protecting membranes from free radical and lipid peroxidation induced damage, thus preventing the atherogenesis and helping protect against the hardening of the arteries, heart attacks, and stroke.

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### 3. CLINICAL VITAMIN E DEFICIENCY

Deficiency states arise either from malabsorption or in association with a defective ATT protein; the latter is responsible for autosomal recessive ataxia with Vitamin E deficiency, AVED [4,5].

#### 3.1. Malabsorption Syndrome

Clinical Vitamin E deficiency that is alleviated by Vitamin E administration is seen in individuals with chronic malabsorption syndrome, premature infants and patients on Total Parenteral Nutrition (TPN). Conditions that interfere with normal digestion, absorption or transport of fat have been associated with low serum levels of Vitamin E. Serum Vitamin E concentrations can be less than 20% of normal in individuals with malabsorption syndromes such as celiac disease, cystic fibrosis and biliary atresia, cholestatic liver disease [6], CVID patients, with enteropathy and gastrectomy [7-9]. Patients with abetalipoproteinemia frequently have very low serum Vitamin E concentrations, below measurable levels.

#### 3.2. Clinical Features

Clinical features of symptomatic Vitamin E deficiency include pigmentary retinopathy, limb ataxia, hypoflexia, limb weakness, loss of proprioception, loss of fine touch and paraesthesia and rarely myoclonic dystonia [10].

Symptoms of neurological dysfunction develop within 18 - 24 months in children with Vitamin E deficiency but in adults, symptoms may develop after approximately 10 - 20 years of malabsorption [10]; indicating the length of time required for depletion of Vitamin E stores and for accumulation of clinically significant neuronal damage.

Neurological function has been shown to improve with appropriate Vitamin E therapy and progressive neurological damage may be prevented by initiation of Vitamin E therapy at an early age in children with chronic cholestatic disease [7]. Doses of replacement Vitamin E needed to normalize serum concentrations in patients with documented Vitamin E malabsorption range from 100 to 200 I.U.  $\text{kg}^{-1}\cdot\text{day}^{-1}$  orally and from 1 to 2  $\text{mg}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$  parenterally [11].

### 4. SOURCES, INTAKES

#### 4.1. Sources

The richest dietary sources of Vitamin E are vegetable oils (primarily soy, sunflower and corn oils), sunflower seeds and nuts.

#### 4.2. Recommendations

The 1989 Recommended Dietary Allowance (RDA) for Vitamin E was 10 mg (15 I.U.) for men and 8 mg (12

I.U.) for women. The 2000 RDA, which is also the Dietary Reference Intake (DRI) for Vitamin E, is 15 mg alpha-tocopherol (22.5 I.U.) for both men and women. [12].

Dietary Vitamin E intakes of 10 - 30 mg per day will maintain serum Vitamin E concentrations in the normal range. However, a number of studies have shown that Vitamin E intakes considerably above these recommended levels have a beneficial role in the prevention of chronic diseases and conditions in which free radical-mediated cell damage is implicated in their development. Additional dose-dependent studies will help to determine optimal Vitamin E intakes, which may be in the range of 100 I.U. - 400 I.U. per day [1].

#### 4.3. Natural-Source vs Synthetic Vitamin E

Vitamin E is the exception to the paradigm that natural and synthetic Vitamins are equivalent. Natural-source Vitamin E (RRR-alpha-tocopherol or d-alpha-tocopherol) is derived from vegetable oils and is a single isomer. Synthetic Vitamin E (all-rac-alpha-tocopherol or dl-alpha-tocopherol) is a mixture of eight isomers, only one of which is d-alpha-tocopherol. The 2000 National Academy of Sciences report recognizes four of the eight isomers (2R isomers) to have Vitamin E activity and the other four isomers to have none.

Physiological differences between natural-source and synthetic Vitamin E relate to preferential retention of d-alpha-tocopherol in blood and tissues compared to other tocopherols.

#### 4.4. Safety [13]

Since Vitamin E intakes considerably above those needed to prevent deficiency are taken by many individuals over long periods of time to help prevent free radical-mediated conditions and diseases and to maintain health, safety is an important consideration. In double-blind, placebo-controlled human studies, very few observed side effects were seen with oral daily intakes of 600 I.U. - 3200 I.U. for three weeks to six months. Side effects associated with Vitamin E were also uncommon in other human studies.

Although high Vitamin E intakes have not been demonstrated to cause abnormalities in blood clotting in normal adults, they may intensify an existing blood coagulation defect produced by Vitamin K deficiency due to mal absorption or blood thinners. In two clinical trials of patients on blood thinning drugs, Vitamin E intakes of 100 or 400 I.U. in one study and 800 or 1200 I.U. in the other study did not significantly affect blood clotting in these groups. Based on potential effects of Vitamin E on blood clotting, the Tolerable Upper Intake Level (UL) set by the National Academy of Sciences in 2000 for all forms of alpha-tocopherol is 1000 mg per day for adults. Since Vitamin E supplementation could potentially affect

blood clotting in patients on blood thinners, high Vitamin E dosages may be contraindicated for these patients or should be used only under medical supervision. Except for a Vitamin K interaction in patients on blood thinners, there are no specific side effects associated with Vitamin E intake. Thus, based on a review of both animal and human data, oral Vitamin E is safe and well tolerated over a wide range of intakes and over long periods of time.

## 5. PROTECTIVE ROLE IN DISEASE PREVENTION

There is extensive evidence implicating oxidative damage in the development of degenerative diseases and conditions. A number of studies have evaluated the role of Vitamin E, alone or in combination with other antioxidants, in preventing or minimizing oxidative damage associated with development of Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, stroke, ataxia with Vitamin E deficiency and peripheral neuropathy.

### 5.1. Alzheimer's Disease

The exact biochemical mechanism of the pathogenesis of AD is still unknown, but much attention is given to the role of the massive loss of the neurotransmitter acetylcholine and to the possible implication of oxidative stress in its development. Oxidative injury may play a role in Ab deposition and the complex relationships between this event, excitotoxicity, calcium dysregulation and ROS generation in AD have been recently summarized. In addition to the direct induction of oxidative stress, Ab can also indirectly generate an oxidative microenvironment mediated by the local immune response; indeed, cellular and soluble mediators of inflammation are found in post-mortem AD tissue [14].

Oxidative damage is also implicated in brain aging and in development of certain degenerative conditions affecting the brain, such as Alzheimer's disease. Studies have shown that increased intakes or blood levels of Vitamin E were associated with reduced risk of Alzheimer's disease [15].

A multicenter two-year trial evaluated the effects of Vitamin E or the drug selegiline on disease progression in patients with moderately severe Alzheimer's disease. Study results showed that either Vitamin E or selegiline slowed the progression of the disease compared to the placebo group. The researchers concluded that cost and convenience may be involved in treatment decisions since both Vitamin E and selegiline were effective.

The Alzheimer's disease Cooperative Study has initiated a three-year multicenter trial in patients with mild cognitive impairment to evaluate whether Vitamin E can prevent or delay the clinical diagnosis of Alzheimer's

disease [16]. Current clinical practice guidelines from the American Psychiatric Association recommend that Vitamin E or selegiline be considered for patients with moderate Alzheimer's disease to delay the mental deterioration and that Vitamin E may be preferred from a safety standpoint.

### 5.2. Parkinson's Disease

The evidence for the role of oxidative stress in PD patients comes from the selective toxicity against the substantia nigra of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which induces Parkinson's like symptoms in primates. MPTP acts through its metabolite MPP<sup>+</sup>, which inhibits Complex I of the mitochondrial respiratory chain and acts by increasing the vulnerability of cells to oxidative stress [14]. Recent studies show that neurons from PD affected brains accumulate mitochondrial DNA deletions that cause impaired cellular respiration. The putative role of mitochondrial dysfunction and oxidative stress in PD pathogenesis has led to trials of antioxidant and pro-mitochondrial compounds, including coenzyme Q10, Vitamin E and creatine [17].

Studies have demonstrated both Vitamin E-mediated protection and lack of protection.

DATATOP (Deprenyl and tocopherol antioxidative therapy of parkinsonism) was a placebo-controlled clinical trial designed to test the hypothesis that long-term treatment of patients with early Parkinson's disease with deprenyl 10 mg/d and/or  $\alpha$ -tocopherol 2000 I.U./d may extend the time until disability requires therapy with levodopa. After a follow-up of  $14 \pm 6$  months, there was no beneficial effect of tocopherol or any interaction between tocopherol and deprenyl. Conversely, the beneficial and still unexplained effects of deprenyl significantly delayed the onset of disability requiring levodopa therapy [18,19].

More recently, Zhang and co-workers reported that a diet rich in Vitamin E reduces the risk of developing PD. Other studies have shown contradictory results about dietary intake of Vitamin E, Vitamin C and carotenoids and their efficacy to prevent PD progression. Vitamin E is considered to protect against oxidative damage, due to its antioxidants properties. However, based on the available literature, there are many disputes about the efficacy of  $\alpha$ -tocopherol in the prevention and/or treatment of PD [20].

### 5.3. Amyotrophic Lateral Sclerosis

In 1996, data from SOD1 transgenic mice showed that Vitamin E intake slowed the onset and the progression of the disease. More recently, a large prospective study that involved 508,334 men and 676,288 women, indicated that individuals who regularly used Vitamin E supple-

ments for 10 or more years had less than half the risk of death from ALS than nonusers [20]. The results are controversial. Two double-blind, placebo-controlled, randomized trials have been performed, administering to sporadic ALS patients 500 and 5000 mg of Vitamin E per day, respectively. Both trials demonstrated no significant differences with respect to placebo, although a trend toward improvement was shown in those patients receiving Vitamin E [21]. A lack of significant associations between intakes of antioxidant Vitamins and ALS risk was also reported in two case-control studies, but both were too small to estimate the specific effect of Vitamin E supplementation [22].

#### 5.4. Ataxia with Vitamin E Deficiency (AVED)

The symptoms are the consequence of a dying-back neuropathy in sensory neurons and the cerebellum resulting from the loss of the protective effect of Vitamin E against several neurotoxic agents. Muscle fibers are also affected [23].

It is unknown whether the degenerative neurological symptoms in patients with Vitamin E deficiency syndromes are the result of insufficient protection by antioxidants or are due to a lack of specific and non-antioxidant effects mediated by  $\alpha$ -tocopherol. In these diseases, the transport of  $\alpha$ -tocopherol is impaired in either the liver or intestine by the complete absence of a transport pathway, leading to extreme low plasma  $\alpha$ -tocopherol levels [20].

Individuals with an inherent lower efficiency of tocopherol uptake may benefit most from supplemental intake of  $\alpha$ -tocopherol. Moreover, if polymorphisms in transport and/or action of Vitamin E exist, they could significantly affect the outcome of epidemiological studies, in which the initial plasma level and the individual efficiency of uptake and transport of  $\alpha$ -tocopherol often are not known [20]. Adequate Vitamin replacement stops progression and can even ameliorate some of the symptoms, but the more advanced the deficit, the more limited the response to therapy.

AVED resulting from the 744 del A mutation is as frequent in Morocco as FA, it began at an earlier age, and is a clinically distinguishable entity characterized by head titubation, less frequent neuropathy and slower disease progression, as well as decreased visual acuity and retinitis pigmentosa that it shares with AVED caused by H101 Q missense mutations in the  $\alpha$ -TTP gene [24,25].

#### 5.5. Stroke

The meta-analysis of randomized controlled trials of Vitamin E treatment reporting on stroke outcomes indicates that the risk of hemorrhagic stroke is significantly increased by 22% whereas the risk of ischemic stroke is

significantly reduced by 10%. These associations are obscured when total stroke is evaluated as the outcome. Many large randomized controlled trials investigating the effect of Vitamin E on incident major cardiovascular events were performed during the past two decades, but most did not find an overall significant effect. Likewise, two recent meta-analyses did not find an effect on mortality from all causes, cardiovascular death, and stroke from all causes [26]. The Alpha Tocopherol, Beta Carotene Cancer Prevention trial was the first, showing that in male smokers 50 mg/day of Vitamin E increased the risk of hemorrhagic stroke. This result was confirmed in the Physicians' Health Study II, which randomized 14,641 male physicians from the United States to 400 I.U. Vitamin E on alternate days or placebo. Results from the Women's Health Study, which randomized 39,876 apparently healthy women to 600 I.U. Vitamin E on alternate days or placebo, however, do not indicate increased risk of hemorrhagic stroke in women [26]. In this meta-analysis of randomized trials, we found that Vitamin E increased the risk for hemorrhagic stroke by 22% and reduced the risk of ischemic stroke by 10%. Using total stroke as the outcome obscures these harms and benefits. However, given the relatively small reduction in risk of ischemic stroke and the generally more severe outcome of hemorrhagic stroke, indiscriminate widespread use of Vitamin E should be cautioned against [26].

#### 5.6. Peripheral Neuropathy

A randomized, controlled trial was performed to assess the efficacy and safety of Vitamin E supplementation for prophylaxis against Paclitaxel-Induced Peripheral Neuropathy (PIPN). This study shows that Vitamin E effectively and safely protects patients with cancer from the occurrence of paclitaxel-induced peripheral nerve damage. A double-blind, placebo-controlled trial is needed to confirm these results [27].

The clinical use of cisplatin chemotherapy is limited by severe peripheral neurotoxicity reported in up to 90% of patients receiving a cumulative dose higher than 300 mg/m<sup>2</sup>. The phase III of study confirms the neuro-protective role of Vitamin E against cisplatin peripheral neurotoxicity. Vitamin E supplementation should be adopted in patients receiving cisplatin-based chemotherapy. Classification of evidence: This study provides Class II evidence that Vitamin E supplementation significantly reduces the relative risk of developing signs or symptoms of neurotoxicity (relative risk = 0.14) (95% confidence interval = 0.02 - 1.00,  $p < 0.05$ ) [28].

### 6. PERSPECTIVE RESEARCHES

In our department, we are conducting prospective studies

aimed to demonstrate the effectiveness of Vitamin E in neurodegenerative disease.

The first study was interesting 60 patients with amyotrophic lateral sclerosis.

The second study was conducted to evaluate efficacy of Vitamin E in all types of ataxias including AVED form, and finally the profit association of Vitamin E and Vitamin C in multiple sclerosis.

## 7. CONCLUSIONS

As the major fat-soluble antioxidant, Vitamin E is protective against oxidative damage.

It appears that Vitamin E treatments should be started much earlier, continue for a longer period, and be consumed with Vitamin C for its effect to become measurable. The population of choice should be selected according to age, Apo E genotype, gender, and Vitamin E status.

Vitamin E is very interesting drug for: cerebellar ataxia with Vitamin E deficiency in neuropathy after chemotherapy and reduced the risk of ischemic stroke by 10%. But the paradox of benefit of Vitamin E still in other disease: Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis.  $\alpha$ -Tocopherol is beginning to reveal important, non-antioxidant functions. It is possible that novel reactions and novel genes, found to be under  $\alpha$ -tocopherol control, may help and clarify the relationships between molecular and clinical events. A review of safety data has shown that oral Vitamin E is safe and well tolerated over a wide range of daily intake levels.

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