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Vitamin E Serum Levels and Controlled Supplementation and Risk of Amyotrophic Lateral Sclerosis

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Abstract

Objective—There are no observational studies or controlled trials of amyotrophic lateral sclerosis (ALS) and circulating α-tocopherol (vitamin E) for prevention of ALS. This study addresses that gap.

Methods—The study population comprised 29,127 Finnish male smokers, aged 50–69 years, who participated in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study, which is both a prospective cohort and a randomized, double-blind, placebo-controlled trial of α-tocopherol (50 mg/day) and β-carotene (20 mg/day). Serum α-tocopherol and β-carotene was assayed at baseline (1985–1988). Follow-up (median 16.7 years) continued through 2004. ALS cases were identified through the national Hospital Discharge Register with diagnostic verification by hospital records and death certificates.

Results—During 407,260 person-years of follow-up, 50 men were identified with ALS. For men with serum α-tocopherol concentration above the median (≥11.6 mg/l), the age-adjusted relative risk (RR) compared to α-tocopherol below the median, was 0.56 (95% confidence interval= 0.32–0.99), p=0.046. The RR among α-tocopherol supplement recipients was 0.75 (95% CI=0.32–1.79), p=0.52. Neither serum β-carotene level nor β-carotene supplementation was associated with ALS.

Conclusions—The results are consistent with a hypothesized protective effect of α-tocopherol on ALS risk. However, pooled analyses of cohorts with serum and controlled trials are needed to clarify the role of α-tocopherol in ALS risk.

Keywords

Amyotrophic lateral sclerosis; vitamin E; cohort studies; risk factors in epidemiology

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Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive degenerative disease of motor neurons, which is generally fatal within five years of diagnosis.[1] Although several genetic mutations are known to be associated with ALS, the ultimate pathophysiologic causes of ALS remain largely unknown.[2] Oxidative stress, probably interacting with other neurodegenerative processes, is hypothesized to play a leading role in pathogenesis.[3–4] Because of its function as a major antioxidant in cell membranes, including neurons, vitamin E or α-tocopherol (the predominant isoform in blood) has been the focus of experimental, therapeutic, and epidemiologic studies of ALS.

Such studies have suggested some health benefits of α-tocopherol, particularly in delaying or preventing ALS. In a transgenic mouse model of familial ALS that develops a disease with a clinical phenotype similar to ALS, dietary vitamin E supplementation delayed disease onset and slowed progression, although it did not prolong survival.[5] When used as an experimental therapy in human trials, vitamin E did not affect survival significantly,[6–8] but possibly slowed ALS progression.[6–7] Two recent large, prospective epidemiologic studies suggest that long-term use of vitamin E supplements could be inversely associated with risk of ALS [9] or ALS death.[10] However, these cohort analyses were based on recalled historical supplement use. There have been no prospective studies of serum α-tocopherol concentrations and ALS risk, nor controlled prevention trials of α-tocopherol for ALS.

This study addresses these gaps by utilizing baseline serum measurements of α-tocopherol and β-carotene and the controlled trial design of the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study. ATBC was a randomized, double-blind, placebo-controlled, primary-prevention trial of male smokers initiated to determine whether supplementation with α-tocopherol or β-carotene reduces lung cancer or other cancer incidence.[11] The trial had a priori secondary hypotheses about non-cancer outcomes, and provides a basis for evaluating the effects of supplements and serum concentrations on other diseases, such as ALS.

Methods

The ATBC Study was conducted in Finland jointly by the National Public Health Institute of Finland (now National Institute for Health and Welfare) and the U.S. National Cancer Institute. The rationale, design, population, and objectives have been described in detail elsewhere.[11–12] Briefly, the trial recruited a total of 29,133 male smokers, residing in southwestern Finland from 1985 through 1988. Eligibility was limited to men aged 50 to 69 who were smokers. Subjects were excluded if they had any serious disease limiting their capacity to participate, used vitamins E, A or β-carotene supplements in excess of specified amounts or received anticoagulant therapy. For this study we also excluded six men who had signs and symptoms of ALS at study entry, resulting in a cohort of 29,127 men. Prior to randomization, subjects completed a questionnaire on their medical and smoking histories and other characteristics[13]

Participants were randomly assigned to one of four groups (and blinded to treatment assignments): (a) α-tocopherol (50 mg/day synthetic dl-α-tocopheryl acetate); (b) β-carotene (20 mg/day all trans-β-carotene); (c) both supplements; or (d) placebo. Compliance with the supplementation regimen was good: 88% of men took more than 90% of prescribed capsules during the trial, and intervention groups did not differ in capsule compliance.[11] Compliance was also confirmed by the large increases in serum α-tocopherol and β-carotene levels in the intervention groups, and the minimal changes in those not receiving

the intervention agents.[12] The effects of the two supplements on ALS risk can be assessed independently because no interaction between the supplements was evident (p=0.55).

Fasting serum samples were collected at baseline and stored at −70°C until assayed. Serum concentrations of α-tocopherol and β-carotene were measured by high-performance liquid chromatography.[14] The coefficient of variation (between-batch) was 2.2% for serum α-tocopherol, and 3.6% for β-carotene.

The trial intervention continued for five to eight years (median 6.1 years) until April 30, 1993. Men were followed by national registers after the trial through December 2004, for a median total follow-up of 16.7 years. The institutional review boards of the participating institutions approved the study, and all subjects provided informed consent.

Case identification

Participants diagnosed with motor neuron disease (ICD-9, 335.2, or ICD-10, G12.2) through December 2004 (n = 61) were identified through the national Hospital Discharge Register, which documents diagnoses of all hospital discharges in Finland. The hospital records of the cases were reviewed by one or two study physicians. This review disclosed six cases with pre-existing signs and symptoms at study entry and five cases deemed not to be ALS When the El Escorial (revised)[15] clinical diagnostic criteria were applied, the remaining 50 cases included four definite, 21 probable, seven possible, and 18 suspect cases of ALS. We included all 50 cases because all were diagnosed with ALS by hospital neurologists who had access to the results of electromyography examination. Also, of the 18 categorized as suspect cases, all had death certificates that listed motor neuron disease as a cause of death or part of the disease history.

Statistical Analyses

We used Cox regression methods to estimate association between serum α-tocopherol and β-carotene concentration at baseline and ALS risk, and the effect of α-tocopherol and β-carotene supplementation on ALS risk. Follow-up ran through the earliest available date of diagnosis, date of death, or December 31, 2004.

We used follow-up time as the time metric and adjusted for age at randomization as a continuous variable. We initially ran the models with the covariate smoking pack-years (continuous variable) because some observational studies have identified smoking as a possible risk factor for ALS.[16–18] Final models, however, did not include smoking pack-years because the variable minimally affected the associations of interest.

Serum α-tocopherol was adjusted for serum cholesterol by residual regression analysis.[19] Serum variables were analyzed as categorical variables split at the median and/or in tertiles, with the lowest category serving as the reference group. Tests for trend across tertiles were modeled by an ordinal score value based on median tertile values.

Trial participants receiving α-tocopherol alone, or β-carotene alone, or the combination were compared with those receiving placebo. Analyses were based on the intention-to-treat principle.

We explored potential interaction between baseline serum α-tocopherol (median cut-point) and α-tocopherol supplementation (yes/no) and other factors by including the factors and their cross-product terms in modeling.

The proportional hazards assumption was satisfied for baseline serum α-tocopherol levels, α-tocopherol supplementation, β-carotene levels and β-carotene supplementation. All

analyses were conducted using SAS software ((version 9.2) SAS Institute, Inc., Cary, NC), and the two-tailed $p< 0.05$ level was accepted for significance testing.

Results

During the 407,260 person-years of follow-up, we documented 50 cases of ALS. Baseline characteristics of ALS cases and non-cases are shown in Table 1. None of the characteristics significantly differed between the two groups.

For men with serum α-tocopherol concentration above the median (≥ 11.6 mg/l), the age-adjusted relative risk (RR) of ALS compared to serum α-tocopherol concentration below the median, was 0.56 (95% confidence interval (CI)= 0.32–0.99), p=0.046. Across tertiles of serum α-tocopherol, the risk was 1.00, 0.84, 0.58, with a non-significant trend in declining risk (p for trend=0.14) (Table 2). No significant interaction was found between serum α-tocopherol level and age, BMI, alcohol intake, and smoking pack-years, all stratified at the median (data not shown). Baseline serum β-carotene was not associated with ALS risk (Table 2).

In comparison to those randomized to placebo, assignment to the α-tocopherol alone intervention arm was associated with a RR of 0.75 (95% CI=0.32–1.79, p=0.52) (Table 3). The RR in the β-carotene alone arm was 1.20 (95% CI= 0.55–2.58, p=0.65), and was 1.27 (95% CI=0.60–2.72, p=0.53) in the combined β-carotene/α-tocopherol arm (Table 3).

We explored the risk of ALS in the combined strata of serum α-tocopherol (median split, 11.6 mg/l) and α-tocopherol supplementation (yes/no) (Table 4). In men with baseline serum α-tocopherol below the median, there was a non-significant decrease of ALS risk in those receiving α-tocopherol supplementation compared to those not receiving α-tocopherol, RR= 0.72 (95% CI=0.36–1.48), p=0.37. If baseline serum α-tocopherol was above the median, α-tocopherol supplementation had no effect on the risk of ALS. There was, however, no interaction between serum α-tocopherol concentration and α-tocopherol supplementation (p=0.28).

Discussion

This is the first study to assess risk of ALS in association with pre-diagnostic serum levels of α-tocopherol, as well as the effect of α-tocopherol supplementation on ALS risk. We found that higher baseline serum α-tocopherol was associated with lower subsequent risk of ALS. There was no overall significant effect of α-tocopherol supplementation on ALS risk. However, a modest, non-significant protective effect from supplementation was seen in subjects with baseline serum α-tocopherol levels below the median, whereas no added benefit from supplementation was seen among those with serum α-tocopherol above the median. Higher baseline serum β-carotene levels or supplementation was not protective against ALS.

Oxidative stress is hypothesized to play a major role in neurodegeneration.[4, 20] Several studies indicate that markers of oxidative stress are elevated in ALS.[4, 21–23] Further support for the role of oxidative injury in ALS is suggested by the benefits provided by antioxidants in transgenic mice [5] and neuronal cell cultures modeled on familial ALS.[24–25]

The lipid-soluble α-tocopherol is a particularly potent scavenger of reactive oxygen and nitrogen species,[4] a rationale that underlies research on α-tocopherol and ALS. Experimental evidence has also recently suggested that α-tocopherol has non-antioxidant cell regulatory functions, including inhibiting protein kinase C activity, signal transduction, gene expression, and inflammation responses,[26–27].

Other lines of evidence support a neuroprotective role for vitamin E, [28–30] including the established relationship between vitamin E deficiency and a Friedreich ataxia-like disorder.[31] In addition, vitamin E supplementation improves neurologic symptoms in chronic disorders involving fat malabsorption that cause vitamin E deficiency.[32]

The inverse association between baseline serum α-tocopherol and ALS risk in our study provides additional support for the hypothesis of the protective role of α-tocopherol on the risk of developing ALS. Although it is possible that factors related to (or causing) the α-tocopherol levels, e.g., other tocopherols, other nutrients, explain the association identified, strong confounding by such factors seems unlikely given the findings of previous cohort studies assessing long-term α-tocopherol supplementation[9–10] and experimental animal studies.[5]

The lower risks associated with higher serum α-tocopherol levels were not dependent on prior use of vitamin E supplements. When those (10%) who reported prior use were excluded from the analysis, the ALS risk in men with higher serum α-tocopherol concentration remained lower (data not shown). Thus, diet and host factors could account for the circulating α-tocopherol levels, and the lower risks. To the extent that diet (rather than host factors) contributed to these levels, foods rich in vitamin E, such as vegetable oils, nuts, seeds, whole grains, and dark green leafy vegetables, may have played a role.

α-Tocopherol supplementation did not have a significant protective effect on ALS risk. This may reflect a true null relationship; or alternatively, given the fact that the ATBC Study was not designed to study the impact of α-Tocopherol supplementation on ALS risk, it could reflect insufficient statistical power to detect a significant supplementation effect. We note that the modestly decreased risk with α-tocopherol supplementation, RR = 0.75 (based on only nine cases), was similar to the non-significant association observed in the pooled cohort project for those who had taken vitamin E supplements for two to four years, a period slightly less than the six years intervention analyzed here.[9] The modest effect in our study was limited to subjects with low baseline serum α-tocopherol.

Study participants were exclusively male, Finnish smokers, which may limit the generalizability of this study. However, a smoking covariate based on pack-years did not affect association with serum α-tocopherol level. The American Cancer Society's large cohort study also found no interaction between use of vitamin E supplements and smoking history or gender on the risk of ALS.[10] Nonetheless, it is possible that associations between ALS and circulating α-tocopherol would differ in a nonsmoking or female population.

The absence of a protective effect for β-carotene was not unexpected. In contrast with α-tocopherol, to our knowledge, no experimental, clinical or observational studies suggest β-carotene is effective in preventing ALS.

The key strength of this study is the use of a biochemical measurement and randomized controlled intervention rather than self-reported supplement use or dietary intake. Measured circulating levels of α-tocopherol describe biological status objectively, integrate the full range of dietary and supplement sources, and take into account individual absorption patterns, which is valuable given limited knowledge of α-tocopherol absorption.[30]

By using a single measure of serum α-tocopherol to reflect past exposure we assumed α-tocopherol status remained stable, an assumption supported by study data. In those who were not randomized to α-tocopherol supplementation, the correlation coefficient between serum α-tocopherol concentrations measured at baseline and 3-years later was 0.71,[33] which suggests relatively stable levels over several years.

The major study limitation is the small number of ALS cases, only 50 in more than 400,000 person years. Due to the low incidence of ALS, it will be necessary to pool cohort studies with blood specimens on the one hand, and controlled trials of vitamin E on the other, irrespective of their original purposes, to provide sufficient number of cases to confirm the possible role of α-tocopherol in the pathophysiology of ALS.

Despite the small case numbers, this prospective cohort provides support that higher (but within normal limits) serum α-tocopherol levels are associated with a lower risk of ALS. In addition, the decreased risk of ALS, although not significant, in men with low baseline serum α-tocopherol who received α-tocopherol supplementation is consistent with the hypothesis that α-tocopherol may be protective against ALS.

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Table 1

Selected baseline characteristics (mean (SD)) of ALS cases and non-cases in the ATBC cohort study, N=29,127*

Characteristics	ALS cases (n=50)	Non-cases (n=29,077)	P-value
Age at baseline (years)	57.3 (5.3)	57.2 (5.1)	0.97
Height (cm)	174.5 (5.5)	173.6 (6.2)	0.26
Weight (kg)	79.5 (11.0)	79.3 (12.9)	0.58
Body Mass Index (kg/m^2)	26.1 (3.2)	26.3 (3.8)	0.87
Pack-years of smoking	38.3 (18.0)	37.1 (18.3)	0.62
Alcohol intake (g/day)	14.1 (13.1)	18.0 (21.6)	0.72
Total energy intake (kcal/day)	2880 (875)	2688 (753)	0.14
Fat intake (g/day)	114.7 (44.3)	105.6 (36.2)	0.21
α-Tocopherol intake (mg/day)	11.1 (5.5)	10.4 (5.0)	0.36
β-Carotene intake (mg/day)	2.1 (1.4)	2.1 (1.5)	0.98
Serum total cholesterol (mmol/l)	6.1 (1.1)	6.2 (1.2)	0.56
Serum HDL cholesterol (mmol/l)	1.2 (0.3)	1.2 (0.3)	0.89
Serum retinol (μg/l)	580 (94)	588 (131)	0.79
Serum α-Tocopherol (mg/l)†	11.5 (2.2)	11.9 (2.8)	0.20
Serum β-Carotene (μg/l)	197 (124)	212 (184)	0.92

*Comparisons based on the Wilcoxon two-sample non-parametric test.

†Adjusted for cholesterol.

Table 2

Relative risks (RR)* and 95% confidence intervals (CI) of ALS in tertiles of baseline serum α-tocopherol† and β-carotene concentrations

	α-Tocopherol, mg/l			β-Carotene μg/l		
Tertiles	**1**	**2**	**3**	**1**	**2**	**3**
Median Range	9.7 (1.4 to 10.7)	11.7 (10.8 to 12.6)	14.0 (12.7 to 110.6)	90 (0 to 130)	171 (131 to 224)	315 (225 to 5686)
No. cases	20	18	12	15	16	19
RR	1.0 (ref)	0.84	0.58	1.0 (ref)	0.97	1.10
95% CI		0.45 to 1.59	0.29 to 1.20		0.48 to 1.97	0.56 to 2.18
P for trend			0.14			0.74

*Adjusted for age.

†Adjusted for serum cholesterol.

Amyotroph Lateral Scler Frontotemporal Degener. Author manuscript; available in PMC 2013 June 05.

Table 3

Relative risks (RR)* and 95% confidence intervals (CI) of ALS by intervention arms

	Placebo	β-Carotene†	β-Carotene† and α-Tocopherol‡	α-Tocopherol‡
No. cases	12	14	15	9
RR	1.0 (ref)	1.20	1.27	0.75
95% CI		0.55 to 2.58	0.60 to 2.72	0.32 to 1.79
P-value		0.65	0.53	0.52

*Adjusted for age.

†(20 mg/d)

‡(50 mg/d)

Table 4

Relative risk (RR)* and 95% confidence intervals (CI) of ALS according to both median baseline serum α-tocopherol† and α-tocopherol supplementation

	Serum α-tocopherol			
	Low (< 11.6mg/l)		High (≥11.6mg/l)	
α-Tocopherol Supplementation	No	Yes	No	Yes
No. cases	18	13	8	11
RR	1.0 (ref)	0.72	0.41	0.56
95% CI		0.36 to 1.48	0.18 to 0.93	0.26 to 1.18
P-value		0.37	0.03	0.13

*Adjusted for age.

†Adjusted for cholesterol.