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ARTICLE

Effect of α-tocopherol and β-carotene supplementation on the incidence of type 2 diabetes

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Abstract
Aims/hypothesis Type 2 diabetes is associated with reduced antioxidant defence. Only a few human studies have investigated the role of antioxidants in the pathogenesis of diabetes. This study aimed to examine whether α-tocopherol or β-carotene affected the occurrence of type 2 diabetes.
Methods In the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study, a double-blind, controlled trial, 29,133 male smokers aged 50–69 years were randomised to receive either α-tocopherol (50 mg/day) or β-carotene (20 mg/day) or both agents or placebo daily for 5–8 years (median 6.1 years). Baseline serum samples were analysed for α-tocopherol and β-carotene using HPLC. Cases of diabetes were identified from a nationwide Finnish registry of patients receiving drug reimbursement for diabetes. Of 27,379 men without diabetes at baseline, 705 men were diagnosed with diabetes during the follow-up of up to 12.5 years.
Results Baseline serum levels of α-tocopherol and β-carotene were not associated with the risk of diabetes in the placebo group: the relative risk (RR) between the highest and lowest quintiles of α-tocopherol was 1.59 (95% CI 0.89–2.84) and that for β-carotene was 0.66 (95% CI 0.40–1.10). Neither supplementation significantly affected the incidence of diabetes: the RR was 0.92 (95% CI 0.79–1.07) for participants receiving α-tocopherol compared with non-recipients and 0.99 (95% CI 0.85–1.15) for participants receiving β-carotene compared with non-recipients.
Conclusions/interpretation Neither α-tocopherol nor β-carotene supplementation prevented type 2 diabetes in male smokers. Serum levels of α-tocopherol and β-carotene were not associated with the risk of type 2 diabetes.

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Keywords α-Tocopherol · β-Carotene · Type 2 diabetes · Randomised controlled trial

Abbreviations

ATBC	alpha-tocopherol, beta-carotene cancer prevention
RR	relative risk

Introduction

Diabetes is a multifactorial disease that leads to deleterious effects on many organ systems within the body. Oxidative stress mediated by free radicals has been implicated in the pathogenesis of diabetes, and thus antioxidants could protect against diabetes [1]. However, only a few human studies have examined the association between antioxidant status and the risk of type 2 diabetes and the findings have been contradictory [2–6].

The use of vitamin supplements was associated with a 24% lower risk of diabetes during 20 years of follow-up in the First National Health and Nutrition Examination Survey (NHANES I) Epidemiologic Follow-up Study [7]. The results of controlled trials do not support the hypothesis that antioxidants play a preventive role in the development of type 2 diabetes [8–10].

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The aim of this study was to examine the effects of supplementary α-tocopherol and β-carotene on the incidence of type 2 diabetes in middle-aged male smokers who participated in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study. We also studied the association between baseline serum concentrations of α-tocopherol and β-carotene and the risk of diabetes. Although the primary aim of the ATBC Study was to examine the effects of the supplements on the risk of lung and other cancers, the study design provided a useful basis for evaluating the effects of the supplements on other diseases.

Methods

Participants The ATBC Study was a randomised, double-blind, placebo-controlled clinical trial with a 2×2 factorial design [11]. The participants were screened from among the total male population aged 50–69 years living in south-western Finland (n=290,406).

A postal survey was performed to identify current smokers willing to participate in the trial. Men who reported smoking five or more cigarettes per day who were willing to participate in the study (n=42,957) were invited to undergo baseline examinations. Exclusion criteria were prior malignancy (other than non-melanoma skin cancer or carcinoma in situ), severe angina on exertion, chronic renal failure, cirrhosis of the liver, alcoholism, anticoagulant therapy, other medical problems that might limit long-term participation, or current use of vitamin E (>20 mg/day), vitamin A [>20,000 IU/day (>6,000 μg/day)] or β-carotene (>6 mg/day) supplements.

A total of 29,133 eligible men were randomly assigned in blocks of eight to one of four intervention groups: α-tocopherol (DL-α-tocopheryl acetate, 50 mg/day), β-carotene (20 mg/day), both agents or placebo. Enrolment took place between 1985 and 1988, and the trial intervention continued until 30 April 1993. Active intervention ranged from 5 to 8 years (median 6.1 years).

The institutional review boards of the National Public Health Institute, Finland, and the National Cancer Institute, USA, approved the ATBC Study. All participants provided their written, informed consent before randomisation.

Data collection At baseline, data on background characteristics such as medical and dietary histories, smoking, alcohol consumption and physical activity were collected by questionnaire and checked by specially trained registered nurses. Use of alcohol during the previous year was assessed by enquiring about the amount and type (beer, wine, spirit) consumed, and the mean daily intake of pure ethanol in grams was calculated. Leisure-time physical activity during the past year was assessed as sedentary (e.g. reading, watching television), moderate (e.g. walking, hunting, gardening) and heavy (e.g. running, skiing, swimming). Height and weight were measured, and the BMI was calculated. Blood pressure was measured by mercury sphygmomanometry of the right arm while the participant remained seated. The lower of two measurements taken at least 1 min apart was recorded.

A blood sample was drawn and the serum was stored at −70°C. Serum cholesterol concentrations were determined enzymatically [CHOD-PAP (cholesterol oxidase-phenol ampyrone) method; Boehringer Mannheim, Mannheim, Germany]. HDL-cholesterol was measured after precipitation with dextran sulphate and magnesium chloride. Serum concentrations of α-tocopherol and β-carotene were determined by high-performance liquid chromatography [12]. The between-run coefficients of variation were 2.2% for α-tocopherol and 3.6% for β-carotene. Serum glucose was determined by the enzymatic hexokinase method using an Optima analyser (ThermoFischer, Vantaa, Finland).

The participants made a follow-up visit to local field centres three times each year. During each visit they returned their remaining study capsules and received a new supply. Capsule compliance (median 99% of on-study capsules taken) and the dropout rate (31%) were similar across the four intervention groups [13]. A follow-up serum sample was taken 3 years after study entry and analysed for α-tocopherol and β-carotene.

The metabolic syndrome was defined by means of BMI, blood pressure, and HDL-cholesterol according to the criteria set by the International Diabetes Federation [14]: BMI >30 kg/m^2, physician-diagnosed hypertension or systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg, and HDL-cholesterol <1.03 mmol/l. Indicators for insulin resistance or the prothrombic or proinflammatory state were unavailable.

Assessment of diabetes In Finland, all patients requiring prescription treatment for diabetes are entitled to reimbursement of their medication expenses. This requires a detailed medical certificate from the attending physician. The Social Insurance Institution checks that the case fulfils the criteria set for diabetes and maintains a register of these cases. The ATBC study participants were linked to the register through the unique personal identity number assigned to each Finnish citizen. At study entry, 1,272 participants were entitled to reimbursement of diabetes medication, or they reported receiving diabetes medication or having physician-diagnosed, diet-treated diabetes. Of the incident cases up to December 1997, 482 had a high concentration of serum glucose (i.e. ≥7.0 mmol/l) in the baseline serum sample. After exclusion of these cases, the final cohort for this study comprised 27,379 men, among whom 705 incident cases of diabetes with baseline serum glucose below 7.0 mmol/l were identi-

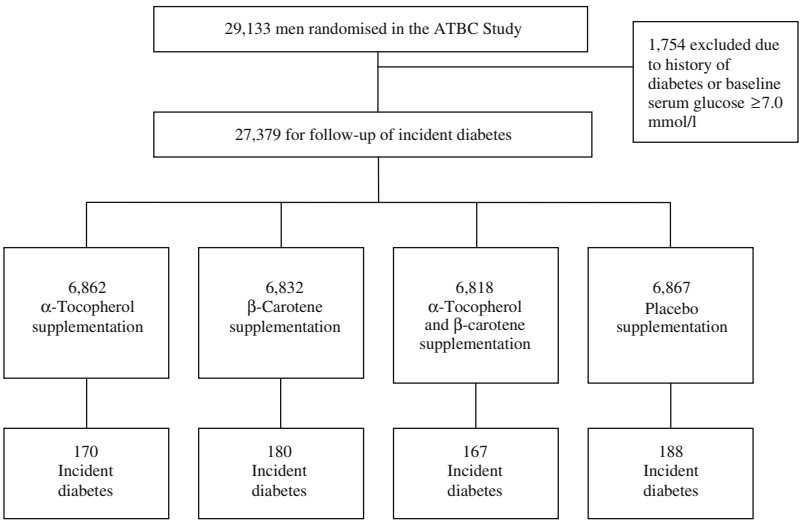

Fig. 1 Study design and participants

fied from the drug reimbursement register up to December 1997 (Fig. 1). Of these incident cases, 305 men were entitled to drug reimbursement during the intervention period by April 1993.

We also analysed a random sample of 500 non-cases of the final cohort for baseline serum glucose. In this analysis, the serum glucose concentration in ten non-cases was 7.0 mmol/l or higher; in seven men it varied from 7.07 to 7.53 mmol/l and in only three men did it exceed the drug reimbursement criterion of 8.0 mmol/l.

Statistical analysis All analyses were by intention to treat. The intervention-specific cumulative incidence of diabetes was calculated by the Kaplan–Meier method using the log-rank test to calculate the statistical significance of differences between intervention groups. The effect of intervention was estimated by Cox proportional hazards regression and expressed as the relative risk (RR) and its 95% CI. We present the effects for each supplementation separately after testing for interaction between α-tocopherol and β-carotene: α-tocopherol compared with no α-tocopherol, and β-carotene compared with no β-carotene. We tested the proportional hazards assumption with no evidence of non-proportional hazards (for α-tocopherol vs no α-tocopherol, $p=0.14$; for β-carotene vs no β-carotene, $p=0.82$) [15]. The follow-up time extended from the date of randomisation until entitlement to drug reimbursement for diabetes, death or the end of follow-up (i.e. December 1997), with a total of 261,868 person-years. The effect of each supplementation during the follow-up period was expressed by calculating relative risks and 95% CIs within consecutive time intervals each containing 30 cases of diabetes and plotting the estimates using 'super smoother' [16].

The likelihood ratio test was used to study whether baseline metabolic syndrome modified the effects of α-tocopherol and β-carotene on diabetes incidence by comparing models with and without the cross-product term.

Table 1 Baseline characteristics of the cohort for follow-up of incident diabetes in the four intervention groups

Characteristic	α-Tocopherol	β-Carotene	α-Tocopherol and β-carotene	Placebo
Number of participants	6,862	6,832	6,818	6,867
Age (years)	57.1	57.2	57.3	56.8
Number of cigarettes per day	20	20	20	20
Smoking (years)	36	37	36	36
Total cholesterol (mmol/l)	6.15	6.16	6.19	6.15
HDL-cholesterol (mmol/l)	1.15	1.16	1.15	1.16
BMI (kg/m^2)	25.8	25.8	25.9	25.8
Systolic blood pressure (mmHg)	140	140	140	140
Diastolic blood pressure (mmHg)	88	88	88	88
Alcohol consumption (g/day)	11	11	11	11
Moderate or heavy leisure-time physical activity (%)	59	58	59	58

Data are median or percentage
Alcohol consumption data were missing for 6.8% of participants; other characteristics were missing for 0–0.2%

The associations between quintiles of baseline serum concentrations of α-tocopherol and β-carotene and the incidence of diabetes were calculated by Cox regression analysis in the placebo group. These analyses were adjusted for the continuous variables age, BMI, number of daily cigarettes, years of smoking, serum total cholesterol, HDL-cholesterol, systolic and diastolic blood pressures, alcohol intake and leisure-time physical activity. All analyses were carried out with the R statistical programme [17].

Results

At baseline, the median age of the participants was 57 years, they smoked a median of 20 cigarettes daily at that time, and their median BMI was 26 kg/m^2. We found no differences in background characteristics between the intervention groups at baseline (Table 1).

Serum concentrations of α-tocopherol increased from a median of 26.8 μmol/l at baseline to 40.2 μmol/l at 3 years in the α-tocopherol-supplemented group. Similarly, β-carotene supplementation increased serum β-carotene concentrations from a median of 0.34 μmol/l at baseline to 5.60 μmol/l at 3 years. In the non-supplemented α-tocopherol and β-carotene groups, we observed no change in serum concentrations of α-tocopherol and β-carotene, respectively, during 3 years.

The incidence of diabetes per 1,000 person-years varied from 2.6 to 2.8 in the intervention groups (Table 2). The differences in incidence between the groups were not statistically significant (log-rank test, 1.34; p=0.72). No interaction was found between α-tocopherol and β-carotene supplementation (p=0.85).

In the 2×2 factorial comparison, no statistically significant difference in risk of diabetes was observed between α-tocopherol recipients and non-recipients (RR 0.92; 95% CI 0.79–1.07) or between β-carotene recipients and non-recipients (RR 0.99; 95% CI 0.85–1.15). When excluding cases occurring during the first 2 years of follow-up the RR was 0.91 (95% CI 0.78–1.06) for α-tocopherol and 0.99 (95% CI 0.85–1.16) for β-carotene. When including only cases from the intervention period (up to April 1993) the RR was 0.97 (95% CI 0.77–1.22) for α-tocopherol and 1.01 (95% CI 0.80–1.26) for β-carotene.

The relative risk of diabetes varied non-significantly around unity with follow-up time both for α-tocopherol recipients compared with non-recipients and for β-carotene recipients compared with non-recipients (Fig. 2).

Baseline metabolic syndrome did not modify the effect of α-tocopherol or β-carotene supplementation on the incidence of diabetes (p for interaction, 0.40 and 0.29 respectively).

There was no significant difference in the risk of diabetes between the quintiles of baseline serum α-tocopherol or β-carotene concentration (Table 3). When the four highest quintiles of serum β-carotene were combined, a decreased risk of diabetes was seen compared with the lowest quintile (RR 0.70; 95% CI 0.49–0.99). The effect of supplementary β-carotene was similar in the four highest quintiles combined and in the lowest quintile of serum β-carotene (p for interaction 0.12).

Table 2 Incidence and relative risk of diabetes in the four intervention groups

Intervention group	Number of cases	Person-years	Incidence per 1,000 person-years	Relative risk (95% CI)
α-Tocopherol	170	65,822	2.6	0.91 (0.73–1.12)
β-Carotene	180	65,151	2.8	0.97 (0.79–1.20)
α-Tocopherol and β-carotene	167	64,892	2.6	0.91 (0.73–1.12)
Placebo	188	66,003	2.8	1.00 (reference)

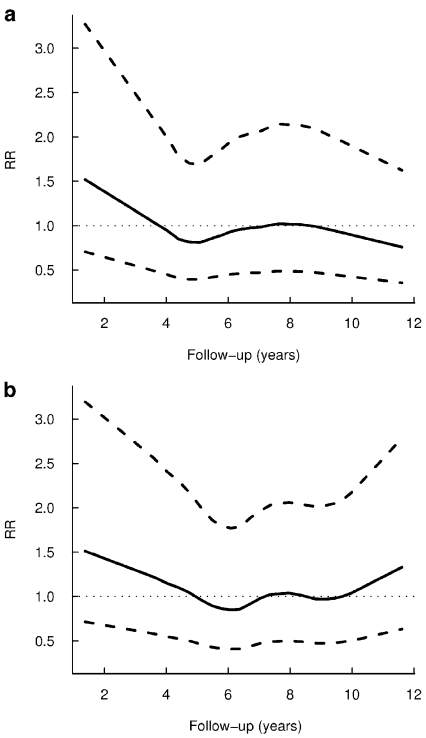

Fig. 2 RR of diabetes with 95% CIs for **a** α-tocopherol vs no-α-tocopherol and **b** β-carotene vs no-β-carotene supplementation with follow-up time

Discussion

We found no effect of supplementary α-tocopherol on the incidence of type 2 diabetes in middle-aged male smokers. This is in keeping with the outcomes of other controlled trials. In the Heart Outcomes Prevention Evaluation (HOPE) Trial, 124 participants supplemented with a natural source of vitamin E (400 IU; *RRR*-α-tocopheryl acetate, 294 mg) daily and 137 participants taking placebo reported incident diabetes during an average follow-up of 4.5 years (p=0.55) [8]. Recently the Women's Health Study reported that 827 incident cases of type 2 diabetes occurred in the vitamin E group (600 IU α-tocopherol every other day for 10 years) and 869 in the placebo group (RR 0.95; 95% CI 0.87–1.05) [9]. In our study, supplementation with β-carotene had no effect on diabetes incidence. This finding is consistent with the Physicians' Health Study, a placebo-controlled trial of supplementation with 50 mg β-carotene on alternate days for 12 years, in which 396 men reported type 2 diabetes in the β-carotene group and 402 men did so in the placebo group (RR 0.98%; 95% CI 0.85–1.12) [10]. A combination of 120 mg vitamin C, 30 mg vitamin E, 6 mg β-carotene, 100 μg selenium and 20 mg zinc daily for 7.5 years had no effect on fasting plasma glucose [18].

Our findings on the baseline serum concentrations of α-tocopherol and β-carotene were consistent with those regarding supplementation: baseline concentrations of α-tocopherol and β-carotene were not associated with the risk of diabetes. The lower risk of diabetes in the four highest quintiles combined compared with the lowest quintile of serum β-carotene concentration was probably due to residual confounding. These findings contradict the results of two prospective observational studies, from Finland and the USA, in which a low concentration of plasma vitamin E was associated with excess risk of type 2 diabetes [4, 5]. In a Finnish prospective study, the inverse association between serum α-tocopherol and β-carotene and the incidence of diabetes disappeared after adjustment for cardiovascular risk factors [3]. The numbers of incident cases of diabetes in these three studies were small, however, ranging from 45 to 106. A recent study among US women found no prospective association between baseline plasma β-carotene and the risk of type 2 diabetes, based on 470 incident cases of diabetes [6].

Certain hypotheses suggest that vitamin E could potentially influence insulin sensitivity. The antioxidant property of vitamin E is often considered a key activity, although vitamin E does cause other effects that could potentially modify the action of insulin. For example, vitamin E inhibits protein kinase C activity, which has been associated with insulin resistance experimentally [19]. Vitamin E regulates several genes; for example, it upregulates the expression of *PPARG*, the gene for peroxisome proliferator activated receptor γ (PPARγ) [20]. PPARγ is a nuclear receptor the stimulation of which improves glucose tolerance and insulin sensitivity in type 2 diabetes mellitus patients and in animal models of insulin resistance [21]. Vitamin E possesses a structural similarity to glucose-lowering agents such as thiazolidinediones, which are agonists for PPARγ.

β-Carotene as an antioxidant has been hypothesised to provide protection against diabetes [22]. Although we found that supplementation with α-tocopherol and β-

Table 3 Relative risk (RR) and 95% CI of diabetes by quintiles of baseline serum α-tocopherol and β-carotene in the placebo group

Serum factor	Quintiles					p value for homogeneity	p value for trend
	1	2	3	4	5		
α-Tocopherol (mg/l)							
Median	8.30	10.11	11.40	12.90	15.70		
Range	0.14–9.34	9.35–10.77	10.78–12.09	12.10–13.97	13.98–39.71		
Number of cases	29	36	35	33	55		
Person-years	12,673	13,267	13,091	13,664	13,274		
Multivariate RR[a]	1.00	1.09	1.24	1.07	1.59		
95% CI		0.65–1.82	0.72–2.11	0.61–1.88	0.89–2.84	0.41	0.16
β-Carotene (μg/l)							
Median	72	125	174	241	379		
Range	0–101	102–147	148–203	204–292	293–5445		
Number of cases	51	42	33	35	27		
Person-years	12,472	12,974	13,265	13,573	13,686		
Multivariate RR[a]	1.00	0.74	0.65	0.73	0.66		
95% CI		0.49–1.14	0.41–1.02	0.46–1.16	0.40–1.10	0.34	0.11

[a] RR adjusted for the continuous variables age, BMI, number of cigarettes per day, years of smoking, total cholesterol, HDL-cholesterol, systolic and diastolic blood pressures, alcohol consumption and leisure-time physical activity

carotene had no effect on the risk of diabetes, it is possible that there was no effect because the intervention period was too short or the timing of the intervention was wrong. Also, the findings do not exclude the possibility that other antioxidants might protect against type 2 diabetes.

Our study had several strengths. The randomisation resulted in even distributions of baseline characteristics across intervention groups. The successful supplementation was evidenced by high capsule compliance and substantial increases in serum α-tocopherol and β-carotene concentrations in the respective supplementation groups.

We were able to control the baseline serum glucose level in the register-based incident cases of diabetes and thus to exclude cases who had elevated serum glucose indicating the presence of diabetes at baseline. We also determined baseline serum glucose concentrations in a random sample of 500 non-cases and found that ten men in this analysis had serum glucose levels of 7.0 mmol/l or higher. Extrapolating from this, about 530 non-cases had elevated baseline serum glucose. Since as a result of randomisation they were equally distributed to the supplementation groups, their identification and exclusion would have increased the incidence rates only by up to 0.06 per 1,000 person-years or 2.2%. Thus, their inclusion in the study population cannot explain our finding of no effect.

We retrieved cases of incident diabetes from a nationwide register of drug reimbursements. The criteria for reimbursement for diabetes drugs required a fasting whole blood glucose concentration of 7.0 mmol/l or higher or a fasting plasma glucose concentration of 8.0 mmol/l or higher. Thus, the register identified only the more advanced cases of diabetes. Our study is therefore not informative regarding diabetes cases with fasting whole blood glucose between 6.1 and 6.9 mmol/l or plasma glucose between 7.0 and 7.9 mmol/l, as defined by the WHO-99 criteria [23].

In a Finnish study in which participants were screened for diabetes with an oral glucose tolerance test, 13.6% of men aged 55–64 years had prevalent diabetes based on WHO-99 criteria, and 44% of these were unaware of their diabetic condition [24]. We do not have data to estimate how many of the ATBC Study participants might have had undiagnosed diabetes fulfilling the criteria of drug reimbursement at the end of follow-up in December 1997. There is, however, no reason to suppose that supplementation had influenced differently the diagnosis of diabetes, and thus the undiagnosed cases fulfilling the criteria of drug reimbursement are unlikely to affect our risk estimates of the effect of supplementation.

The register provides no information about whether the diabetes is type 1 or type 2. In a Finnish survey, 96% of all diabetic participants diagnosed after the age of 55 years had type 2 diabetes [25]. Participants in our study were 50–69 years of age at study entry, and thus the incident cases of diabetes represent primarily type 2 diabetes.

Our study included only older middle-aged male smokers since the primary aim of the ATBC Study was to examine the preventive effects of α-tocopherol and β-carotene on lung cancer. Therefore, our results cannot be generalised to non-smokers and females. This is especially noteworthy since smoking increases the risk of diabetes. In a 12-year prospective cohort study of 275,190 men, the rate of diabetes was 45% higher among those who smoked at least two packs daily at baseline than among those who had never smoked [26]. In a 6-year follow-up study of 41,810 health professionals, the relative risk of diabetes among men who smoked at least 25 cigarettes daily was 1.94 (95% CI, 1.25–3.03) times higher than that of non-smokers [27].

In conclusion, supplementation with α-tocopherol or β-carotene had no preventive effect on the risk of type 2 diabetes in middle-aged male smokers. Baseline serum levels of α-tocopherol and β-carotene were also not associated with the risk of diabetes. However, since our endpoint assessment identified diabetes cases requiring drug treatment, the possible roles of α-tocopherol and β-carotene in the development of early insulin resistance remain open and require further study.

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Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

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