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The effect of alpha-tocopherol and beta-carotene supplementation on symptoms and progression of intermittent claudication in a controlled trial

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Abstract

We evaluated the effect of long-term supplementation with vitamin E (alpha-tocopherol) and beta-carotene on occurrence of claudication symptoms and risk for peripheral vascular surgery among men with intermittent claudication. Subjects, 50–69-year old male smokers, were participants in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, who reported intermittent claudication through a structured questionnaire (Rose) at study entry ($n = 1484$). They were randomly assigned to receive either 50 mg/day of alpha-tocopherol, or 20 mg/day of beta-carotene, or both, or placebo, in a 2×2 design. During follow-up, claudication was evaluated by repeating use of the questionnaire once a year. Information on peripheral vascular surgery came from the National Hospital Discharge Register. We observed no effect of alpha-tocopherol and beta-carotene supplementation on claudication during a mean follow-up of 3.7 years. A slightly increased risk (odds ratio (OR) 1.60, 95% confidence interval (CI) 1.05–2.44) for vascular surgery was observed among beta-carotene supplemented men compared to those who did not receive beta-carotene. Alpha-tocopherol supplementation had no effect. In conclusion, long-term supplementation with alpha-tocopherol and beta-carotene showed no beneficial effect on symptoms and progression of intermittent claudication. © 1999 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Intermittent claudication; Alpha-tocopherol; Beta-carotene; Supplementation; Smoking

1. Introduction

Intermittent claudication—calf-pain induced by exertion—is a sign of peripheral atherosclerosis. In Europe and North America, prevalence of intermittent claudication among middle-aged or older men has varied between 2.2 and 5.8% [1,2]. The prevalence of intermittent claudication increases with age and is higher among smokers than non-smokers [3].

Since the 1940s, large doses of vitamin E have been suggested to relieve symptoms of intermittent claudication. In those early studies (mainly clinical observations) the pain-free walking distance increased or symptoms disappeared totally with a few months of alpha-tocopherol supplementation [4,5]. The results from the few controlled, double-blind studies are, however, contradictory [6–9].

Alpha-tocopherol (a form of vitamin E) and beta-carotene are suggested to retard development of atherosclerosis by inhibiting oxidative modification of low-density lipoprotein (LDL) [10]. In addition, alpha-tocopherol has been reported to prevent oxidized LDL-induced arterial dysfunction [11]. This effect may be mediated through inhibition of protein kinase C activation [11].

Until now, the effect of antioxidant supplementation on intermittent claudication has not been evaluated in large clinical trials. We studied the effect of long-term supplementation with alpha-tocopherol and beta-carotene on occurrence of claudication by means of

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annual interviews, and on the risk for vascular surgery in those participants of the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study who reported symptoms of intermittent claudication at study entry.

2. Methods

The ATBC Study was a randomized, double-blind, placebo-controlled trial testing the possible cancer-preventive properties of alpha-tocopherol and beta-carotene supplementation [12,13]. The participants were recruited from among the total population of men 50–69 years old, living in southwestern Finland. Enrollment took place in 1985 through 1988 and the intervention continued until April 30, 1993. To be eligible, participants at entry had to smoke at least five cigarettes per day. Subjects with prior cancer, any serious disease limiting long-term participation, or use of anticoagulants, or vitamin E or A, or beta-carotene supplements were excluded. A total of 29 133 men were randomly assigned in blocks of eight into four intervention groups: 50 mg of alpha-tocopherol (dl-alpha-tocopheryl acetate) daily, or 20 mg of beta-carotene daily, or both, or placebo. The ATBC Study was approved by the institutional review boards of the National Public Health Institute, Finland and the National Cancer Institute, USA. All subjects provided written informed consent before randomization. A data and safety monitoring committee was convened twice annually throughout the study to evaluate unblinded data relevant to safety and efficacy.

At baseline, background characteristics such as medical, smoking, and dietary histories were collected through questionnaires. Symptoms of intermittent claudication and angina pectoris were discovered in an interview with the Rose questionnaire [14]. Blood pressure, height and weight were measured, and serum sampled and stored at −70°C. Serum total and high-density lipoprotein (HDL) cholesterol were determined enzymatically (CHOD-PAP method, Boehringer Mannheim) [15]. HDL cholesterol was measured after precipitation with dextran sulphate and magnesium chloride [16].

The subjects of this study were the 1484 men who at study entry had intermittent claudication. Claudication was solely assessed by the Rose questionnaire. Intermittent claudication was defined as pain in one or both calves induced on exertion and relieved by resting 10 min or less. This definition includes typical intermittent claudication, both severe (pain occurring even while walking at an ordinary pace on level ground) and mild (pain occurring while walking uphill or hurrying).

Each participant made a follow-up visit to his local study center three times per year. Current smoking was asked about at each visit. If a subject had not smoked during two consecutive 4-month follow-up periods, he was defined as having stopped smoking. At every follow-up visit, men returned the packet with the remaining study capsules and received a new supply. Overall capsule compliance was estimated by dividing the number of capsules taken by the number of days in the trial.

The Rose questionnaire was used for a reinterview once a year. Follow-up continued until peripheral vascular surgery or until the last visit, when the subject was reinterviewed. If a subject failed to enter the follow-up visit at the final administration of the questionnaire, he was considered a drop-out.

Information on peripheral vascular surgery, such as endarterectomy and an arterial bypass operation on the lower extremities, served as another endpoint. Information came from the National Hospital Discharge Register. The first operation occurring during the trial was considered in the analysis.

2.1. Statistical methods

The effect of alpha-tocopherol and beta-carotene supplementation on occurrence of intermittent claudication during follow-up was analyzed by the logistic regression GEE model for dependent data, which takes into account the intraindividual correlation in repeated measurements of claudication [17]. In the analysis, a 2×2-factorial design was used, meaning those who received alpha-tocopherol were compared to those who did not receive it, and those who received beta-carotene were compared to those who did not. Baseline factors considered as risks for intermittent claudication were included in the model: age, years of smoking, number of cigarettes smoked per day, body mass index (BMI), consumption of alcohol, systolic and diastolic blood pressure, total- and HDL-cholesterol (all continuous variables), and baseline diabetes (dichotomous). Additionally we included in the GEE model cessation of smoking as a time-dependent variable. Interaction between alpha-tocopherol and beta-carotene supplementation was tested by the Wald test. Similarly, interaction was tested between the supplements and baseline factors. We studied the effect of alpha-tocopherol and of beta-carotene on claudication separately among those subjects who reported severe or mild claudication at study entry. We also evaluated the effect of supplementations on occurrence of different symptoms by the proportional odds model including subject random effect, where severity of intermittent claudication was used as an ordinal response with three categories (none, or mild, or severe typical claudication) [18].

Analysis of risk for peripheral vascular surgery was by intention to treat. The effect of alpha-tocopherol and beta-carotene supplementation on the risk for

surgery was analyzed by the Cox proportional hazards model. All risk ratios reported were calculated by stratified study area. Interactions, as mentioned above, were tested by the likelihood ratio test.

The effect of occurrence of claudication on dropping out was modelled by the Poisson regression. We excluded the first follow-up year from the analysis, because intermittent claudication was not evaluated for the first time until 12 months after recruitment.

3. Results

The 1484 subjects were evenly distributed in the four intervention groups and all baseline factors were similar among the groups (Table 1). At baseline, 49% of the subjects had severe and 51% mild intermittent claudication. Mean follow-up time with supplementation was 3.7 years. Average capsule compliance was 91%. The drop-out rate was 44%, including deaths. Risk for dropping out was similar in all intervention groups, and occurrence of intermittent claudication did not affect drop-out risk. Total mortality was 26% and was similar in all intervention groups.

Subjects reported at the annual interviews 2683 occurrences of symptoms of intermittent claudication during 5444 person-years. The annual prevalence of symptoms of claudication was about 48%. The crude odds ratio (OR) for occurrence of intermittent claudication by the GEE model was 0.97 (95% confidence interval (CI) 0.81–1.15) among those who received alpha-tocopherol compared to those who did not, and 1.02 (95% CI 0.86–1.21) among those who received beta-carotene compared to those who did not (Table 2). These odds ratios remained similar after adjustment for baseline factors. No interaction was observed between alpha-tocopherol and beta-carotene supplementation in their effect on claudication ($P = 0.71$). Significant interaction was observed between beta-carotene supplementation and systolic blood pressure ($P = 0.004$), and number of cigarettes smoked daily ($P = 0.003$) in their effect on occurrence of claudication. With systolic blood pressure below the median, the risk for claudication was 1.27 (95% CI 0.98–1.63) among subjects supplemented with beta-carotene compared to those not supplemented, whereas among those with median or higher blood pressure, the risk was 0.78 (95% CI 0.60–1.01). For those smoking < 20 cigarettes per day, risk for claudication was 1.21 (95% CI 0.98–1.51); for those smoking ≥ 20 cigarettes it was 0.70 (95% CI 0.51–0.97). The effect of alpha-tocopherol and beta-carotene supplementation on occurrence of claudication did not differ between men reporting severe or mild claudication at baseline. Neither did the supplementations affect the severity of claudication (none, or mild, or severe symptoms), as analyzed by the proportional odds model.

Peripheral vascular surgery was performed on 101 (7%) subjects with mean follow-up time of 5.3 years and 7849 person-years. A total of 29 men underwent endarterectomy and 72 bypass grafting. Relative risk for peripheral vascular surgery was 1.02 (95% CI 0.69–1.51) among those who received alpha-tocopherol compared to those who did not, and 1.51 (95% CI 1.01–2.26) among those who received beta-carotene compared to those who did not (Table 3). Adjustment for risk factors affected the results only slightly. Subjects reporting mild intermittent claudication at baseline and receiving beta-carotene had a significantly elevated risk for surgery (OR 2.44, 95% CI 1.08–5.53) compared to those who did not receive beta-carotene, whereas beta-carotene did not increase the risk among those reporting severe symptoms of claudication at baseline (OR 1.15, 95% CI 0.72–1.83). No interaction occurred between alpha-tocopherol and beta-carotene supplementation in their effect on risk for surgery ($P = 0.23$), nor any interaction between supplements and baseline factors in their effect on risk for surgery.

Table 1
Medians and percentages of baseline characteristics by intervention groups among 1484 men with intermittent claudication at baseline[a]

Characteristics	Alpha-tocopherol, $n = 344$	Alpha-tocopherol and beta-carotene, $n = 390$	Beta-carotene, $n = 377$	Placebo, $n = 373$
Age, years	60	60	60	60
Years of smoking, years	40	40	41	40
Number of cigarettes/day	20	20	20	20
BMI, kg/m^2	26	26	26	26
Alcohol intake, g/day	8.8	10.7	8.9	9.9
Systolic blood pressure, mmHg	144	146	146	144
Diastolic blood pressure, mmHg	88	88	88	88
Total cholesterol, mmol/l	6.3	6.3	6.3	6.4
HDL-cholesterol, mmol/l	1.1	1.1	1.1	1.1
Diabetes at baseline, %	9	10	10	8

[a] Median values compared by Kruskal Wallis test; no differences appeared.

Table 2
Odds ratios and 95% confidence intervals for occurrence of typical intermittent claudication by supplementation with either alpha-tocopherol or beta-carotene[a]

Odds ratio	Alpha-tocopherol, $n = 734$	No alpha-tocopherol, $n = 750$	Beta-carotene, $n = 767$	No beta-carotene, $n = 717$
Crude	0.97 (0.81–1.15)	1.00	1.02 (0.86–1.21)	1.00
Adjusted[b]	1.00 (0.83–1.20)	1.00	1.00 (0.83–1.20)	1.00

[a] Odds ratios calculated by logistic regression, GEE model.
[b] Adjusted for age, years of smoking, number of cigarettes smoked per day, BMI, mean daily intake of alcohol, systolic and diastolic blood pressure, total and HDL-cholesterol, and diabetes at baseline.

During the follow-up, 19% of the subjects stopped smoking—a figure similar for all intervention groups. Cessation of smoking decreased subsequent risk for occurrence of claudication, but not significantly (OR 0.82, 95% CI 0.67–1.01). No interaction appeared between supplementation groups and smoking-cessation in their effect on claudication symptoms.

4. Discussion

This randomized, double-blind, placebo-controlled study showed no effect of alpha-tocopherol and beta-carotene supplementation on claudication symptoms as evaluated by the Rose questionnaire. Our findings contradict observations indicating beneficial effects of alpha-tocopherol on intermittent claudication [4,5]. However, prior evidence is only suggestive, and the few controlled, double-blind studies have given inconsistent results [6–9]. Major limitations of those studies were small number of patients and supplementation lasting only some months; thus for the time being, no recommendation on vitamin E supplementation has been given [19]. Our dose of alpha-tocopherol was about one-tenth that used in those studies, but was administered over a much longer period. Furthermore, our result is consistent with our earlier finding of no primary preventive effect of alpha-tocopherol or of beta-carotene supplementation on intermittent claudication [20].

We evaluated, additionally, the effect of alpha-tocopherol and beta-carotene supplementation on risk for peripheral vascular surgery. A significantly more elevated risk appeared among those receiving beta-carotene than among those who did not, but the mechanism remains unknown. Beta-carotene has a tendency to be incorporated into the atherosclerotic plaque [21], but no data indicate how beta-carotene or its metabolites might function there. Increased risk for surgery was found only among those reporting at baseline mild symptoms of claudication. If mild symptoms indicate smooth, 'active' atherosclerotic plaques rather than calcified ones, beta-carotene might be preferentially incorporated into the former, making the atheroma plaque more prone to rupture, leading to acute thrombosis requiring emergency surgery.

Smoking is a major risk factor for intermittent claudication; cessation of smoking relieves its symptoms [22], and we indeed observed a slight, non-significant reduction in risk for occurrence of symptoms among those smokers who ceased. However, cessation did not modify the effect of alpha-tocopherol and beta-carotene on claudication.

Our definition of intermittent claudication was based solely on the Rose questionnaire, which is designed for large field surveys. The sensitivity and specificity of the questionnaire are reported to be 60–92%, and 91–100%, respectively [14,23]. We are unaware of the number of false-positive and false-negative cases, but based on the Edinburgh Artery Study, the number of false positives can be assumed to be some 30% [24]. Our study lacked objective measurement of symptoms such as treadmill exercise testing, but in a large trial with nearly 30 000 participants it was not feasible to perform such tests. The questionnaire did allow us to detect changes in symptoms from severe to mild, in addition to resolution of symptoms. In contrast, the other endpoint—peripheral vascular surgery—was based on register data. In an evaluation performed in Finland, codes for surgery from the Hospital Discharge Register matched hospital records in 85% of cases [25]. In our opinion, the register data thus can be considered valid for purposes of analysis.

The number of dropouts was moderately high, as all subjects had symptoms of atherosclerotic disease at the beginning of this study. However, the drop-out rate was similar in all intervention groups and occurrence of claudication had no effect on drop-out risk.

In conclusion, we observed no benefit from alpha-tocopherol or beta-carotene supplementation in regard to occurrence of intermittent claudication, as evaluated by a questionnaire among male smokers, whereas beta-carotene supplementation slightly increased risk for peripheral vascular surgery. There is thus no reason to recommend supplementation with either substance.

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Table 3
Relative risks and 95% confidence intervals for peripheral arterial surgery by supplementation with either alpha-tocopherol or beta-carotene[a]

Relative risk	Alpha-tocopherol, $n = 734$	No alpha-tocopherol, $n = 750$	Beta-carotene, $n = 767$	No beta-carotene, $n = 717$
Number of cases	50	51	61	40
Crude	1.02 (0.69–1.51)	1.00	1.51 (1.01–2.26)	1.00
Adjusted[b]	0.88 (0.58–1.33)	1.00	1.60 (1.05–2.44)	1.00

[a] Relative risks calculated by Cox proportional hazards model and stratified by study area.
[b] Adjusted for age, years of smoking, number of cigarettes smoked per day, BMI, mean daily intake of alcohol, systolic and diastolic blood pressure, total and HDL-cholesterol, and diabetes at baseline.

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