

Six-year supplementation with alpha-tocopherol and beta-carotene and age-related maculopathy

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ABSTRACT.

Purpose: Animal research and observational studies in man suggest a protective effect of antioxidant vitamins in the development of age-related maculopathy (ARM).

Methods: The ATBC study, a population-based, controlled clinical trial of alpha-tocopherol and beta carotene to prevent lung cancer, took place in Finland between 1984 and 1993. Over 29,000 smoking males aged 50 to 69 years were randomly assigned to alpha-tocopherol (AT; 50 mg/day), beta-carotene (BC; 20 mg/day), both of these, or placebo. We performed an end-of-trial ophthalmological examination on a random sample of 941 participants aged 65 years or more from two of the fourteen study areas, to discover if the five to eight-year intervention with alpha-tocopherol and/or beta-carotene had been associated with a difference in ARM prevalence. Age-related maculopathy was assessed using colour photographs of the macula.

Results: Altogether, 269 cases of ARM were found; there were more cases in the AT group (32%; 75/237), BC group (29%; 68/234), and combined antioxidant group (28%; 73/257) than in the placebo group (25%; 53/213). However, neither substance was significantly associated with the risk of ARM in a logistic regression analysis controlling for possible risk factors.

Conclusions: No beneficial effect of long-term supplementation with alpha-tocopherol or beta-carotene on the occurrence of ARM was detected among smoking males.

Key words: alpha-tocopherol – beta-carotene – antioxidant – vitamin – ARM – macula – degeneration – visual acuity – AMD – maculopathy.

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Age-related macular degeneration (AMD) is the leading cause of irreversible blindness in Western populations (Sorsby 1966; Kahn & Moorhead 1973; Thompson et al. 1989), including Finns (Ojamo et al. 1990). Visual function can even deteriorate to the level of legal

blindness, especially in the neovascular form of the disease (Ferris et al. 1984). The majority of AMD cases are mild, hence the term Age Related Maculopathy (ARM) has been introduced. The rising prevalence of the disease is related to population ageing, and an estimated 25%

of people over 65 years have some manifestation of ARM (Klein et al. 1992). The etiology of ARM and factors determining its irreversible progression are largely unknown. While some advanced forms can be treated with laser photocoagulation, this only delays the progression of the disease and may even weaken visual function initially (Macular Photocoagulation Study Group 1991). The most common form of ARM, atrophic “dry” degeneration, cannot be treated, and hence prevention is of paramount interest.

The retina, one of the most oxygen-rich tissues in vertebrates (Sickel 1972), is under constant oxidative stress from the incident radiant energy of visible light. The co-presence of oxygen and light can give rise to the formation of single oxygen and free radicals – highly reactive compounds promoting changes in DNA, proteins and lipids (Ames et al. 1993). Radical-induced peroxidation may be a significant factor in the development of ARM (Amstrong et al. 1982; Organisciak et al. 1983; Weigand et al. 1983). Many natural antioxidants (Heath et al. 1961; Farnsworth & Dratz 1976; Organisciak et al. 1984) and enzymes with antioxidant activity (Hall & Hall 1975; Feeney & Bertram 1976; Schalch 1992) have been observed in the retina. Evidence that antioxidants such as alpha-tocopherol (AT) and beta-carotene (BC) may protect against ARM comes from three sources: animal models of maculopathy (Hayes 1974; Organisciak et al. 1985; Katz &

Robinson 1987), observational studies of dietary and blood levels of vitamins and micronutrients in ARM patients (Goldberg et al. 1988; The Eye Disease Case-Control Study Group 1993; West et al. 1994) and one small clinical trial with zinc (Newsome et al. 1988). Other protection theories focus on findings that some vitamins diminish the loss of photoreceptor cell nuclei, or of rhodopsin, or reduce damage to the retinal pigment epithelium (RPE) (Noell 1980; Organisciak et al. 1984, 1985; Woolford & Tso 1984).

Material and methods

The ATBC study

The present study was conducted within the ATBC study, a randomized, double-blind, placebo-controlled, 2-factorial primary-prevention trial to determine whether daily supplementation with alpha-tocopherol (50 mg), beta-carotene (20 mg), or both, would reduce the incidence of lung cancer and possibly other cancers (The ATBC Cancer Prevention Study Group 1994; The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study Group 1994a). The study participants were recruited from the total male population aged 50 to 69 years in 14 areas of southwestern Finland (n=290,406). To be eligible, they had to be smoking five or more cigarettes per day at study entry, and willing to participate and give informed consent. Excluded were those with a history of cancer or serious disease limiting their ability to participate, those taking supplements of vitamin E, vitamin A, or beta-carotene in excess of predefined doses, and those being treated with anticoagulants. A total of 29,133 participants were randomly assigned to one of four supplementation regimens: alpha-tocopherol (n=7278), beta-carotene (n=7282), the combination of alpha-tocopherol and beta-carotene (n=7278), and placebo (n=7287). The follow-up time was 5 to 8 years (median, 6.1). At the end of intervention, 20,072 participants (69%) were still active in the study. Capsule compliance was excellent, with four out of five active participants taking over 95% of their scheduled capsules. There was no difference in drop-out rate or capsule compliance between the treatment groups.

The maculopathy study

Two of the fourteen trial areas were selected for this study. A random sample of

Table 1. Quality of fundus photographs among the subjects in the ARM study by intervention group (AT=alpha-tocopherol, BC=beta-carotene, ATBC=combination of alpha-tocopherol and beta-carotene). Grades vary from 0 (impossible to grade) to 3 (excellent).

| Treatment | grade 0 | grade 1 | grade 2 | grade 3 |
|-----------|-----------------|-----------------|-----------------|-----------------|
| | right/left % | right/left % | right/left % | right/left % |
| AT | 1.7/0.8 | 3.0/3.8 | 14.0/18.6 | 81.3/76.8 |
| ATBC | 1.9/0.8 | 1.9/1.6 | 12.3/13.7 | 83.9/84.0 |
| BC | 2.1/1.7 | 5.1/2.2 | 13.1/17.2 | 80.0/79.0 |
| Placebo | 1.4/3.2 | 2.8/2.8 | 12.6/14.8 | 83.3/79.2 |

Table 2. Characteristics (medians unless defined otherwise) of the participants in the study of age-related maculopathy by treatment group (AT=alpha-tocopherol, BC=beta-carotene, ATBC=combination of alpha-tocopherol and beta-carotene).

| | AT n=237 | ATBC n=257 | BC n=234 | Placebo n=213 |
|---|-------------|---------------|-------------|------------------|
| <i>AT baseline</i> | | | | |
| Alcohol use (%) | | | | |
| nondrinkers | 11.1 | 10.9 | 15.9 | 10.5 |
| <=30 g/day | 69.3 | 72.3 | 71.8 | 74.1 |
| 30 >=60 g/day | 16.4 | 14.3 | 10.9 | 13.4 |
| 60 <=g/day | 3.1 | 2.5 | 1.4 | 2.0 |
| Hypertension (%) ¹ | 30.8 | 23.3 | 31.6 | 25.4 |
| Total cholesterol (mmol/L) | 6.2 | 6.2 | 6.3 | 6.2 |
| Diabetes (%) | 6.8 | 4.3 | 4.7 | 3.8 |
| Cigarettes (nr/day) | 15 | 15 | 15 | 15 |
| Smoking history (years) | 42 | 42 | 41 | 42 |
| Body Mass Index (%) | | | | |
| <=20 (kg/m ²) | 6.8 | 5.1 | 4.3 | 2.8 |
| 20 >=25 (kg/m ²) | 41.1 | 40.1 | 41.9 | 47.0 |
| 25 >=27 (kg/m ²) | 18.6 | 23.7 | 23.1 | 18.8 |
| 27 < (kg/m ²) | 33.5 | 31.1 | 30.8 | 31.5 |
| Education (total years) | 8 | 8 | 8 | 8 |
| Visual acuity | | | | |
| right eyes with glasses | 1.0 | 0.9 | 1.0 | 0.9 |
| left eyes with glasses | 1.0 | 1.0 | 1.0 | 1.0 |
| right eyes without glasses | 0.5 | 0.5 | 0.5 | 0.5 |
| left eyes without glasses | 0.5 | 0.5 | 0.5 | 0.6 |
| Serum levels and dietary intake of alpha-tocopherol and beta carotene | | | | |
| Serum | | | | |
| Alpha tocopherol (mg/l) | 12.0 | 11.8 | 12.2 | 11.7 |
| Beta carotene (µg/l) | 173.0 | 184.0 | 213.5 | 201.0 |
| Dietary | | | | |
| Alpha-tocopherol (mg/day) | 10.7 | 10.9 | 10.8 | 10.6 |
| Beta carotene (mg/day) | 1.9 | 1.9 | 2.0 | 2.0 |
| <i>At the time of eye examination</i> | | | | |
| Age (years) | 68.8 | 68.6 | 68.7 | 68.1 |
| UV exposure (h/day) | 1.5 | 1.5 | 1.5 | 1.5 |
| Length of intervention (years) | 6.7 | 6.6 | 6.6 | 6.6 |
| Total follow-up (person-years) | 2438.0 | 2400.0 | 2422.0 | 2423.0 |
| Myopia (%) ² | 5.1 | 6.1 | 5.2 | 6.0 |
| Compliance (% of capsules taken) | 99.3 | 99.2 | 99.3 | 99.0 |

¹ Systolic blood pressure >=160mmHg and/or diastolic >=95 mmHg.

² Glasses for far vision before 20 years of age.

1035 men with postal addresses in Helsinki or the surrounding province of Uusimaa and aged 65 years or older at the time of the ophthalmological examin-

ation were invited to participate. The prevalence of ARM is known to increase sharply after 65 years (Leibowitz et al. 1980). The ophthalmological examin-

Table 3. Baseline visual acuity (median) of participants and non-participants in the ARM examination.

| | right | | left | |
|------------------------|-------|-----|------|-----|
| | VA | n | VA | n |
| With glasses | | | | |
| Participants | 1.0 | 522 | 1.0 | 521 |
| Non-participants | 1.0 | 56 | 1.0 | 56 |
| Without glasses | | | | |
| Participants | 0.6 | 939 | 0.6 | 938 |
| Non-participants | 0.5 | 94 | 0.6 | 94 |

Table 4. Distribution of age-related maculopathy classes by treatment (AT=alpha-tocopherol, BC=beta-carotene, ATBC=combination of alpha-tocopherol and beta carotene).

| ARM Class ¹ | AT n=237 | ATBC n=257 | BC n=234 | Placebo n=213 |
|--------------------------|-------------|---------------|-------------|------------------|
| No ARM | 162 (68.4%) | 184 (71.6%) | 166 (70.9%) | 160 (75.1%) |
| I | 65 | 64 | 64 | 46 |
| II | 2 | 6 | 2 | 6 |
| III | 6 | 2 | 2 | 0 |
| IV | 2 | 1 | -- | 1 |
| Total with ARM (p=0.468) | 75 (31.6%) | 73 (28.4%) | 68 (29.1%) | 53 (24.9%) |

¹ O=no ARM, I=dry maculopathy, with hard drusen and/or pigmentary changes, II=soft macular drusen, III=disciform degeneration, IV=geographic atrophy.

ation took place during their final follow-up trial visit between December 1992 and March 1993. A total of 941 persons participated (91 %), and non-participation rates were similar across the intervention groups.

Procedures

The men sampled for the eye study were invited to participate and sent an additional questionnaire two weeks before their follow-up appointment, with an informed written consent form enclosed. The questionnaire covered severe eye diseases and trauma. Exposure to sunlight was assessed by asking how many hours were spent outdoors during weeks and weekends. If a participant had received glasses to correct far vision before reaching 20 years, he was considered to have myopia in adolescence. History of diseases, smoking, use of alcohol, body mass index (BMI), blood pressure, total serum cholesterol and length of education were obtained from the baseline evaluations of the ATBC Study, as were the serum levels of AT and BC (The ATBC Cancer Prevention Study Group 1994; The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study Group 1994). Consumption of alcohol and die-

tary intakes of vitamin E and BC were assessed via a detailed food use questionnaire completed at home by the participants (Pietinen et al. 1988).

The eye examination included autorefractometry, slit lamp examination and applanation tonometry. Fundus photographs were taken with a Canon photo-camera at 40 and 60 degree angles after dilatation of the pupils using tropicamide drops (5mg/ml). Three pictures were taken of each eye on Kodak Ektachrome 100 ASA HC slide film. The films were coded and filed for later grading.

Nuclear sclerosis cataracts were assessed using slit lamp photography classification (grade NO II or higher) according to the Lens Opacity Classification System (LOCS II) (Chylack et al. 1988).

Classification of ARM

The retinal specialist in our group, LL, assessed the ARM from the fundus photographs. She examined six photographs (three per eye) of each participant without knowledge of the subject's treatment group, medical history or physical findings. The fundus photographs were first scored from 0 to 3 for quality; 0 was assigned to pictures impossible to grade, and 3 to excellent quality photographs.

Picture quality was similar across the intervention groups (Table 1). Each fundus was classified from 0 to IV (Table 4). A person was considered to have ARM if he had a class I or higher change in either eye, and severity was classified according to the worst eye. In all 5 classes the proportion of excellent quality photographs exceeded 85%.

Statistical analyses

ARM was treated as a dichotomous response in the main analyses; zero in the classification meant no ARM while scores I-IV indicated ARM. ARM rates were first tested for interaction between antioxidant treatments by the chi-square test. The next step involved logistic regression with the general estimation equations approach (GEE) (Liang & Zeger 1986) to reveal intervention effect (as odds ratio, OR) when controlling influences of relevant factors. This method also accounts for the relatedness of left and right eye observations in one cluster (person), giving correct confidence limits as well as estimates for intra-cluster correlation (correlation of both eyes within a person). The AT and BC treatments were introduced to the model one at a time. Diabetes, high blood pressure, outdoor ultraviolet exposure, amount of smoking, use of alcohol, total serum cholesterol, length of education, body mass index, myopia in adolescence and nuclear cataract were used as explanatory variables.

Results

Some 62 % of the participants were aged 65 to 70 years, 31 % 71 to 75 years, and 7 % over 75 years. The distribution of relevant background characteristics was even across the intervention categories (Table 2).

Capsule compliance (percentage of scheduled capsules taken) among participants of the ARM study was 98 %, compared to 99 % among those who refused the eye study, and visual acuity was also similar (Table 3).

Baseline serum alpha-tocopherol and beta-carotene levels were lower among participants with ARM (s-AT 12.2 mg/l vs. 12.4 mg/l and s-BC 244.3 µg vs. 258.0 µg/l). The same tendency was apparent when we studied the placebo group separately (total N=213) (s-AT 11.3 mg/l vs. 12.6 mg/l, and s-BC 251.2 µg/l vs. 272.8 µg/l).

There were 269 cases with ARM (29

Table 5. Effect of supplementation with alpha-tocopherol or beta-carotene for 5-8 years on the occurrence of age-related maculopathy and its possible risk factors among the 941 participants of the ARM study. Odds ratios (OR) and their 95% confidence intervals (95% CI) according to the general estimation equations analysis.

| | OR | 95% CI |
|----------------------------------|------|-----------|
| Alpha-tocopherol | 1.13 | 0.81-1.59 |
| Beta-carotene | 1.04 | 0.74-1.47 |
| Right/left eye | 1.11 | 0.93-1.32 |
| History of diabetes ¹ | 0.89 | 0.41-1.94 |
| Hypertension | 1.43 | 0.98-2.10 |
| Ultraviolet exposure (h/day) | 0.98 | 0.84-1.14 |
| Cigarettes | | |
| 10 >=20 (nr/day) | 1.11 | 0.68-1.79 |
| 20 >=80 (nr/day) | 1.11 | 0.66-1.87 |
| Use of alcohol ¹ | | |
| 0 >=30 (g/day) | 0.75 | 0.43-1.29 |
| 30 >=60 (g/day) | 0.66 | 0.33-1.32 |
| 60 >=100(g/day) | 0.71 | 0.20-2.49 |
| Cholesterol ¹ | | |
| 5 >=6 (mmol/l) | 0.99 | 0.57-1.73 |
| 6 >=7 (mmol/l) | 0.73 | 0.42-1.26 |
| 7 >=15(mmol/l) | 0.70 | 0.39-1.25 |
| BMI ¹ | | |
| 20 >=25 (kg/m ²) | 1.45 | 0.59-3.61 |
| 25 >=27 (kg/m ²) | 0.75 | 0.29-1.96 |
| 27 >=40 (kg/m ²) | 0.85 | 0.33-2.15 |
| Education ¹ | | |
| 9 >=12 (years) | 0.94 | 0.60-1.48 |
| 12 >=17 (years) | 0.84 | 0.50-1.42 |
| Myopia at adolescence | 1.06 | 0.47-2.39 |
| Nuclear cataract | 0.67 | 0.42-1.05 |

¹=baseline value.

); the highest proportion was in the alpha-tocopherol supplementation group (32 %) and the lowest in the placebo group (25 %) (Table 4).

There was no interaction between the interventions (AT and BC; $p=0.21$). There were more ARM cases in the AT treatment (30%; 148/494) than the no-AT (27%; 121/447) group, and more in the BC (29%; 141/491) than in the no-BC (28%; 128/450) group, although these differences were not statistically significant.

Supplementation with AT showed no association with the prevalence of ARM (OR 1.10, 95% CI 0.83-1.45) in the univariate model. Nor did BC (OR 1.01, CI 0.77-1.33) when entered into the GEE model alone. Correlation between fellow-eyes in the GEE analysis was 0.7. No statistically significant protective effect of either alpha-tocopherol or beta-carotene could be detected in the GEE analysis, even after adjusting for potential risk factors for ARM (Table 5). Arterial hypertension increased the risk of ARM (borderline significance OR 1.43, CI 0.98-

2.10) and nuclear cataract decreased it (borderline significance OR 0.67, CI 0.42-1.05).

Discussion

These findings do not support the hypothesis that antioxidant supplementation with alpha-tocopherol or beta-carotene protects against age-related maculopathy. Although case-control studies have indicated inverse associations of both AT (West et al. 1994) and BC (The Eye Disease Case-Control Study Group 1993) with ARM incidence, there are presently no clinical trials against which to compare our results.

Either our results are true, or bias, incomplete case ascertainment, inaccurate diagnosis of ARM, wrong dose of the antioxidants or a too short supplementation period could explain the findings.

As the design of the ARM study allowed us to explore the effect of AT and BC in a population-based sample ran-

domly assigned to the treatment groups, bias is unlikely. The methodological superiority of a controlled clinical trial was weakened here by the lack of endpoint registration at baseline. Randomization is assumed to have ensured balance in ARM and its possible risk factors at the start of intervention, and this is supported by the lack of any essential differences among the intervention groups in any of the characteristics we could evaluate at baseline. More importantly, visual acuity was similar in all four intervention groups at baseline, with and without glasses, which suggests they were also equal in the prevalence and severity of maculopathy at the start of the trial.

There is no reason to suspect that men with signs or risk factors of ARM dropped out of the trial between the recruitment and the eye examination in different rates by intervention since no imbalance has been found (The ATBC Cancer Prevention Study Group 1994; The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study Group 1994). Neither was there any statistically significant difference in visual acuity at baseline across the intervention categories among the 1811 drop-outs of the trial cohort in the Helsinki-Uusimaa areas.

It might be assumed that the overall health status of those who refused to take part in our ARM study was inferior to that of the participants. However, baseline visual acuity was again similar between these two groups (Table 3). Thus selection bias of any kind is highly unlikely.

Inclusion of the major risk factors for ARM in the logistic regression model effectively adjusted for any possible imbalance due to confounding factors among the participants.

Case ascertainment was virtually complete, no photographs of eligible cases were missing, and poor quality pictures were few. The prevalence of ARM in our sample is in accordance with population prevalence studies (Vinding 1989; Klein et al. 1992).

Diagnosis of ARM can be unreliable, especially if the examination is performed on-site (Kahn et al. 1975). When only small pigmentary changes are considered, the prevalence may vary between 5% and 41% by examiner. We diagnosed ARM from macular colour photographs, and the diagnostic criteria were set before the pictures were examined. Drusen indicate early ARM and are distinct clinical findings in the macular region of the fundus.

It was impossible for the examiner to identify individuals from the coded fundus photographs and ARM assessment was done without knowledge of the subjects' treatment group or medical history. Furthermore, fundus picture diagnosis does not allow the examiner to see possible signs of beta-carotene use by the participant under study (e.g. yellowing of the skin). There is thus no reason to suspect any assessment bias between the intervention groups.

The known association of ARM and cataract needs to be kept in mind (Sperduto & Seigel 1980; Liu et al. 1989; Klein et al. 1994). It has been suggested that AMD and senile nuclear cataracts have the same pathogenesis (Klein et al. 1994), which may indicate similar risk factors and mechanisms of prevention. If any of the antioxidants were able to prevent (or enhance) lens opacity, it could be hypothesized that this would increase the incidence of ARM, because a clear lens would not protect the macula from deleterious effects of ultraviolet or visible light. This would cause a bias, weakening any protective effect of alpha-tocopherol or beta-carotene on ARM. In our sample nuclear cataract protected against ARM in the GEE model (although the OR was of borderline significance) although controlling its effect did not change the estimated effects of AT or BC.

The important questions raised by this study are: are alpha-tocopherol and beta-carotene necessarily the most important antioxidants in ARM, and was the dose appropriate to observe any protective effect? AT and BC are both powerful antioxidants acting in separate ways. The doses in this study are many times greater than the dietary intake of these nutrients in Finland as well as the U.S. Recommended Daily Allowances (The ATBC Cancer Prevention Study Group 1994). There are no clinical trial data to support or contradict our findings.

The speed of the early developmental changes of ARM is slow. We might have missed the disease by a too short intervention. In persons with bilateral drusen the cumulative incidence of developing new lesions is reportedly 23.5 % at 3 years for patients older than 65 years (Holtz et al. 1994). ARM decreases visual acuity significantly when drusen develop into geographic atrophy or disciform exudative lesions. Over a 4.9-year follow-up Gass found a significant decrease in visual acuity in 18 per cent of 49 patients presenting with bilateral drusen at base-

line (Gass 1973). When we analyzed cases that were over 70 years of age separately, the result after multiple regression analysis was the same. As severe forms of ARM might react differently to antioxidant supplementation than the mild forms of the disease (West et al. 1994), we analyzed the effects of AT and BC separately for the class II and class III ARM cases. Although there were far fewer cases, the result remained essentially the same.

Many patients take vitamin supplements these days based on their physician's recommendation. The possible harmful effects of such supplements need to be considered. In addition to skin coloration, changes in scotopic B-wave in electroretinography, and crystal formation in the macula have been observed with prolonged beta-carotene supplementation (Yoser & Heckenlively 1989). The possibly higher mortality due to ischemic heart disease and lung cancer with the use of beta-carotene also needs to be borne in mind (The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study Group 1994).

In summary, we found no effect of supplementation with alpha-tocopherol or beta-carotene on the prevalence of age-related maculopathy. Our findings indicate that if any such protective effect does exist, its magnitude has no clinical or public health implications. More controlled clinical trials are needed to clarify the role of antioxidant vitamins on the development of ARM.

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