Association between Low Plasma Vitamin E Concentration and Progression of Early Cortical Lens Opacities

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The authors evaluated the association between plasma vitamin E content and progression of eye lens opacities. A total of 410 hypercholesterolemic eastern Finnish men participated in the study from January 1990 to September 1993 in Kuopio, Finland. Lens opacities were classified three times at 18-month intervals using the Lens Opacities Classification System II. A low plasma vitamin E level (lowest quartile) was associated with a 3.7-fold excess risk (95% confidence interval 1.2-11.8) of the progression of early cortical lens opacities compared with the highest quartile (p = 0.028). In addition, the number of cigarettes smoked daily was a significant predictor of the progression of cortical lens opacity (relative risk = 1.06 per cigarette, 95% confidence interval 1.003-1.12). The progression of nuclear lens opacities was not associated with either the plasma vitamin E content or smoking. The data suggest that low plasma vitamin E content may be associated with increased risk of the progression of early cortical lens opacity. Am J Epidemiol 1996; 144:496-500.

Cataracts are a significant global health problem and a major cause of blindness among the elderly (1). With age, a number of degenerative changes occur in the lens, leading to opacification and eventually to cataract formation. The lens is subject to oxidative stress and, with age, becomes less capable of handling such stress (2). Free radical-mediated chemical modification has been suggested as one mechanism of cataract formation (2). There are epidemiologic studies suggesting that the use of multivitamin supplements (3-7), e.g., vitamins E and C (3, 8), are associated with reduced risk of senile cataract. Low levels of plasma antioxidant vitamins have been shown to be associated with cataracts in some (9, 10), but not all, studies (11, 12). In a number of studies, there was an association between some types of lens opacities and some antioxidant vitamins. For example, vitamin E had an inverse association with the risk of nuclear sclerosis (3, 13), but in another study, higher levels of alpha-tocopherol were directly associated with increasing nuclear sclerosis (14). Differences in study designs make the interpretation of the results difficult; the term “cataract” may mean those undergoing cataract surgery (type unspecified) (8, 9, 12, 15), lens opacities that decrease visual acuity (3), lens opacities without visual acuity criteria (10, 13), or typed and graded lens opacities (4, 6, 7, 11, 14). However, to our knowledge, no prospective longitudinal studies of risk factors for the progression of early lens opacity have been published.

For epidemiologic studies of lens opacification, many methods have been developed. One of them, the Lens Opacities Classification System II (LOCS II), has been shown to be an accurate, reliable, and reproducible method for classifying lens opacities in vivo (16, 17). LOCS II is based on standardized reference tables, and the lens opacity is examined either by slit lamp or by photographing the lens (16). LOCS II has been used both in cross-sectional (6, 18) and longitudinal (19, 20) cataract studies. In a large cataract incidence and progression study of 1,193 persons, LOCS II was observed to be sufficiently sensitive to detect changes in the lens status during a 3-year follow-up time (20).

The purpose of this study was to investigate the association between plasma vitamin E level and the progression of lens opacities.

MATERIALS AND METHODS

This study was carried out with participants of the Kuopio Atherosclerosis Prevention Study, a population-based trial concerning the effect of pravastatin on...
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ultrasonographically assessed atherosclerotic progression (21). A total of 447 middle-aged men with elevated serum low density lipoprotein cholesterol (LDL cholesterol) were eligible for the study, and they were randomized to receive either pravastatin or a placebo for 3 years. The criteria for eligibility were serum LDL cholesterol of at least 4.0 mmol/liter, total serum cholesterol below 7.5 mmol/liter, and no specified contraindications, e.g., insulin-dependent diabetes and corticosteroid therapy. Prior to entry, all participants signed a written informed consent. The study protocol was approved by an international policy advisory board and by the Research Ethical Committee of the University of Kuopio. The advisory board also acted as the safety committee. Two independent monitors ascertained that the study was conducted according to good clinical practice standards.

A total of 410 subjects completed the trial and underwent all three ophthalmologic examinations carried out at 18-month intervals. Lens opacity assessment at baseline was obtained from 810 eyes, but due to missing data, results of the LOCS II classification were available from 806 eyes. Anophthalmia, pseudophakia, and contraindications to mydriatics were the reasons for not grading the lens opacities. Because of cataract extractions during the follow-up (four eyes), allergic reaction to phenylephrine, refusal of pupillary dilation, and missing data, LOCS II classification was available for 792 eyes at all three study visits. All of the ophthalmologic examinations were carried out by a single ophthalmologist (P. R.). Pupils were dilated with fixed-ratio combination drops containing 0.8 percent tropicamide and 5.0 percent phenylephrine.

To minimize the effect of measurement variability, we chose to use the criteria for change introduced by Magno et al. (19, 22). Since three consecutive measurements were performed, a progression was considered to have taken place only if an increase in the LOCS II grading from baseline to the 18-month examination was verified at the 36-month visit. Similar criteria were used for regression. If the grading was equal at the baseline and 18-month examinations, the lens status was considered stable. All remaining eyes were included in the “noise” category and excluded from the statistical analysis.

Plasma alpha-tocopherol concentration (µmol/liter) was determined by a high-performance liquid chromatographic method (23). To separate the effect of vitamin E from those of serum lipids, lipid-standardized vitamin E concentration was used in the statistical analysis. The lipid-standardized vitamin E concentration was computed as the ratio of the measured plasma vitamin E concentration to the vitamin E concentration, predicted by a linear regression equation on the basis of serum total cholesterol and serum triglyceride concentrations (24). Consequently, the lipid-standardized vitamin E variable had no unit. Serum LDL cholesterol was precipitated using polyvinyl sulphate (Boehringer Mannheim, Mannheim, Germany) and calculated as the difference between total and supernatant cholesterol. Serum total cholesterol was measured enzymatically with an autoanalyzer (Kone Specific, Kone, Ltd., Espoo, Finland). Smoking history, including the present smoking status (cigarettes/day, smoking-years), alcohol consumption (converted to absolute alcohol grams per month), and exercise (global exercise score, 0–3) at baseline were assessed by public health nurses in an interview. The ophthalmologist was unaware of the laboratory values and smoking and alcohol consumption histories. Intakes of nutrients were assessed at the 12-month visit by a nutritionist using a quantitative food frequency questionnaire.

The association between baseline plasma vitamin E levels and the probability of progression of lens opacities was analyzed using the generalized estimating equation (GEE) with an SPSS macro (SPSS, Inc., Chicago, Illinois). This marginal regression modeling estimates the relation between outcome (in this study, lens opacity progression) in each eye and risk factors, taking into account the correlation between eyes in the same subject (25).

In analyses concerning the association between progression of lens opacity and plasma vitamin E or lipid-standardized vitamin E levels, the model included age, smoking, alcohol use, serum cholesterol, and serum LDL cholesterol content as covariates. Indicator variables for vitamin E and standardized vitamin E quartiles were used, and the highest quartile served as the reference.

The association between plasma vitamin E or lipid-standardized vitamin E and both lifestyle and dietary factors was analyzed by using multiple linear regression model. The explanatory variables were alcohol intake, cigarette smoking, exercise, and all dietary variables except vitamin E. Linoleic acid (g); carbohydrates (g) other than starch, sucrose, lactose, and fructose; vitamin C (mg); and cholesterol (mg) were statistically significantly associated with plasma vitamin E or lipid-standardized vitamin E and entered the GEE analysis as additional covariates.

RESULTS

The mean age of the participants at baseline was 57.3 years (minimum, 44.0 years; maximum, 63.0 years). The baseline plasma vitamin E level varied from 8.0 to 53.6 µmol/liter, the mean was 28.09 µmol/liter, and the standard deviation was 7.66 µmol/liter.
Corresponding numbers for lipid-standardized vitamin E were: variation, 0.28–1.84; mean = 1.0; and standard deviation = 0.27. The distribution of the LOCS II grading at baseline is presented in table 1.

In the LOCS II category for nuclear opalescence, 10 eyes (1.3 percent) did not meet the criteria for regression, progression, or stability and were thus regarded as noise. Seventeen eyes (2.1 percent) showed progression, 498 (68.5 percent) remained stable, and 73 (9.2 percent) showed progression of nuclear opacity. For cortical opacities, the numbers were: noise, 54 eyes (6.8 percent); regression, 22 eyes (2.8 percent); stable, 678 eyes (85.6 percent); and progression, 38 eyes (4.8 percent). In the category posterior subcapsular opacities, four eyes (0.5 percent) met the criteria for regression, 781 (98.6 percent) remained stable, and four (0.5 percent) showed progression. Three eyes (0.4 percent) did not meet the criteria for regression, 781 (98.6 percent) remained stable, and 73 (9.2 percent) showed progression of nuclear opacity. For cortical opacities, the numbers were: noise, 54 eyes (6.8 percent); regression, 22 eyes (2.8 percent); stable, 678 eyes (85.6 percent); and progression, 38 eyes (4.8 percent). In the category posterior subcapsular opacities, four eyes (0.5 percent) met the criteria for regression, 781 (98.6 percent) remained stable, and four (0.5 percent) showed progression. Three eyes (0.4 percent) were regarded as being in the noise category. Because the progression group for posterior subcapsular opacities was so small, the risk factors for this lens opacity type were not analyzed.

There was a statistically significant ($p < 0.01$) positive association between age and cigarette smoking with progression of cortical lens opacities. Plasma vitamin E ($\mu$mol/liter) and lipid-standardized vitamin E (not shown) were inversely associated with the progression of nuclear opacity (table 2). When indicator variables for vitamin E and lipid-standardized vitamin E quartiles were entered, the relative risk for the lowest quartile was 3.68 (95 percent confidence interval (CI) 1.15–11.76, $p = 0.028$) for vitamin E and 3.67 (95 percent CI 1.22–11.09, $p = 0.021$) for lipid-standardized vitamin E compared with the highest quartile. The middle two vitamin E quartiles did not differ statistically significantly from the highest quartile; the relative risks for these groups were 1.67 (95 percent CI 0.43–6.58) and 1.15 (95 percent CI 0.32–4.19) (figure 1). An additional adjustment for antidy-

**TABLE 1.** Distribution of observations in the Lens Opacities Classification System II categories at baseline examination (1990) among 410 hypercholesterolemic men from eastern Finland

<table>
<thead>
<tr>
<th>Grade</th>
<th>Nuclear opalescence</th>
<th>Cortical opacities</th>
<th>Posterior subcapsular opacities</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>0</td>
<td>98</td>
<td>12.2</td>
<td>643</td>
</tr>
<tr>
<td>1</td>
<td>681</td>
<td>84.5</td>
<td>103</td>
</tr>
<tr>
<td>2</td>
<td>22</td>
<td>2.7</td>
<td>42</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>0.2</td>
<td>14</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>0.4</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>0.1</td>
<td></td>
</tr>
</tbody>
</table>

* Data missing from one eye.

**DISCUSSION**

Only a few epidemiologic studies have been reported concerning the association of serum or plasma vitamin E with cataracts. The results of these studies are inconsistent. For example in a nested case-control study in Finland, there was a 1.9-fold (95 percent CI 0.9–4.1) risk of cataract in men and women in the lowest third of serum alpha-tocopherol concentration at baseline, and this association was strengthened by adjustment for smoking, serum cholesterol, and other confounding factors (9). On the other hand, in a small case-control study, there was no difference in vitamin E concentration between cataract patients and controls; however, no adjustment for confounding factors was made (12).

In a study in 660 subjects in which lens opacities were typed and graded dichotomously as present or absent, Vitale et al. (13) observed that higher levels of alpha-tocopherol, measured up to 4 years earlier, were associated with reduced probability of nuclear opacity (odds ratio = 0.52, 95 percent CI 0.27–0.98) and middle levels were associated with reduced risk of cortical opacity (odds ratio = 0.57, 95 percent CI 0.32–1.02). Jacques et al. (10), however, found no consistent relation in their case-control study using similar outcome classification. In both studies, results were adjusted for age, sex, and diabetes (10, 13).

In two cross-sectional studies, there was also an assessment of mild lens opacities of different types. There was no association between lens opacities and vitamin E either in a study of 685 Hong Kong fisher-

**TABLE 2.** Risk factors* at baseline for the progression of cortical lens opacities in 3 years (1990–1993) among hypercholesterolemic men from eastern Finland

<table>
<thead>
<tr>
<th>Baseline risk factor</th>
<th>Relative risk</th>
<th>95% confidence interval</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma vitamin E ($\mu$mol/liter)</td>
<td>0.933</td>
<td>0.874–0.995</td>
<td>0.033</td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.181</td>
<td>1.060–1.316</td>
<td>0.002</td>
</tr>
<tr>
<td>Smoking (cigarettes/day)</td>
<td>1.060</td>
<td>1.003–1.120</td>
<td>0.038</td>
</tr>
<tr>
<td>Alcohol intake (g/month)</td>
<td>1.000</td>
<td>0.999–1.002</td>
<td>0.696</td>
</tr>
</tbody>
</table>

* The model also included baseline serum total and low density lipoprotein cholesterol concentrations and dietary intake of cholesterol, linoleic acid, vitamin C, and carbohydrates (none statistically significant).

† Based on *robust* Z statistic.
men (11) or in a study of 400 randomly selected persons in Beaver Dam, Wisconsin (14).

In our follow-up study, the majority of the lens opacities at the beginning were mild, and thus, we were able to obtain information about risk factors affecting the early stage of lens opacity formation and progression. The participants in this study were all middle-aged hypercholesterolemic men, none of whom were really of "cataract" age, and subjects with such known risk factors for lens opacities as insulin-dependent diabetes and corticosteroid therapy were excluded. Because study subjects were drawn from an observational population study representing the eastern Finnish male population, except for their hypercholesterolemia (21), they cannot be regarded as nutritionally deprived.

There was a large variation in the baseline plasma vitamin E level (from 8.0 to 53.6 μmol/liter). Subjects in the lowest quartile of plasma vitamin E (<22.9 μmol/liter) had 3.7 times greater risk for progression of cortical opacity than those in the highest quartile (plasma vitamin E > 32.7 μmol/liter). Plasma vitamin E level was not correlated with the amount of smoking, and the association of vitamin E with progression of cortical lens opacity was not affected by the adjustment for smoking.

For nuclear opalescence progression, no difference between the vitamin E groups was observed. It has been suggested that different lens opacity types have different etiologies (1). This postulation is also supported by our study since no association between vitamin E and nuclear opacification was observed.

In this nutritionally nondeficient study population, low plasma vitamin E content was observed to be a risk factor for progression of early cortical opacity. Additional research is needed in other populations.

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REFERENCES

1. The cataract guideline. Ophthalmology 1993;100 (Suppl.):15-16S.


