

Three of the four bandages had to be ordered by the district supplies department as they could not be obtained on prescription. The cost of bandages for all six clinics for one year was about £35-40 000. The family health services committee probably already pays a similar or larger amount for materials currently available and used on FP10 prescription but which are largely ineffective in achieving ulcer healing. Transfer of this budget to district supplies or the recognition of these bandages on drug tariff would seem to be the way forward.

About a tenth of the patients in this study had significant arterial disease shown by low ankle/brachial pressure indices, so that compression bandaging was contraindicated and may have lead to pressure necrosis and amputation.^{3 11} It is therefore essential that the community staff are trained to assess patients for arterial disease so that the correct treatment is offered.

The main thrust of this study was the setting up of community ulcer clinics and assessing the results of this service. Despite the success of this service in treating ulcerated legs it must be acknowledged that reulceration is a major problem in these patients. Preliminary analysis of rates of recurrence in this study has shown that about a fifth of legs reulcerate within six months of healing and a third by one year, despite regular visits for compression hosiery. These results may be improved by using skin grafting techniques or venous surgery in more patients than was possible in this first attempt at a comprehensive community ulcer service.

This study has drawn together community and

hospital staff around a single common problem. Community nurses have observed real improvements in the care of their patients, which has given them additional job satisfaction. There is a clear need for a coordinated community based approach to this common and socially isolating condition, centred on a nurse specialising in venous ulcers.

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Serum antioxidant vitamins and risk of cataract

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Abstract

Objective—To investigate serum concentrations of α tocopherol, β carotene, retinol, and selenium for their prediction of end stage cataract.

Design—A case-control study, nested within a cohort study, based on the linkage of records of subjects aged 40-83 from a health survey with those from the national Finnish hospital discharge register.

Subjects—47 patients admitted to ophthalmological wards for senile cataract over 15 years and two controls per patient individually matched for sex, age, and municipality.

Main outcome measure—Concentration of serum micronutrients, development of cataract according to whether operation was performed.

Results—Low serum concentrations of antioxidant vitamins predicted the development of senile cataract, the odds ratio between the lowest third and the two higher thirds of the distribution of serum concentrations of α tocopherol and β carotene being 1.9 (95% confidence interval 0.9 to 4.1) and 1.7 (0.8 to 3.8), respectively. Patients with both α tocopherol and β carotene concentrations in the lowest third had an odds ratio of 2.6 (1.0 to 6.8) of cataract compared with subjects in the top two thirds. The associations were strengthened by adjustment for potential confounding factors such as occupation, smoking, blood pressure, serum cholesterol concentration, body mass index, and diabetes. No association was found between the serum concentrations of selenium, retinol, and retinol binding protein and the risk of cataract.

Conclusions—Low serum concentrations of the antioxidant vitamins α tocopherol and β carotene are risk factors for end stage senile cataract. Controlled trials of the role of antioxidant vitamins in cataract prevention are therefore warranted.

Introduction

Age related cataract is the common cumulative response to various damaging influences attacking the capsule, epithelium, and constituent fibres of the lens of the eye.¹ The oxidation of lens proteins by free radicals is believed to play an important part in the multifactorial process leading to lens opacification.² This process may be modified by micronutrients with an antioxidant capacity, such as α tocopherol, β carotene, and selenium. Some evidence from experimental² and cross sectional case-control studies³⁻⁶ supports this hypothesis, but it has not previously been tested in a longitudinal study.

We examined the association between serum α tocopherol, β carotene, and selenium concentrations and the subsequent risk of end stage senile cataract over a median follow up of 15 years.

Subjects and methods

The mobile clinic unit of the Social Insurance Institution carried out multiphasic health examinations in 58 440 Finns aged 15-99 years in various parts of Finland during 1966-72.⁷ Serum concentrations of micronutrients were determined from a sample of 1419 people who initially served as a sex and age matched

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control group for cancer cases in a nested case-control study of micronutrients and incidence of cancer.⁷ The controls were free of cancer at the baseline and throughout follow up.

A self administered questionnaire supplied information about previous and current illnesses, smoking habits, medication, and occupation. Subjects were classified as either non-smokers or current smokers. Casual blood pressure was recorded in a sitting position from the right arm after a rest of five minutes. Body height and weight were measured, and body mass index (weight/height²) was computed. Diabetes mellitus was defined according to the current World Health Organisation criteria.⁸ Serum cholesterol concentrations were determined from venous blood samples with an autoanalyser with a modified Liebermann-Burchard reaction.

The 1419 serum samples drawn at baseline were kept at -20°C until 1974, when they were thawed for determining the concentrations of α tocopherol, β carotene, selenium, retinol, and retinol binding protein. Retinol, β carotene, and α tocopherol concentrations were determined simultaneously by using high pressure liquid chromatography.⁹ α Tocopherol was measured with a spectrophotofluorometric detector and retinol and β carotene with ultraviolet absorption detectors. Serum concentrations of retinol binding protein were determined by the immunodiffusion technique (Boehring Diagnostics, Hoechst, Germany). Serum concentrations of selenium were determined by using graphite furnace atomic absorption spectrometry.¹⁰ The coefficient of variation for analytic reproducibility of the measured concentrations ranged from 2.1% to 10.9%.⁷

The cataract cases were identified by linking the data from the health examinations with the Finnish hospital discharge register kept by the National Board of Health.¹¹ This national register covers all diagnoses for people discharged from general hospitals in Finland, including all the ophthalmological units in the country. In the study population of 1419 people, 47 (22 men and 25 women) had been admitted to ophthalmological wards between 1 January 1970 and 31 December 1984 with a diagnosis of senile cataract (ICD (eighth revision) code 374.02). To focus on the incidence of mature senile cataract that required extraction, we did not consider cataracts of other types as end points. Two controls matched for sex, age, and municipality were selected for each patient from subjects who had no record of a hospital discharge for cataract by the date of the admission of the patient with whom they were matched. The maximum age difference was zero in 32 triplets, one year in 11 triplets, two years in three triplets, and four years in one triplet. Matching for municipality was done to control for the time of the baseline examination and for the length of storage of serum samples.

The association between serum concentrations of antioxidants and the risk of cataract operation, including confounding factors, was estimated with the conditional logistic model.^{12,13} The odds ratios were computed for thirds of the distribution of serum concentrations of antioxidants. Significances of the differences in mean concentrations of cases and controls were tested by the paired *t* test.

Results

Table I shows the baseline characteristics of patients with cataract and controls. The age of patients and controls at baseline ranged from 47 to 83 (mean 66) years. There were more smokers among the patients, who also had slightly lower concentrations of serum cholesterol and lower systolic and diastolic blood pressures and body mass indices than the controls. The

TABLE I—Baseline characteristics of patients with senile cataract and controls

	No (%) of cases (n=47)	No (%) of controls (n=94)
Sex		
Male	22 (47)	44 (47)
Female	25 (53)	50 (53)
Age		
40-59	11 (23)	21 (22)
60-69	19 (41)	38 (41)
70-83	17 (36)	35 (37)
Occupation		
Agriculture	10 (21)	32 (34)
Industry	17 (36)	14 (15)
Service, other groups	11 (23)	29 (31)
White collar	5 (11)	11 (12)
Housewives	4 (9)	8 (8)
Smoking		
Non-smoker	27 (57)	65 (69)
Current smoker	20 (43)	29 (31)
Serum cholesterol in thirds*		
Lowest	16 (34)	30 (32)
Middle	17 (36)	32 (34)
Highest	14 (30)	32 (34)
Body mass index in thirds*		
Lowest	19 (40)	30 (32)
Middle	15 (32)	35 (37)
Highest	13 (28)	29 (31)
Systolic blood pressure in thirds*		
Lowest	17 (36)	28 (30)
Middle	19 (41)	30 (32)
Highest	11 (23)	35 (38)
Diastolic blood pressure in thirds*		
Lowest	23 (49)	27 (29)
Middle	11 (23)	32 (34)
Highest	13 (28)	34 (37)
Diabetes		
No	42 (89)	86 (91)
Yes	5 (11)	8 (9)

*All thirds based on sex specific distributions among controls. Middle third for serum cholesterol was 6.24-7.63 mmol/l in men and 7.09-8.27 mmol/l in women; for body mass index 24.5-28.5 kg/m² in men and 25.5-29.5 kg/m² in women; for systolic blood pressure 146-166 mm Hg in men and 156-185 mm Hg in women; and for diastolic blood pressure 82-91 mm Hg in men and 85-96 mm Hg in women.

TABLE II—Odds ratio (95% confidence interval) of senile cataract between lowest third and higher thirds of serum antioxidants

Variable	Third*	No of cases	No of controls	Odds ratio	95% Confidence interval
α Tocopherol	Higher	25	62	1.0	
	Lowest	22	32	1.9	0.9 to 4.1
β Carotene	Higher	23	55	1.0	
	Lowest	20	30	1.7	0.8 to 3.8
α Tocopherol and β carotene	Other	28	69	1.0	
	Both low	15	16	2.6	1.0 to 6.8
Retinol	Higher	31	59	1.0	
	Lowest	16	35	0.8	0.3 to 2.0
Selenium	Higher	29	62	1.0	
	Lowest	17	29	1.3	0.5 to 3.3

*Thirds based on distribution among controls. Lowest third for α tocopherol was <17.2 μ mol/l in men and <20.0 μ mol/l in women; for β carotene <0.095 μ mol/l in men and <0.114 μ mol/l in women; for retinol <2.06 μ mol/l in men and <1.96 μ mol/l in women; and for selenium <0.722 μ mol/l in men and <0.684 μ mol/l in women.

prevalence of diabetes was similar in both groups as was the use of some drugs (antihypertensives, corticosteroids, diuretics, and tranquillisers).

The mean serum concentrations of α tocopherol and β carotene in patients with cataract (20.5 μ mol/l and 0.178 μ mol/l, respectively) were lower than those of controls (21.2 μ mol/l and 0.185 μ mol/l), but the differences were not significant ($p=0.47$ and $p=0.75$, respectively). Patients and controls had similar serum concentrations of retinol (2.26 μ mol/l *v* 2.28 μ mol/l, $p=0.88$), retinol binding protein (53.1 mg/l *v* 54.0 mg/l, $p=0.61$), and selenium (0.792 μ mol/l *v* 0.804 μ mol/l, $p=0.77$).

Low serum concentrations of α tocopherol and β carotene predicted an increased risk of cataract. The odds ratios for the lowest thirds of the distribution of serum α tocopherol and β carotene relative to the higher thirds were, respectively, 1.9 (95% confidence interval 0.9 to 4.1) and 1.7 (0.8 to 3.8) (table II). Low concentrations of serum α tocopherol and β carotene often coexisted. The odds ratio of cataract in the

people with both serum α tocopherol and β carotene in the lowest third was 2.6 (1.0 to 6.8). The risk increased somewhat after adjustment for potential confounding factors, which included smoking, diastolic blood pressure, serum cholesterol, body mass index, and occupation (4.7, 1.2 to 17.5). Serum concentrations of retinol, retinol binding protein, and selenium were not related to the risk of senile cataract.

Discussion

The mechanisms of development of cataracts related to age are still disputed, but oxidative damage of lens proteins is believed to play an important part in the process.² The resistance of the lens declines with age, as does its intrinsic defence system. Antioxidants such as vitamins C and E and β carotene may thus modify the antioxidant defence and age related development of cataracts.² This hypothesis is strongly supported by the findings of our 15 year follow up study, which showed an almost threefold risk of end stage senile cataract in elderly Finns with serum concentrations of α tocopherol and β carotene in the lowest third of the distribution.

Our findings confirm those of some previous cross sectional case-control studies that reported an increased risk of cataract in subjects with low supplementary intake of vitamin E⁵ or low serum concentrations of α tocopherol¹⁴ or β carotene.¹⁵ Our findings are also consistent with those of experimental studies in animals¹⁶ and three cross sectional case-control studies reporting a low risk of cataract in people with high serum concentrations of two or more antioxidants.^{3,5} In this study no data were available on vitamin C state, which cross sectional studies have shown to be strongly associated with the risk of cataract.^{5,15}

Several methodological issues should be taken into account when interpreting the present findings. We cannot fully rule out the possibility of a common underlying cause for both senile cataract and low serum concentrations of α tocopherol and β carotene, such as an insidious disease process predisposing patients to senile cataract and depressing serum concentrations of micronutrients. This is unlikely, however, as the patients with cataract survived throughout the long follow up and were identified from a population that presumably was in better than average health—that is, free of cancer.

The observed associations may have been due to confounding by one or more of the several personal, medical, and environmental risk factors identified for formation of cataracts.⁶ We were able to control for many of these and generally found only weak associations between them and risk of cataract. We could not adjust for dietary intake or nutritional state, which might account for some of the observed associations.³ These, however, were probably not important in the present study as the patients and controls had similar concentrations of retinol binding protein, a well documented indicator of nutritional state.¹⁷

The patients with cataract in our study were admitted to ophthalmological wards for an operation for uncomplicated senile cataract. In Finland the decision to extract this type of cataract is based on fairly uniform criteria of functional limitation caused by the loss of visual acuity, but the possibility of selection and referral bias¹⁸ cannot be fully excluded. For example, cataracts associated with diabetes may be under-represented because concomitant retinopathy is a relative contraindication for surgery. This may be one explanation why there was no association between diabetes and risk of admission for cataract. Such a bias,

however, is unlikely for the association found between serum concentrations of antioxidant vitamins and risk of cataract.

The significance of our results rests on the accurate identification of cases. The validity of the diagnoses recorded in the Finnish hospital discharge register has been amply demonstrated for stroke,¹¹ myocardial infarction,¹¹ acute glaucoma,¹⁹ sciatica due to herniated lumbar disc,²⁰ and disease related to intake alcohol.²¹ Although not tested for validity, the hospital discharge data on cataracts can reasonably be expected to be equally accurate. The control group may have contained subjects with cataract, which would cause a bias of relative risk estimates toward 1.0.

Antioxidant vitamins may have degraded somewhat during storage of the serum samples. This should not bias case-control comparisons, however, as the serum samples of patients and controls were handled identically during storage, and length of storage (that is, municipality) was one of the matching factors in the selection of controls.⁷

Our findings show that low serum concentrations of the antioxidant vitamins α tocopherol and β carotene predict the development of end stage senile cataract. The relation may be causal, reflecting defective antioxidant defence of the lens against oxidative damage. Controlled trials of antioxidant vitamins in cataract prevention seem to be warranted.

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