Dietary Antioxidant Intake and Risk of Type 2 Diabetes

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OBJECTIVE — The intake of antioxidants was studied for its ability to predict type 2 diabetes.

RESEARCH DESIGN AND METHODS — A cohort of 2,285 men and 2,019 women 40–69 years of age and free of diabetes at baseline (1967–1972) was studied. Food consumption during the previous year was estimated using a dietary history interview. The intake of vitamin C, four tocopherols, four tocotrienols, and six carotenoids was calculated. During a 23-year follow-up, a total of 164 male and 219 female incident cases occurred.

RESULTS — Vitamin E intake was significantly associated with a reduced risk of type 2 diabetes. The relative risk (RR) of type 2 diabetes between the extreme quartiles of the intake was 0.69 (95% CI 0.51–0.94, P for trend = 0.003). Intakes of α-tocopherol, γ-tocopherol, δ-tocopherol, and β-tocotrienol were inversely related to a risk of type 2 diabetes. Among single carotenoids, β-cryptoxanthin intake was significantly associated with a reduced risk of type 2 diabetes (RR 0.58, 95% CI 0.44–0.78, $P < 0.001$). No association was evident between intake of vitamin C and type 2 diabetes risk.

CONCLUSIONS — This study supports the hypothesis that development of type 2 diabetes may be reduced by the intake of antioxidants in the diet.

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Although obesity and physical inactivity are known to be major risk factors for type 2 diabetes, recent evidence suggests that oxidative stress may contribute to the pathogenesis of type 2 diabetes by increasing insulin resistance or impairing insulin secretion (1). Dietary antioxidants have been hypothesized to have a protective effect against the development of diabetes by inhibiting peroxidation chain reactions (2). It seems plausible that a sufficient intake of antioxidants plays an important role in protection against type 2 diabetes. However, little epidemiological evidence is available on the role of dietary antioxidant intake in prevention of type 2 diabetes.

In one prospective cohort study, vitamin C intake was significantly lower among incident cases of type 2 diabetes (3). In three prospective observational studies, serum α-tocopherol levels were associated with lower risk of type 1 or type 2 diabetes (4–6). Serum β-carotene and α-tocopherol concentrations were nonsignificantly associated with a reduced risk in a cohort of Finns (7). In some case-control and cross-sectional studies, significantly lower serum levels of α-tocopherol, carotene, or vitamin C have been observed in individuals with diabetes than in control subjects (8–13). In one American study, α-tocopherol concentrations were even higher in diabetic patients than in control subjects (14). Some prospective studies have shown that higher vegetable and fruit consumption may lower the risk of developing diabetes, suggesting that antioxidants in the diet may have a synergistic effect (3,15,16).

Dietary vitamin E, four tocopherols, four tocotrienols, vitamin C, and six carotenoids were investigated for their ability to predict type 2 diabetes in a large prospective Finnish population study.

RESEARCH DESIGN AND METHODS

Subjects

The Finnish Mobile Clinic Health Examination Survey carried out health examinations in various regions of Finland during 1966–1972. Selection and characteristics of the population examined were described previously (17). A dietary study including 10,054 people was initiated in 1967. The study population comprised 2,285 men and 2,019 women after including only individuals 40–69 years of age and those who reported a daily energy intake of 800–6,000 kcal but excluding those who were pregnant or had a history of diabetes or heart disease.

Baseline characteristics

A questionnaire yielded information on occupation, current pregnancy, babies born with birth weight over 4,500 g, potential family history of diabetes, previous and current illnesses, consumption of medicines, and health-related habits, such as smoking. Occupation was grouped into nine categories and geographical area into six regions covering the whole country. The subjects were also classified according to smoking status (18). Body weight and height were measured, and BMI was calculated. Casual blood pressure was measured with the auscultatory method. Four hypertension categories were formed on the basis of systolic and diastolic blood pressure and antihypertensive medication (18). Serum cholesterol concentration was determined with an autoanalyzer modification of the Liebermann-Burchard reaction. Known cases of diabetes were identified by information given by the participants. A glucose tolerance test was carried out to diagnose new diabetes at baseline, using

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A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

diagnostic criteria of the World Health Organization (19). Previously known or new diabetic subjects were excluded from the analyses.

Food consumption data

Total habitual food consumption during the previous year was estimated using a dietary history interview (20). Trained interviewers used a questionnaire listing over 100 food items and mixed dishes common to the Finnish diet. Energy intake was calculated based on the intake of protein, fat, and available carbohydrate. The vitamin C, pyridoxine, and folic acid contents in food items were derived from Finnish food composition tables (21), and vitamin E components and carotenoids were completed using analyzed values of Finnish foods (22,23). Vitamin E activity in α-tocopherol equivalents was estimated from tocopherols and tocotrienols using published factors (24). Total carotenoid intake was calculated as a sum of six carotenoids. The estimation of fiber, fatty acids, and flavonoids is presented elsewhere (17,18,25).

Outcome

During a 23-year follow-up, a total of 164 male and 219 female incident cases were identified from a nationwide registry of patients receiving drug reimbursement, which is maintained by the Social Insurance Institution (7). Participants in the present study were linked to this register by unique social security codes assigned for each Finnish citizen.

Table 1—*Age-, sex-, and energy-adjusted mean ± SD levels and percentages of baseline variables in cases of type 2 diabetes and noncases: the Finnish Mobile Clinic Health Examination Study, 1967–1972*

Variable	Cases	Noncases	*P*
n	383	3,921	
Age (years)*	53.7 ± 8.0	51.7 ± 7.6	<0.001
BMI (kg/m^2)	29.4 ± 4.5	26.2 ± 3.8	<0.001
Serum cholesterol (mmol/l)	6.8 ± 1.3	7.0 ± 1.4	0.001
Sex (men %)†	47	54	0.006
Hypertension (%)	29	15	<0.001
Current smoker (%)	28	33	0.02
Family history of diabetes (%)‡	27	19	<0.001
Child with birth weight >4,500 g (% women)	16	11	0.02
Saturated fat (g/day)	60.4 ± 27.9	60.2 ± 26.3	0.70
Energy (kcal/day)§	2,422 ± 857	2,501 ± 580	0.06
Vitamin E (α-tocopherol equivalents mg/day)	6.4 ± 2.1	7.2 ± 6.9	0.06
α-Tocopherol (mg/day)	5.6 ± 1.8	5.8 ± 2.0	0.06
β-Tocopherol (mg/day)	0.52 ± 0.22	0.54 ± 0.25	0.29
γ-Tocopherol (mg/day)	2.3 ± 3.1	2.5 ± 3.8	0.28
δ-Tocopherol (mg/day)	0.46 ± 0.96	0.51 ± 1.1	0.37
α-Tocotrienol (mg/day)	1.6 ± 0.71	1.6 ± 0.72	0.19
β-Tocotrienol (mg/day)	2.2 ± 0.73	2.2 ± 0.75	0.14
γ-Tocotrienol (mg/day)	0.10 ± 0.09	0.10 ± 0.10	0.34
δ-Tocotrienol (mg/day)	0.02 ± 0.04	0.02 ± 0.05	0.95
Vitamin C (mg/day)	71.7 ± 33.6	73.7 ± 36.4	0.32
Total carotenoids (μg/day)‖	3,466 ± 2,773	3,713 ± 2,880	0.10
α-Carotene (μg/day)	78.7 ± 140	87.6 ± 143	0.24
β-Carotene (μg/day)	1,695 ± 2,032	1,849 ± 2,108	0.17
γ-Carotene (μg/day)	39.7 ± 54.2	41.1 ± 47.9	0.58
Lycopene (μg/day)	703 ± 961	735 ± 868	0.48
β-Cryptoxanthin (μg/day)	2.7 ± 5.6	3.5 ± 5.6	0.01
Lutein + zeaxanthin (μg/day)	947 ± 341	997 ± 339	0.01

*Adjusted for sex and energy intake; †adjusted for age and energy intake; ‡proportion of persons having first-degree relatives with diabetes; §adjusted for age and sex; ‖sum of six carotenoids.

Statistical methods

Nutrient intakes were adjusted for total energy by the method described by Willet and Stampfer (26) and categorized as appropriate. The relative risks (RRs) of type 2 diabetes with 95% CIs between quartiles of antioxidant nutrients were calculated using Cox's life table regression model. Potential confounding factors (age, energy intake, sex, geographical area, smoking, BMI, occupation, and family history of diabetes) were entered into the model. A model including hypertension and serum cholesterol was also used. Tests for trends were carried out based on a likelihood ratio test by including nutrients as continuous variables in the model. In additional analyses, we examined whether alternative hypotheses could explain the associations by including in the model intakes of saturated fat, pyridoxine, folic acid, flavonoids, and cereal fiber.

RESULTS — Individuals who developed diabetes during the 23-year-follow-up were older, more obese, and more likely to be hypertensive (Table 1). They also more often had a family history of diabetes, and women with incident diabetes more often had given birth to babies weighing over 4,500 g. Distribution of dietary antioxidants did not show strong differences between incident cases and noncases with the exception of β-cryptoxanthin, lutein, and zeaxanthin.

Total vitamin E intake and total carotenoids were associated with a reduced risk of type 2 diabetes, whereas vitamin C intake was not (Table 2). Of the individual tocopherols and tocotrienols, the intakes of α-tocopherol, γ-tocopherol, δ-tocopherol, and β-tocotrienol were inversely associated with the diabetes risk. Among the carotenoids considered, β-cryptoxanthin intake showed the strongest inverse association with diabetes risk. In general, the results were similar among men and women with the exception of α-carotene, which showed a difference between sexes. Among women, the RRs across the three upper quartiles were 0.73 (95% CI 0.49–1.08), 1.04 (0.72–1.50), and 0.63 (0.41–0.96, *P* for trend = 0.15), respectively, when compared with the lowest quartile. Among men, the corresponding RRs were 1.22 (0.77–1.94), 1.47 (0.93–2.31), and 0.99 (0.61–1.62, *P* = 0.86). The *P* value for interaction between sexes was 0.05.

After adding five potential nutritional

Table 2—*Adjusted* RR of type 2 diabetes between quartiles of energy-adjusted intake of antioxidants*

	Quartile of intake				
	1 Referent	2	3	4	*P* for trend
Vitamin E (α-tocopherol equivalents mg/day)	<5.51	5.51–6.26	6.27–7.31	>7.31	
Cases/persons at risk	128/1,076	93/1,076	82/1,076	80/1,076	
RR (95% CI)	1	0.79 (0.60–1.04)	0.78 (0.58–1.06)	0.69 (0.51–0.94)	0.02
α-Tocopherol (mg/day)	<4.66	4.66–5.30	5.31–6.20	>6.20	
Cases/persons at risk	129/1,076	89/1,076	84/1,076	81/1,076	
RR (95% CI)	1	0.72 (0.54–0.96)	0.80 (0.59–1.08)	0.66 (0.49–0.90)	0.02
β-Tocopherol (mg/day)	<0.38	0.38–0.49	0.50–0.64	>0.64	
Cases/persons at risk	110/1,076	92/1,076	106/1,076	75/1,076	
RR (95% CI)	1	0.97 (0.73–1.29)	1.09 (0.82–1.43)	0.76 (0.56–1.03)	0.18
γ-Tocopherol (mg/day)	<0.79	0.79–1.23	1.24–2.06	>2.06	
Cases/persons at risk	111/1,076	99/1,076	80/1,076	93/1,076	
RR (95% CI)	1	0.91 (0.69–1.20)	0.75 (0.56–1.01)	0.77 (0.57–1.03)	0.04
δ-Tocopherol (mg/day)	<0.09	0.09–0.15	0.16–0.28	>0.28	
Cases/persons at risk	113/1,076	99/1,076	86/1,076	85/1,076	
RR (95% CI)	1	0.85 (0.64–1.13)	0.81 (0.60–1.08)	0.69 (0.51–0.93)	0.02
α-Tocotrienol (mg/day)	<1.07	1.07–1.54	1.55–2.05	>2.05	
Cases/persons at risk	111/1,076	100/1,076	88/1,076	84/1,076	
RR (95% CI)	1	0.95 (0.72–1.25)	0.91 (0.68–1.21)	0.91 (0.67–1.23)	0.47
β-Tocotrienol (mg/day)	<1.69	1.69–2.15	2.16–2.67	>2.67	
Cases/persons at risk	110/1,076	106/1,076	86/1,076	81/1,076	
RR (95% CI)	1	0.97 (0.74–1.28)	0.77 (0.58–1.03)	0.76 (0.56–1.03)	0.03
γ-Tocotrienol (mg/day)	<0.04	0.04–0.07	0.08–0.12	>0.12	
Cases/persons at risk	96/1,076	107/1,076	92/1,076	88/1,076	
RR (95% CI)	1	0.95 (0.72–1.26)	0.88 (0.65–1.18)	0.79 (0.59–1.07)	0.11
δ-Tocotrienol (mg/day)	<0.002	0.002–0.006	0.007–0.01	>0.01	
Cases/persons at risk	105/1,076	110/1,076	76/1,076	92/1,076	
RR (95% CI)	1	1.01 (0.77–1.32)	0.69 (0.51–0.93)	0.84 (0.63–1.13)	0.06
Vitamin C (mg/day)	<49.7	49.7–66.2	66.3–87.9	>87.9	
Cases/persons at risk	96/1,057	96/1,063	87/1,061	98/1,068	
RR (95% CI)	1	0.97 (0.73–1.29)	0.91 (0.68–1.22)	0.97 (0.72–1.32)	0.77
Total carotenoids (μg/day)†	<1,862	1,863–2,865	2,867–4,519	>4,519	
Cases/persons at risk	112/1,062	74/1,064	110/1,062	81/1,061	
RR (95% CI)	1	0.71 (0.53–0.96)	0.97 (0.74–1.27)	0.71 (0.52–0.96)	0.07
α-Carotene (μg/day)	<9.4	9.4–34.4	34.5–103	>103	
Cases/persons at risk	86/1,058	102/1,067	97/1,062	92/1,062	
RR (95% CI)	1	1.11 (0.83–1.49)	1.02 (0.75–1.38)	0.94 (0.69–1.28)	0.55
β-Carotene (μg/day)	<698	698–1,104	1,105–2,121	>2,121	
Cases/persons at risk	100/1,060	83/1,064	114/1,063	80/1,062	
RR (95% CI)	1	0.83 (0.62–1.11)	1.14 (0.87–1.51)	0.74 (0.54–1.01)	0.25
γ-Carotene (μg/day)	<6.3	6.4–28.5	28.6–60.3	>60.3	
Cases/persons at risk	109/1,057	86/1,070	93/1,066	89/1,056	
RR (95% CI)	1	0.78 (0.59–1.04)	0.88 (0.67–1.18)	0.82 (0.61–1.10)	0.29
Lycopene (μg/day)	<112	113–494	495–1,064	>1,064	
Cases/persons at risk	110/1,058	86/1,068	93/1,067	88/1,056	
RR (95% CI)	1	0.79 (0.59–1.05)	0.86 (0.65–1.14)	0.81 (0.60–1.09)	0.23
β-Cryptoxanthin (μg/day)	<0.24	0.24–1.36	1.37–4.18	>4.18	
Cases/persons at risk	134/1,056	75/1,062	80/1,062	88/1,069	
RR (95% CI)	1	0.54 (0.40–0.73)	0.57 (0.43–0.76)	0.58 (0.44–0.78)	<0.001
Lutein + zeaxanthin (μg/day)	<749	749–935	936–1,156	>1,156	
Cases/persons at risk	112/1,057	92/1,064	96/1,065	77/1,063	
RR (95% CI)	1	0.91 (0.69–1.21)	0.95 (0.71–1.26)	0.74 (0.55–1.01)	0.09

*Adjusted for age, sex, geographic area, occupation, smoking, BMI, and family history of diabetes, and energy intake; †sum of six carotenoids.

confounders (saturated fat, pyridoxine, folic acid, flavonoids, and cereal fiber) to the model, the observed association between β-cryptoxanthin intake and diabetes risk remained significant (RR 0.59, 95% CI 0.44–0.79, $P < 0.001$). Adjustment for potential intermediate factors (serum cholesterol and hypertension) did not notably alter the results (data not shown) nor did exclusion of the first 2 years of the analysis (data not shown).

To shed light on the nature of the observed associations, the subjects were divided into different categories based on factors that potentially modify the association between antioxidant intake and type 2 diabetes incidence. No significant interaction was found in respect of BMI, smoking, hypertension, or serum cholesterol (data not shown).

CONCLUSIONS — The intakes of total vitamin E, α-tocopherol, γ-tocopherol, β-tocotrienol, and β-cryptoxanthin were associated with a reduced risk of type 2 diabetes. Our results add strength to the hypothesis, supported by animal experiments, that a sufficient intake of antioxidants plays a role in type 2 diabetes prevention (27,28). The results corroborate findings in earlier prospective studies, suggesting an inverse association between serum levels of total vitamin E, α-tocopherol, and incidence of type 2 diabetes (4,6). In a previous Finnish prospective study, inverse association between diabetes incidence and serum α-tocopherol and β-carotene concentrations vanished after adjustment for potential confounders (7). However, the number of the observations was rather small in this study (106 case subjects and 201 control subjects). In the present study, we could not observe an inverse association between vitamin C intake and diabetes incidence as reported in a previous study (3). In cross-sectional studies, intakes of vitamin C (29,30) or vitamin E (30,31) and plasma vitamin C concentration (32) have been inversely associated with glycated hemoglobin. Two cross-sectional studies have failed to show a relation between β-carotene and glycated hemoglobin (29,30). Analyses from the Insulin Resistance and Atherosclerosis Study did not show a significant association between insulin sensitivity and intakes of vitamin E and C (33). In clinical experiments, pharmacological doses of vitamin E have improved the insulin-mediated glucose uptake (34,35).

Vitamin E is the most efficient chain-breaking antioxidant that protects tissue membranes from oxidative damage (2). Vitamin C has the ability to regenerate tocopherols and tocotrienols from tocopheroxyl or tocotrionoxyl radicals (36). It has also been postulated that carotenoids may form a part of the antioxidative mechanism of cells, acting as antioxidants or modifying the levels of other antioxidants (37). According to these hypotheses, it appears conceivable that the beneficial effects related to antioxidants could be enhanced by the presence of a variety of antioxidants.

Although epidemiological evidence shows that antioxidants from plant foods are associated with reduced risk of type 2 diabetes, β-carotene supplementation had no effect on diabetes risk in an intervention study of American male physicians (38). The possible protective effects of vegetables and fruits resulting from the combined action of some antioxidant cocktail (3,15,16) has been suggested as a possible reason for the controversial results between supplementation trials and observational studies on the health effects of antioxidants. However, factors other than dietary antioxidants may also explain the findings. It is possible that individuals with diets high in antioxidants have healthier lifestyles than other people.

In addition to chance, several methodological issues may have influenced our results. The dietary history method has its limitations, and the consequential misclassification of subjects tends to alter observable associations between dietary exposure and outcome (39). In the present study, all the interviewers were trained nutrition professionals, and a preformed questionnaire was used to diminish differences between interviewers. The questions were open ended and offered opportunities to specify the answers. Likewise, food models were used to reduce errors of recall. In general, the short-term repeatability of the dietary history method was favorable, but long-term reliability was relatively poor (20). The poorer long-term reliability can be explained by changes in Finnish food consumption (20).

An interaction between sexes and α-carotene was found. Because no other antioxidant showed similar interaction and no biological hypothesis exists on different effects by sex, it was concluded that the sex interaction had occurred by chance.

The information on incident diabetes cases was obtained from a nationwide registry of drug reimbursements. The fact that we were unable to obtain data on cases undergoing dietary therapy only may have weakened the associations. On the other hand, in many cases, it is likely that diabetic patients undergoing dietary therapy only will later proceed to a phase when drug therapy is needed. Thus, it is probable that the cases included in the present study represent a group of patients with a more severe disease of relatively long duration.

Unfortunately, we could not include physical activity in the analysis. However, analyses performed in this study were adjusted for factors connected with health habits. It is possible that physical activity has been accounted for indirectly by these factors. The intakes of antioxidants may also be related to the presence of other biologically active compounds, which could have provided prevention from type 2 diabetes (e.g., phytochemicals). The contribution of vitamin supplements was not considered here. Because the use of vitamin supplements was rare at the time of baseline (40), it is apparent that supplement use has not caused misclassification of nutrient intakes. The high proportion of individuals with dietary intake higher than the potential range of biological relevance may mask the effect of antioxidants from foods. However, it is not yet completely clear whether the pharmacological doses of antioxidants has an effect on diabetes development.

This study adds weight to the hypothesis that antioxidant intake may reduce the risk of development of type 2 diabetes. Although these results, among those of the few other prospective studies, seem promising, more large-scale prospective studies and intervention trials are needed to establish a firm conclusion.

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