Lycopene, Atherosclerosis, and Coronary Heart Disease

TIINA RISSANEN,[1] SARI VOUTILAINEN, KRISTIINA NYYSSÖNEN, AND JUKKA T. SALONEN

Research Institute of Public Health, University of Kuopio, Kuopio, Finland 70211, Department of Public Health and General Practice, Koupio, Finland Inner Savo Health Centre, Suonenjoki, Finland

Diets rich in fruits and vegetables containing carotenoids have been of interest because of their potential health benefit against chronic diseases such as cardiovascular diseases (CVD) and cancer. Interest particularly in lycopene is growing rapidly following the recent publication of epidemiological studies that have associated high lycopene levels with reductions in CVD incidence. Two studies were conducted. In the first one, we examined the role of lycopene as a risk-lowering factor with regard to acute coronary events and stroke in the prospective Kuopio Ischemic Heart Disease Risk Factor (KIHD) Study. The subjects were 725 middle-aged men free of coronary heart disease and stroke at the study baseline. In a Cox's proportional hazards' model adjusting for covariates, men in the lowest quartile of serum levels of lycopene had a 3.3-fold ($P < 0.001$) risk of the acute coronary event or stroke as compared with others. In the second study, we assessed the association between plasma concentration of lycopene and intima-media thickness of the common carotid artery wall (CCA-IMT) in a cross-sectional analysis of the Antioxidant Supplementation in the Atherosclerosis Prevention (ASAP) study data in 520 asymptomatic men and women. In a covariance analysis adjusting for common cardiovascular risk factors, low plasma levels of lycopene were associated with an 18% increase of IMT in men as compared with men in whom plasma levels were higher than median ($P = 0.003$ for difference). In women, the difference did not remain significant after the adjustments. On the basis of these works, it is evident that the circulating levels of lycopene play some role with regard to cardiovascular health in Finland, at least in men. We conclude that circulating levels of lycopene, a biomarker of tomato-rich food, may play a role in early stages of atherogenesis and may have clinical and public health relevance. Exp Biol Med 227:900–907, 2002

Key words: lycopene; coronary event; stroke; artherosclerosis; carotid arteries; nutrition; carotenoids; KIHD study; ASAP study

Nutrition plays an important role in the development of coronary heart disease (CHD). Diets rich in fruits and vegetables containing carotenoids have been of interest because of their potential health benefit against chronic diseases such as cardiovascular diseases (CVD) and cancer. Increased intake and tissue or blood levels of carotenoids are associated with reduced risk of CVD (1–6). Although β-carotene has been investigated for many years, lycopene, the acyclic form of β-carotene without provitamin A, activity has attracted substantial interest more recently. Lycopene is red color pigment and in contrast to most other carotenoids that are widely distributed among great variety of fruits and vegetables, tomatoes and tomato products are main sources of lycopene in the diet. However, it is one of the major carotenoids in European countries and in the U.S. Lycopene has unique structural and chemical features that may contribute to its specific biological properties (7). It is also chemically quite resistant to heat and cooking. Because its high number of conjugated double bonds, lycopene exhibits higher singlet oxygen quenching ability compared with α- or β-carotene (8). The oxidation-protecting effect of tomato or lycopene has been shown in both human and animal studies (9, 10). A decreased oxidative modification of LDL may be one of the mechanisms by which lycopene may reduce the risk of CHD and atherosclerotic progression (11, 12).

As only few previous studies have dealt with the association between a low concentration of circulating lycopene and early atherosclerosis or CVD, we tested the hypothesis that men and women with low serum levels of lycopene have increased intima-media thickness of the common carotid artery wall (CCA-IMT) (13), and that there is increased risk of acute coronary events and stroke (14) in middle-aged men and women from eastern Finland.

Material and Methods

Study Populations. *The Kuopio Ischemic Heart Disease Risk Factor (KIHD) study.* The KIHD study is an ongoing population-based study designed to investigate risk factors for CVD, atherosclerosis, and related outcomes in middle-aged men from eastern Finland, the population with one of the highest recorded rates of CHD (15). The study was approved by the Research Ethics Committee of the University of Kuopio. All study subjects gave their written informed consent. A total of 2682 participants (82.9% of

[1] To whom requests for reprints should be addressed at Research Institute of Public Health, University of Kuopio, Kuopio, Finland 70211. E-mail: Tiina.rissanen@uku.fi

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those eligible), aged 42, 48, 54, or 60 years, was enrolled in the study between March 1984 and December 1989.

Work I is based on the follow-up of the KIHD study. Four-year re-examinations for those examined in 1987 through 1989 were conducted between March 1991 and December 1993. Out of a total of 1229 men eligible for the follow-up study, 52 had died, were suffering from severe illness, or had migrated away from the region, and 139 could not be contacted or refused to participate. Thus, 1038 men were examined in the follow-up study. As previous disease affects the diet, men with a prevalent CHD or stroke (n = 306) were excluded from the present analyses. Of the remaining 732 men, data on serum lycopene concentration were available for 725 men.

The Antioxidant Supplementation in Atherosclerosis Prevention (ASAP) study. The ASAP Study was a randomized double-masked placebo-controlled 2 × 2 factorial trial concerning the effect of vitamin E and C supplementation in the prevention of atherosclerotic progression in smoking and nonsmoking men and postmenopausal women. The study was approved by the Research Ethics Committee of the University of Kuopio. All study subjects gave their written informed consent.

The subjects were regularly smoking (>5 cigarettes/day) or nonsmoking men and postmenopausal women aged 45–69 years with a serum cholesterol concentration of >5.0 m*M*/l at a screening visit. The exclusions included uncontrolled hypertension and severe diseases. Subjects came to the baseline visits at the Research Institute of Public Health, University of Kuopio, between October 1994 and October 1995. For the work II, blood for lycopene and other chemical measurements was drawn before antioxidant supplementation.

Ascertainment of Follow-Up Events and Ultrasonographic Assessment of CCA-IMT. The collection data and the diagnostic classification of acute coronary events and stroke were performed as described previously (14). In the work I, definite acute myocardial infarctions (AMIs), probable AMIs, prolonged chest pain episodes, and definite ischemic strokes were used as outcome events. If a subject had multiple nonfatal coronary events or strokes during the follow-up, the first was considered as the end point. The average follow-up time to the first coronary event or stroke was 5.3 years (range 0.4–6.9 years). Of all 41 outcome events, 19 were definite AMIs, 10 were probable AMIs, four were typical acute chest pain episodes, and eight were ischemic strokes.

The of ultrasonographic measurements of CCA-IMT were performed as described previously (16).

Chemical and Dietary Measurements. In the KIHD study, serum for lycopene determination was extracted with ethanol and hexane, and the measurements were carried out by a reversed-phase high-performance liquid chromatography (HPLC) method in samples that had been kept at –80°C for four to 36 months (17). Briefly, 200 μl of heparinized plasma was extracted with 5 ml of hexane and 1 ml of ethanol containing α-tocopherol acetate as an internal standard. The hexane layer was separated and evaporated to dryness. The residue was dissolved in mobile phase. The mobile phase consisted of acetonitrile-methanol-chloroform, 47 + 47 + 6 by volume. A reversed phase C18 column was used, and peaks were detected at wavelengths of 470 nm for lycopene by a diode array detector (model 168; Beckman Instruments, Fullerton, CA). Pure analytes from Sigma (St Louis, MO) were used as primary standards and their concentrations were determined spectrophotometrically according to Thurnham *et al.* (18). As the stability of the pure carotenoids is poor, a frozen plasma pool was used as the secondary standard with the analysis batches. Extraction efficiency was tested by adding known amounts of lycopene standard (Sigma) and calculating the recovery. The recoveries were 80% for 0.45 μ*M*/l and 75% for 1.35 μ*M*/l of lycopene added. The detection limit for each carotenoid with this method was 0.03–0.07 μ*M*/L. The coefficients of variation (CV) were determined with a serum pool analyzed in 25 separate batches. The CV was 11.0%.

In the ASAP study, plasma was stored at –80°C for 3 to 15 months until it was analyzed (17). The limit of detection for lycopene in these batches was 0.01–0.02 μ*M*/l. The CV was determined with a plasma pool analyzed in 14 separate batches and was 10.1%.

Dietary intake of foods and nutrients was assessed at baseline of the ASAP study by 4-day instructed food recording. Instructions were given and completed food recordings were checked by a nutritionist. Intake of nutrients was calculated using NUTRICA®, version 2.5 software. The data bank of NUTRICA® is complied using mainly Finnish values of nutrient composition of foods. All nutrients were adjusted for dietary energy intake using the residual method (19). Energy adjustment is based on the rationale that a larger, more physically active person requires a high caloric intake, which is associated with a higher absolute intake of all nutrients. Therefore, energy adjustment takes into account differences in energy requirements among individuals. The residuals were standardized by the mean nutrient intake of a subject consuming 10 MJ/d, the approximate average total energy intake in this study population. An assessment of other covariates was performed as described previously (13, 14).

Statistical Methods. In the KIHD study, data were analyzed using SPSS 9.01 for Windows 98. The distributions were expressed as means and ± SD. The means were compared by analysis of variance (ANOVA). The subjects were classified into quarters according to their serum lycopene concentration. The relationship of serum lycopene with the risk of acute coronary events and strokes was analyzed using Cox's proportional hazards' models. Relative hazards (risks), adjusted for other risk factors, were estimated as antilogarithms of coefficients for independent variables. The confidence intervals (CI) were estimated based on the assumption of asymp-

totic normality of estimates. All statistical tests were two-tailed.

In the ASAP study, the data were analyzed using SPSS 9.01 for Windows 98. Cigarette smoking was reported as a percentage and other variables were reported as mean ± SD. Subjects were classified into two categories according to their concentration of plasma lycopene. We compared the higher-than-median level to the lower level. The statistical significance of differences between these two lycopene groups in the main characteristics of the subjects was studied by the Student's *t* test. The association between plasma lycopene and ultrasonographically assessed CCA-IMT was tested for statistical significance also by using covariance analysis, adjusting for age, smoking, serum triglycerides, serum HDL and LDL cholesterol, plasma concentration of total homocysteine (tHcy) and systolic blood pressure, ultrasound observer, and intake of four nutrients (saturated fatty acids, vitamin C, vitamin E, and fiber).

In both studies, the serum/plasma lycopene values below the detection limits of the assay batch were marked as 0.00 μ*M*/l in statistical analysis. All tests were two-tailed, and a *P* value less than 0.05 was considered significant.

Results

Serum Levels of Lycopene and the Incidence of Acute Coronary Events and Stroke, the KIHD Study. During the follow-up time of 5 years and 3 months, 41 men experienced an acute coronary event or stroke. The mean (±SD) level of serum lycopene was 0.17 (±0.14) μ*M*/l, ranging from the detection limit to 1.02 μ*M*/l. Participants who developed an acute coronary event or stroke were more likely to be older, had lower plasma level of vitamin C, and had higher systolic blood pressure than the men who did not experience an event. They also had a 39% lower ($P = 0.003$) serum level of lycopene. The baseline characteristics of the KIHD cohort members are shown in Table I.

We categorized the subjects into quarters of the serum levels of lycopene (less than 0.07 μ*M*/l, 0.08–0.14 μ*M*/l, 0.15–0.24 μ*M*/l, and more than 0.24 μ*M*/l) and we compared the lowest to the other quarters. Age ($P < 0.001$), serum folate ($P < 0.001$), β-carotene ($P < 0.001$), plasma vitamin C ($P < 0.001$), systolic blood pressure ($P = 0.001$), and body mass index ($P = 0.048$) differed statistically significantly between the quarters. During the average follow-up time, 9.6% of men in the lowest quarter of serum lycopene and 2.9% of men in other quarters developed an acute coronary event ($P < 0.001$), and 2.7% of men in the lowest quarter and 0.6% of men in the other quarters developed a stroke ($P = 0.016$). In a Cox' proportional hazards' model adjusting for age, examination years, systolic blood pressure, and three nutritional factors (serum β-carotene, serum folate, and plasma vitamin C), men in the lowest quarter of serum concentration of lycopene had a 3.3-fold (95% CI 1.7–6.4, $P < 0.001$) risk of an acute coronary event or stroke as compared with others ($P = 0.009$ for a linear trend across the quarters).

Plasma Level of Lycopene and Carotid Atherosclerosis, the ASAP Study. The mean (±SD) concentration of plasma lycopene in the study population was 0.16 ± 0.11 μ*M*/l, and ranged from detection limit to 0.64 m*M*/l. Mean plasma levels of lycopene were higher in women (0.17 ± 0.11 μ*M*/l) than in men (0.14 ± 0.12 μ*M*/l; $P = 0.007$ for difference). In men, serum levels of lycopene correlated negatively to mean and maximal CCA-IMT (Pearson's correlation coefficients, $r = -0.23$, $P < 0.001$, and $r = -0.22$, $P < 0.001$, respectively) with a strength of association similar to positive correlation of most known risk factors (Table II). In women, negative correlations were weaker ($r = -0.08$, $P = 0.176$ and $r = -0.11$, $P = 0.081$, respectively). The relationship between plasma levels of lycopene with both mean and maximal CCA-IMT is shown in Figure 1.

The main characteristics of the subjects are presented in Table III. For men, age, plasma concentration of homocysteine, and dietary vitamin C differ statistically significantly between the men who had plasma levels of lycopene lower

Table I. The Main Characteristics of the Subjects of the KIHD Study

	Subjects who developed an acute coronary event or a stroke ($n = 41$)		Other subjects ($n = 684$)		*P* for difference in means	All subjects ($n = 725$)	
	Mean	SD	Mean	SD		Mean	SD
Serum lycopene (μmol/l)	0.10	0.12	0.17	0.14	0.003	0.17	0.14
Serum β-carotene (μmol/l)	0.42	0.41	0.41	0.33	0.839	0.41	0.33
Serum folate (nmol/l)	9.77	4.30	10.48	3.90	0.258	10.44	3.92
Plasma vitamin C (mg/l)[a]	7.82	3.93	9.26	3.77	0.018	9.17	3.79
Age (years)	57.6	6.5	54.9	6.6	0.011	55.0	6.6
Body mass index (kg/m^2)	27.6	3.5	27.4	3.5	0.721	27.4	3.5
Systolic blood pressure (mmHg)	140.1	15.1	134.6	16.4	0.039	134.9	16.4
Serum total cholesterol (mmol/l)	5.69	0.85	5.50	0.91	0.178	5.51	0.91
Serum HDL cholesterol (mmol/l)	1.08	0.29	1.12	0.29	0.350	1.12	0.29
Serum LDL cholesterol (mmol/l)	4.10	0.75	3.90	0.81	0.132	3.91	0.81
Smoking (%)	34		27		0.315	27	

[a] Measured 4 years earlier.

Table II. Pearson's Correlation Coefficients (r) and Statistical Significance for Association Between CCA-IMT and Nutritional Factors and Cardiovascular Risk Factors in Middle-Aged Eastern Finnish Men and Women of the ASAP Study

	Men (n = 256)		Women (n = 264)	
	r	P	r	P
Serum lycopene (μmol/l)	−0.23	<0.001	−0.08	0.176
Age (years)	0.33	<0.001	0.31	<0.001
Systolic blood pressure (mmHg)	0.16	0.009	0.26	<0.001
Body mass index (kg/m^2)	−0.02	0.753	0.09	0.136
Serum LDL cholesterol (mmol/l)	0.08	0.201	0.18	0.004
Serum HDL cholesterol (mmol/l)	−0.16	0.009	−0.19	0.001
Serum triglycerides (mmol/l)	−0.06	0.383	0.57	0.352
Smoking (cigarettes/day)	0.09	0.156	−0.01	0.817
Plasma homocysteine (μmol/l)	0.13	0.034	0.11	0.084

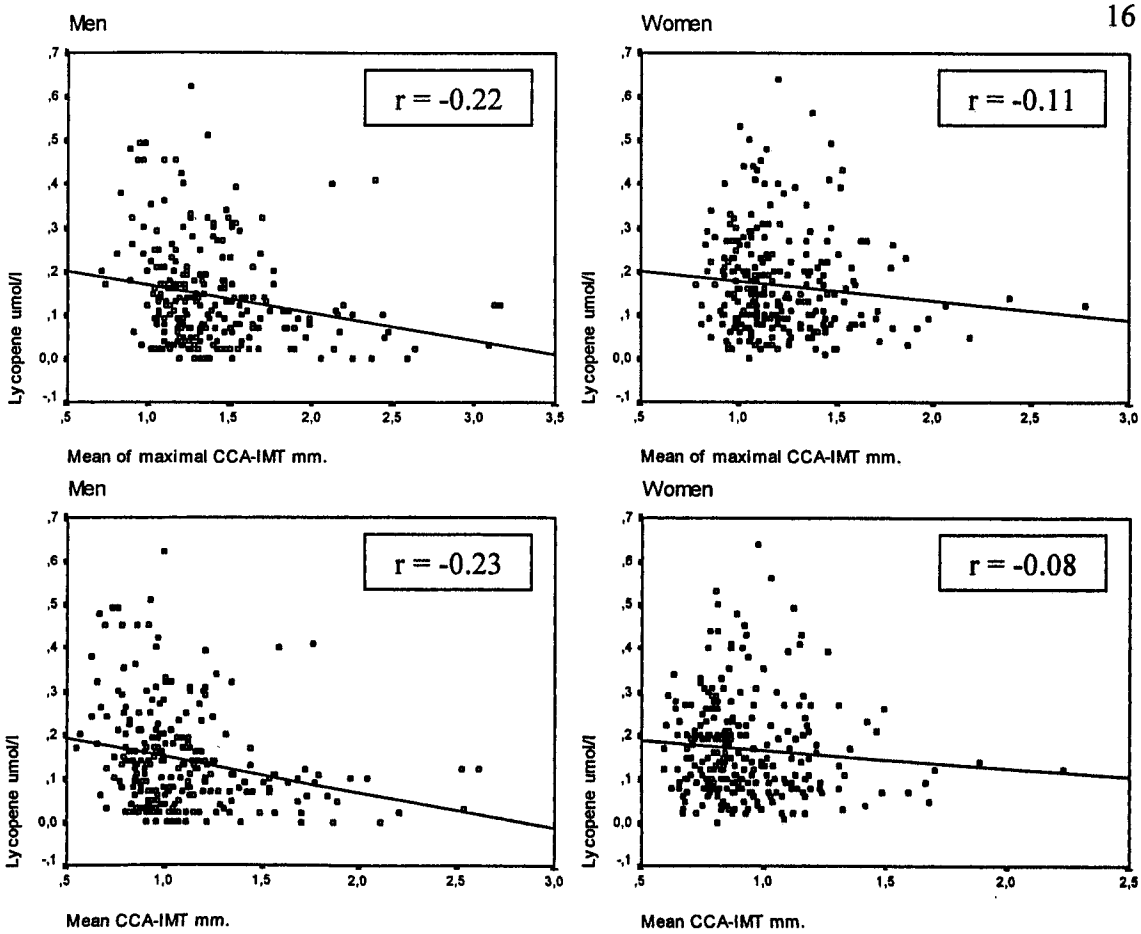

Figure 1. The relationship between plasma levels of lycopene and mean and maximal CCA-IMT in middle-aged eastern Finnish men and women of the ASAP study.

than the median (<0.12 μM/l) as compared with those who had higher values. The women with lower levels of plasma lycopene (<0.15 mM/l) differed significantly with regard to age, systolic blood pressure, serum HDL cholesterol, plasma concentration of tHcy, and dietary vitamin C intake from those with the higher levels of plasma lycopene. Mean IMT of the right and left CCA was 1.18 mm in men and 0.95 mm in women with low plasma lycopene levels, and was 0.97 mm in men (P < 0.001 for difference) and 0.89 mm in women (P = 0.012 for difference) with higher plasma levels of lycopene. In men in the highest quarter of plasma lycopene levels, the CCA-IMT was 17.5% lower and in women was 5.6% lower than in men and women in the lowest quarter of plasma lycopene levels.

In the covariance analysis, adjusting for other cardiovascular risk factors (age, serum triglycerides, serum HDL

Table III. Main Characteristics of the Subjects of the ASAP Study

Plasma lycopene (μmol/l)	Men (n = 256)					Women (n = 264)				
	(n = 136) <0.12 Mean	SD	(n = 120) ≥0.12 Mean	SD	P for difference	(n = 144) <0.15 Mean	SD	(n = 120) ≥0.15 Mean	SD	P for difference
Serum lycopene (μmol/L)	0.06	0.04	0.24	0.10		0.09	0.04	0.26	0.10	
Age (years)	61.6	5.0	58.3	6.2	<0.001	61.1	4.6	58.1	5.8	<0.001
Body mass index, kg/m^2	26.0	3.0	26.1	2.8	0.901	26.4	3.5	25.8	2.9	0.173
Waist to hip-ratio	0.95	0.05	0.95	0.05	0.935	0.82	0.05	0.82	0.04	0.900
Systolic blood pressure, mmHg	135.3	17.7	131.6	18.8	0.103	136.1	20.8	130.2	18.4	0.016
Diastolic blood pressure, mmHg	79.8	8.7	80.9	9.0	0.304	78.7	9.5	77.8	8.3	0.401
Serum total cholesterol, mmol/l	6.30	0.92	6.36	0.88	0.542	6.44	1.00	6.54	1.09	0.454
Serum HDL cholesterol, mmol/l	1.11	0.27	1.16	0.30	0.165	1.31	0.34	1.48	0.36	<0.001
Serum LDL cholesterol, mmol/l	4.56	0.96	4.56	0.89	0.997	4.53	1.00	4.42	1.12	0.428
Serum triglycerides, mmol/l	1.65	0.76	1.64	0.92	0.897	1.58	0.90	1.52	0.71	0.721
Plasma homocysteine, μmol/l	11.09	2.56	10.10	2.51	0.004	9.74	2.39	9.02	2.08	0.010
Dietary saturated fatty, E%	16.6	4.5	15.7	3.7	0.072	15.6	3.6	15.3	3.5	0.416
Dietary fibre, g/day[a]	21.9	6.7	20.3	7.4	0.065	20.6	4.6	21.1	5.3	0.430
Dietary vitamin C, mg/day[a]	80.6	52.4	100.2	66.3	0.010	94.6	53.8	113.7	73.9	0.016
Dietary vitamin E, mg/day[a]	9.5	4.6	9.6	3.6	0.826	9.7	2.4	9.8	2.3	0.691
Smoking, %[b]	53		41		0.053	49		47		0.671
Intima media thickness, mm	1.18	0.39	0.97	0.20	<0.001	0.95	0.25	0.89	0.19	0.027

Note. E% indicates percentage of energy.
[a] Adjusted for energy intake.
[b] Proportion of each group of plasma levels of lycopene.

and LDL cholesterol, plasma tHcy, and systolic blood pressure), ultrasound observer, and intake of four nutrients (proportion of saturated fatty acids of total daily energy, vitamin C, vitamin E, and fiber), low plasma lycopene level was associated with 18% increased IMT in men, as compared with men with higher plasma level of lycopene (P = 0.003 for difference). In women, the difference did not remain significant after the adjustments.

Table IV. Studies on the Association of Circulating and Tissue Levels of Lycopene with the Risk of CHD and Atherosclerosis

Study, publication year, and nationality of subjects	Type of study	Sex	n	Variables	Sample	Mean levels of lycopene	Findings
ARIC study Iribarren et al. 1997, (23) American	Case-control	Women and men	462	Intima-media thickness	Serum	Cases 0.89 μmol/l Controls 0.91 μmol/l	Nonsignificantly lower odds of being case with increases in lycopene
The Rotterdam Study Klipstein-Grobush et al. 2000, (25) Netherlanders	Case-control	Women and men	216	Plaques of the abdominal aorta	Serum	Cases 0.12 μmol/l Controls 0.13 μmol/l	Adjusted odds ratio 0.35 (0.13–0.94) the highest quarter compared with the lowest in smokers
Bruneck study D'Orico et al. 2000, (36) Italian	Cross sectional and prospective 5-year follow-up	Women and men	392	Prevalence and incidence of carotid plaques	Serum	Means 0.53–0.76 μmol/l	Lycopene did not significantly predict the risk of atherosclerosis
Street et al. 1994, (20) American	Nested case-control 14-year follow-up	Women and men	369	Myocardial infarction	Serum	Cases 39.0 μg/l Controls 40.2 μg/l	The excess risk of MI in smokers with serum level of lycopene lower than median
EURAMIC-study Kohlmeier et al. 1997, (5) Multicenter	Case-control	Men	1379	Myocardial infarction	Adipose tissue	0.21–0.36 μg/g	Adjusted odds ratio 0.52 (0.33–0.82) in the 10th, compared with the 90th percentile
The Linköping-Vilnus coronary disease risk assessment study Kristenson et al. 1997, (4) Swedish and Lithuanian	Cross-sectional	Men	210	CHD mortality	Plasma	Linköping 0.62 μmol/l Vilnus 0.33 μmol/l	Lower plasma levels of lycopene and higher risk of CHD mortality in Vilnus than in Linköping

Discussion

Our main finding is that low blood levels of lycopene are associated with atherosclerosis alike before and after clinical manifestation in middle-aged men from eastern Finland. These associations were strong, and other cardiovascular risk factors, including the major plant-derived protective dietary factors, did not explain this association. In women, the protective effect was weaker.

The association between lycopene biomarkers and coronary heart disease or atherosclerosis has been examined only in few studies. The study design and results of five studies in which blood or tissue levels of lycopene and risk of CHD or atherosclerosis were examined are summarized in Table IV. In the multicenter EURAMIC study (5), low adipose tissue concentration of lycopene was associated with elevated risk of a myocardial infarction. In a nested case-control study from Washington County (20), the excess risk of myocardial infarction was associated with low serum levels of lycopene, but this association was limited in smokers. In the prospective Massachusetts Health Care Panel Study (2), high dietary intake of total carotenoids were associated with reduced risk of fatal myocardial infarction and CVD death.

The prevalence of carotid plaques and increased thickness of the intima media have been shown to predict coronary events (21, 22). In a subsample of the Atherosclerosis Risk in Communities (ARIC) study (23), there were 231 age-, sex-, race-, and field center-matched case-control pairs. The increase in serum levels of lycopene was associated with nonsignificantly lower odds of being a case after adjusting for risk factors (odds ratio 0.81). In the same study (24), a high dietary intake of provitamin A carotenoids was associated with lower prevalence of carotid plaques and lower thickness of the artery wall; neither of these associations were statistically significant. In the Rotterdam Study (25), serum lycopene was the only carotenoid that was associated with a decreased risk of aortic atherosclerosis in current and former smokers (adjusted odds ratio 0.35 for the highest versus the lowest quarter). In the Etude sur le Vieillisement Artériel (EVA) study (26), subjects in the highest quarter of plasma total carotenoids had lower CCA-IMT, but after adjustment for common CHD risk factors, this association became nonsignificant. In men, the prevalence of carotid plaques decreased linearly across quarters of plasma levels of carotenoids ($P < 0.016$). In the EVA study, plasma levels of lycopene were not measured.

There are no earlier studies of the association between serum level of lycopene and the risk of stroke. In the α-Tocopherol, β-Carotene Cancer Prevention (ATBC) study (27), high intake of lycopene was associated with elevated risk of cerebral infarction in male smokers after adjusting risk factors. In the prospective Health Professionals study (28), a high dietary intake of lutein was associated with a reduced risk for ischemic stroke, whereas the dietary intake of lycopene or α- or β-carotene had no association with the stroke risk.

The oxidative modification of LDL particles may play a role in the formation of foam cells, atherosclerotic lesions, and CHD (11, 29). Men who have high titers of autoantibodies against oxidatively modified LDL and those with elevated serum 7β-hydroxycholesterol levels have accelerated progression of carotid atherosclerosis (11, 12). Antioxidants can inhibit the oxidative modification of LDL, may retard atherosclerotic progression and, consequently, may prevent clinical complications of atherosclerosis such as myocardial infarction (12, 30). Lycopene and other carotenoids have been shown to act as antioxidants (7, 8, 10, 31). It is probably due to the ability of carotenoids to quench singlet oxygen, a potential initiator of lipid peroxidation (31). Lycopene exhibits the highest physical quenching rate of all carotenoids (8). It also has been shown that serum levels of lycopene are inversely correlated with serum thiobarbituric acid-reactive substances (TBARS) (32), which is an indicator of lipid peroxidation. Both LDL-TBARS and conjugated dienes decreased significantly with dietary lycopene supplementation (10). Also, other mechanisms by which lycopene could inhibit atherosclerosis such as intracellular cap junction communication and hormonal and immune system modulation are pathways that have been suggested (33). In addition, in cell culture, lycopene is the most effective carotenoid to suppress adhesion molecule and monocyte adhesion to endothelial cells (34).

The mean CCA-IMT in our subjects was somewhat higher than that reported in most other studies (22, 23, 26, 35). This is consistent with the high occurrence of clinical CHD in eastern Finland. The mean serum concentration of lycopene in our study was much lower than in most other population-based studies from European countries or the U.S. (4, 23, 36), where lycopene levels have been 2- to 6-fold as compared with our study. There is only one earlier study (25) in which the mean circulating levels of lycopene were similar to that in our study. The most likely explanation for this is the low dietary intake of lycopene in Finland. In the baseline of the KIHD study, dietary intake of lycopene was 0.8 mg/day, and in the ATBC study (27), it was 0.6 mg/day. In the Finnish Mobile Clinic Health Examination Survey (37), the daily intake of lycopene was 0.9 mg for women and 0.7 mg for men, whereas the intake of lycopene was found to be 1.3 mg in Spain (38), and as high as 3.9 mg in the U.S. (39). The fact that in our study, subjects have also low circulating levels of lycopene increases the statistical power to detect the association between the serum or plasma lycopene and the risk of atherosclerosis and coronary heart disease. The lack of low circulating levels of lycopene could be one explanation for the weak effect of some studies with only high tissue levels and low variety of lycopene. It is also possible that the serum levels of lycopene could be an indicator for other beneficial dietary or lifestyle factors. However, the effect of lycopene was sig-

nificant in both the ASAP and KIHD studies after the adjustment for other plant-derived nutrients.

The effect of lycopene on IMT in the ASAP study was different in women and in men. There are some possible causes of this difference. In our study, the women's diet was better than the men's. In addition, these differences became more clear after energy adjustment. This is the most likely explanation for the lack of association between thickness of intima-media and plasma lycopene in women. Another explanation could be that women have a most effective endogenous antioxidative system.

In conclusion, the present studies shows that low blood levels of lycopene are associated with increased CCA-IMT and increased risk of acute coronary event or stroke in middle-aged men from eastern Finland. Together with the previous findings, our results also support the convention that increased lycopene intake in the Finnish, particularly in men, may play a protective role in prevention of CVD. Hence, circulating levels of lycopene, a biomarker of tomato-rich food, may play a role in early stages of atherogenesis and may have clinical and public health relevance.

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