Effect of Supplementation With Tomato Juice, Vitamin E, and Vitamin C on LDL Oxidation and Products of Inflammatory Activity in Type 2 Diabetes

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OBJECTIVE — To compare the effects of short-term dietary supplementation with tomato juice, vitamin E, and vitamin C on susceptibility of LDL to oxidation and circulating levels of C-reactive protein (C-RP) and cell adhesion molecules in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS — There were 57 patients with well-controlled type 2 diabetes aged <75 years treated with placebo for 4 weeks and then randomized to receive tomato juice (500 ml/day), vitamin E (800 U/day), vitamin C (500 mg/day), or continued placebo treatment for 4 weeks. Susceptibility of LDL to oxidation (lag time) and plasma concentrations of lycopene, vitamin E, vitamin C, C-RP, vascular cell adhesion molecule 1, and intercellular adhesion molecule 1 were measured at the beginning of the study, after the placebo phase, and at the end of the study.

RESULTS — Plasma lycopene levels increased nearly 3-fold ($P = 0.001$), and the lag time in isolated LDL oxidation by copper ions increased by 42% ($P = 0.001$) in patients during supplementation with tomato juice. The magnitude of this increase in lag time was comparable with the corresponding increase during supplementation with vitamin E (54%). Plasma C-RP levels decreased significantly (−49%, $P = 0.004$) in patients who received vitamin E. Circulating levels of cell adhesion molecules and plasma glucose did not change significantly during the study.

CONCLUSIONS — This study indicates that consumption of commercial tomato juice increases plasma lycopene levels and the intrinsic resistance of LDL to oxidation almost as effectively as supplementation with a high dose of vitamin E, which also decreases plasma levels of C-RP, a risk factor for myocardial infarction, in patients with diabetes. These findings may be relevant to strategies aimed at reducing risk of myocardial infarction in patients with diabetes.

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Patients with type 2 diabetes are at increased risk of developing coronary heart disease (CHD) compared with the general population. Increased oxidative stress and enhanced oxidation of LDLs are believed to contribute to this excess risk of arterial disease (1). In vitro high glucose levels increase LDL oxidation, and glycated LDL is abnormally susceptible to oxidative modification (2). Also, levels of small dense LDL are increased in diabetic subjects, and these particles are more readily oxidized than larger, more buoyant LDL (2). Oxidation of LDL that becomes trapped in the artery wall is widely regarded as an important step in the development of atherosclerosis (3). There is evidence that mildly oxidized LDL enhances the expression of proinflammatory cytokines, chemoattractants, and cellular adhesion molecules (3) by endothelial cells. These molecules promote adhesion of monocytes to the vascular endothelium followed by transmigration of adhered cells into the intima, where they are retained and transformed into macrophages (3). Macrophages avidly internalize oxidized LDL via scavenger receptors to form lipid-filled cells that are the hallmark of the early atherosclerotic lesion (3). Increased inflammatory activity is also believed to predispose established atherosclerotic plaques to rupture, which can lead to a coronary event (4). In diabetic patients, circulating levels of proinflammatory cytokines (5), C-reactive protein (C-RP) (5), soluble vascular cell adhesion molecule 1 (VCAM-1), and soluble intercellular adhesion molecule 1 (ICAM-1) (6) are elevated, suggesting stimulation of proatherogenic inflammatory activity. Plasma C-RP is a sensitive marker of systemic inflammation, and chronically high levels predict increased risk of future coronary events (7).

There is epidemiologic and clinical evidence that high intake of high plasma or tissue levels or vitamin E, lycopene, and vitamin C may be associated with a decreased risk of CHD (8,9). Laboratory studies suggest that these compounds may potentially attenuate a number of the steps in the postulated pathway of atherosclerotic lesion formation. Supplementation with high doses of vitamin E markedly reduces susceptibility of isolated LDL to oxidation and inhibits secretion of proinflammatory cytokines (10). Enriching cultured endothelial cells (10) or LDL (10) with vitamin E decreases expression of ICAM-1 and VCAM-1 induced by native or oxidized LDL. Lycopene, a major carotenoid in human plasma, also inhibits the oxidative modification of isolated LDL (11). Tomato products in the diet are the

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Abbreviations: apo(a1), apolipoprotein A1; apo(b), apolipoprotein B; CHD, coronary heart disease; C-RP, C-reactive protein; ELISA, enzyme-linked immunosorbent assay; ICAM-1, intercellular adhesion molecule 1; IL, interleukin; PBS, phosphate-buffered saline; VCAM-1, vascular cell adhesion molecule 1.

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

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main source of plasma lycopene, and supplementation with tomato juice increases plasma lycopene levels in healthy subjects (12). Vitamin C is usually added to commercial tomato juices and in the aqueous milieu, can also protect plasma lipids and LDL from oxidative damage.

In diabetic patients, antioxidant protection may be inadequate, and plasma levels of some antioxidants including vitamin C and lycopene (13) are frequently low. Supplementation with vitamin E increases isolated LDL resistance to copper ion oxidation in patients with type 2 diabetes (14,15). However, information is sparse regarding the effects of food products such as tomato juice rather than supplements on the susceptibility of LDL to oxidation and circulating levels of antioxidants and inflammatory products in patients with type 2 diabetes. The present study was therefore designed to compare the effects of supplementation with tomato juice, vitamin E, and vitamin C on these factors in patients with type 2 diabetes in a randomized placebo-controlled trial.

RESEARCH DESIGN AND METHODS

Patients

Patients with type 2 diabetes under the age of 75 years and with an HbA_{1c} level <10% and a fasting plasma glucose level <11 mmol/l were recruited from the Diabetes Clinic at Dunedin Hospital, from local general practitioners, and by a newspaper advertisement. Exclusion criteria included presence of hepatic or renal disease, cigarette smoking, use of dietary antioxidant supplements, and treatment with insulin, lipid-lowering drugs, or hormone therapy during the preceding 6 months. Patients gave written and informed consent before participation in the study, which was approved by the Ethics Committee of the Southern Regional Health Authority (Otago, New Zealand).

At recruitment, a medical history was obtained from the patients. Past smoking habits and medication use were recorded. BMI was calculated (weight [kilograms] divided by height [meters] squared), and blood pressure was measured. Patients were instructed not to change their usual dietary habits for the duration of the study and to take the experimental dietary supplements with meals. A checklist was used to estimate the frequency of tomato product consumption during the study. Patients were also instructed to return any unused supplements, and compliance with study protocol was assessed during the study by counting returned supplements.

Study design and protocol

The study was a randomized placebo-controlled parallel trial. Randomization was carried out independently using a computer-generated scheme (Excel, Microsoft Office for Windows 95). A total of 57 patients were randomized to receive 800 IU/day vitamin E (D-α-tocopherol from a natural source; Red Seal, Auckland, New Zealand), 500 mg/day vitamin C (Redoxin; Roche Consumer Health, Dee Why, Australia), 250 ml tomato juice that did not contain added sugar (Campbells, Sydney, Australia) twice daily, or a placebo gelatin capsule containing pharmaceutical starch. This dose of vitamin E was selected because it leads to maximum resistance of LDL to oxidation in healthy subjects (16). The 500 mg/day dose of vitamin C that was chosen was comparable with the estimated daily intake of 300 mg vitamin C in the tomato juice supplement. The volume of the tomato juice supplement was similar to volumes used previously to increase plasma lycopene levels (12). During the initial 4 weeks of the study, all patients received the placebo capsule and then proceeded to their assigned supplement for the following 4 weeks. Blood samples, blood pressure, and BMI were taken on 2 occasions and 3 days apart, at baseline, at the end of placebo, and at the end of intervention. The mean of values measured at these time points was used as a more reliable measure of variables during the study.

Patients reported to the study center in the early morning after an overnight fast. Venous blood was collected in tubes containing disodium EDTA, sodium fluoride, or heparin. Blood was kept on ice for a maximum of 2 h before plasma was separated by low-speed centrifugation at 4°C. Metaphosphoric acid (900 µl, 5% solution) was added to an aliquot of plasma (100 µl) to be assayed for vitamin C, and these aliquots and others were stored at −80°C. A sample of EDTA plasma to be used for the isolation of LDL was flushed with argon and stored at 4°C in the dark for a maximum of 24 h.

Separation and oxidation of LDL

Native LDL was rapidly separated by ultracentrifuging EDTA plasma for 2 h at 60,000 rpm on a single-step discontinuous gradient in a Beckman NVT 65 rotor (Palo Alto, CA) (17). The LDL isolated by this procedure did not contain appreciable levels of albumin. The LDL was desalted into phosphate-buffered saline (PBS) by gel filtration in Econopac PD-10 columns (Bio-Rad Laboratories, Hercules, CA) (17). The PBS was Chelex-treated to remove any transition metal ions.

Oxidation of LDL was performed essentially as described by Puhl et al. (18). LDL (0.39 µmol cholesterol) was added to 2 ml PBS in a quartz cuvette at an ambient temperature in an air-conditioned room maintained at a constant temperature. The oxidation was initiated by the addition of copper ions (1.6 µmol/l) and was followed by monitoring the formation of conjugated dienes at 234 nm. The temperature in the cuvette was constant within 1 degree of 27°C. The interassay coefficient of variation for the lag time in LDL oxidation was 5%.

Analytical methods

Cholesterol and triglycerides in plasma and lipoprotein fractions were measured using commercial enzymatic kits and a calibrator (Boehringer Mannheim, Mannheim, Germany). HDL cholesterol was measured in the supernatant after precipitation of apolipoprotein B [apo(b)]–containing lipoproteins with dextran/magnesium chloride (19). Plasma apolipoprotein A1 [apo(a1)] and apoB were measured by immunoturbidimetry (20). Plasma glucose was measured enzymatically using a commercial kit (Boehringer Mannheim). HbA_{1c} was measured using a commercial kit (Glycotest 2; Pierce, Rockford, IL). Concentrations of VCAM-1 and ICAM-1 were measured in duplicate by an enzyme-linked immunosorbent assay (ELISA) (R&D Systems, Minneapolis, MN) in 1 of the 2 plasma samples obtained at each time point in the study. The coefficients of variation for the assays were 3.3% (VCAM-1) and 4.9% (ICAM-1). Plasma C-RP concentration was measured in duplicate by a commercial ELISA (Hemagen Diagnostics, Waltham, MA) with a coefficient of variation of 8% and sensitivity of 0.2 mg/l. In the plasma VCAM-1, ICAM-1, and C-RP assays, all samples from a patient were measured in the same run. High-pressure liquid chromatography was used to measure plasma α-tocopherol and lycopene levels (21) and LDL α-tocopherol content (22). Plasma vitamin C was measured by fluorimetry (23).

Statistical analysis

In the study, we detected a change in lag time in LDL oxidation of 10 min at a power of 90% ($P = 0.05$). Variables were log-trans-

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formed before statistical analysis. The multivariate analysis of variances procedure in Statistical Programs for Social Sciences with repeated measures and with covariate correction for baseline values was used to test for differences in the response of variables to the various dietary supplementation regimens. When a significant difference was detected among the treatment groups, unadjusted paired *t* tests were used to test for within-group changes during the active treatment phase of the study. Mean values (95% CI) were also calculated for changes during active treatment. Two-sided tests of significance were used, and a *P* value <0.05 was considered statistically significant. Unless otherwise stated, all data are expressed as means ± SD.

Table 1—*Baseline characteristics of the patients*

	Vitamin E	Vitamin C	Tomato juice	Placebo
n	12	12	15	13
Age (years)	56 ± 14	56 ± 9	63 ± 8	60 ± 6
Sex (M/F)	6/6	6/6	10/5	10/3
Duration of diabetes (years)	5.8 ± 7.6	1.9 ± 1.3	4.9 ± 5.5	3.2 ± 2.4
BMI (kg/m^2)	31.5 ± 7.4	30.7 ± 6.3	30.9 ± 7.0	31.8 ± 4.1
Diastolic blood pressure (mmHg)	89 ± 10	78 ± 27	87 ± 6	89 ± 14
Systolic blood pressure (mmHg)	151 ± 14	123 ± 40	147 ± 13	141 ± 22
Diet therapy alone (*n*)	4	5	6	4
HbA_{1c} (%)	6.7 ± 0.9	6.7 ± 1.0	6.0 ± 0.7	6.6 ± 1.7
Fasting plasma glucose (mmol/l)	8.4 ± 2.1	8.7 ± 1.5	8.2 ± 1.3	9.1 ± 2.4
Plasma total cholesterol (mmol/l)	5.65 ± 1.16	5.96 ± 1.02	5.87 ± 1.02	6.48 ± 1.14
Plasma HDL cholesterol (mmol/l)	1.14 ± 1.21	1.10 ± 1.25	1.01 ± 1.29	0.93 ± 1.17
Plasma triglycerides (mmol/l)	1.86 ± 1.68	1.75 ± 1.64	2.38 ± 1.36	2.70 ± 1.60
Serum apo(a1) (g/l)	1.23 ± 1.17	1.17 ± 1.21	1.16 ± 1.25	1.11 ± 1.16
Serum apo(b) (g/l)	0.89 ± 1.48	0.84 ± 1.24	0.92 ± 1.29	1.09 ± 1.28

Data are *n*, means ± SD, or number of patients.

RESULTS — Five patients withdrew during the study because of difficulties in donating a blood sample ($n = 2$), alterations in medications ($n = 2$), or problems with consuming the tomato juice ($n = 1$). The baseline characteristics of the patients are detailed in Table 1. The majority of participants (86%) had diagnosed diabetes for <6 years. One-third of the study group controlled their diabetes by diet alone, and the remainder received treatment with oral antihyperglycemic drugs. The majority of patients had multiple risk factors for CHD, and many (60%) had a history of cardiovascular disease. Several patients, mainly those randomized to supplementation with tomato juice ($n = 9$) and placebo ($n = 7$), were receiving treatment with ACE inhibitors, which are known to reduce the susceptibility of isolated LDL to oxidation (24). Treatment with ACE inhibitors remained unchanged during the study. Patients were also receiving aspirin (23%), β-blocking drugs (15%), and calcium antagonist drugs (19%). Plasma lipids, lipoproteins, apolipoproteins, and fasting glucose concentrations were similar between the treatment groups at baseline, although plasma triglyceride levels were lower in patients randomized to receive the vitamin C supplement. Plasma total cholesterol concentration increased significantly (0.50 mmol/l [95% CI 0.19 to 0.81]) in patients treated with vitamin E and did not change significantly in those treated with tomato juice (−0.10 mmol/l [–0.45 to 0.25]), vitamin C (0.04 mmol/l [–0.17 to 0.25]), and placebo (0.03 mmol/l [–0.25 to 0.30]). Plasma apo(b) concentration increased significantly in patients receiving vitamin C (0.14 g/l [0.004 to 0.28]) and did not change significantly in the placebo group (0.03 g/l [–0.10 to 0.16]). Fasting glucose ($P = 0.57$), BMI ($P = 0.94$), and blood pressure ($P = 0.56$) did not change significantly during the study.

Plasma antioxidants

Plasma concentrations of antioxidants in the patients during the study are shown in Table 2. Levels of α-tocopherol, vitamin C, and lycopene were similar between treatment groups at baseline and at the end of the placebo phase of the study and increased significantly in the appropriate treatment group, indicating both compliance with the supplementation regimen and good bioavailability of antioxidants in the supplements. The LDL content of α-tocopherol increased significantly ($P = 0.001$) in patients receiving vitamin E (baseline, 2.7 ± 0.9 μmol/mmol cholesterol; end of run-in, 2.7 ± 0.8 μmol/mmol cholesterol; end of study, 5.6 ± 1.5 μmol/mmol cholesterol) and did not change significantly in those receiving tomato juice (baseline, 2.9 ± 0.5 μmol/mmol cholesterol; end of run-in, 2.7 ± 0.5 μmol/mmol cholesterol; end of study, 2.7 ± 0.5 μmol/mmol cholesterol) and in other treatment groups from similar baseline levels. The frequency checklist of tomato products in the diet showed that at baseline, 82% of patients consumed raw tomatoes, 37% baked beans, 8% pizza, 13% canned tomatoes, 5% tomato soup, 67% tomato sauce, and 21% spaghetti/sauce at least once during a 4-day period, and these proportions were similar at the end of the study (excluding the tomato juice supplement).

LDL oxidation

The lag time in copper ion–catalyzed oxidation of LDL isolated from the participants is shown in Table 2. The lag time in conjugated diene formation increased significantly in patients treated with tomato juice (30 min [17 to 43]) and vitamin E (40 min [24 to 57]) and remained unchanged in those who received placebo (−6 min [–24 to 12]) and vitamin C (4 min [–11 to 18]). The coefficient of variation obtained from the 2 measures of lag time at baseline was 3.3% ($n = 57$). Rate of diene formation during the propagation phase ($P = 0.69$) and maximum concentration of conjugated dienes formed ($P = 0.50$) did not change significantly during the study (data not shown). The chemical composition (protein and lipids) of LDL also did not change significantly in patients during the study (data not shown).

C-RP and cell adhesion molecules

Plasma concentrations of C-RP and adhesion molecules in the patients during the study are shown in Table 2. Plasma C-RP levels decreased significantly in patients supplemented with vitamin E (−3.5 mg/l [–1.3 to −5.7]) and did not vary significantly in those treated with vitamin C (−0.1 mg/l [–2.2 to 2.0]), tomato juice (0.6 mg/l [–0.6 to 1.8]), and placebo (0.8 mg/l [–0.2 to 1.8]). Plasma C-RP concentration did not change significantly ($P = 0.51$) in patients with high baseline levels (>3 mg/l) who

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Table 2—*Plasma concentration of antioxidants, lag time in LDL oxidation, and plasma C-RP concentration during the study*

	Vitamin E	Vitamin C	Tomato juice	Placebo
n	12	12	15	13
Lycopene (μmol/l)				
Baseline	0.35 ± 0.24	0.41 ± 0.27	0.39 ± 0.23	0.31 ± 0.26
End of run-in	0.31 ± 0.19	0.41 ± 0.27	0.39 ± 0.26	0.33 ± 0.28
End of study	0.41 ± 0.23	0.44 ± 0.32	1.08 ± 0.39*	0.28 ± 0.21
Vitamin C (μmol/l)				
Baseline	39.6 ± 19.5	40.7 ± 15.4	38.9 ± 25.5	25.0 ± 15.6
End of run-in	42.7 ± 18.0	37.7 ± 12.4	43.8 ± 28.6	27.3 ± 15.4
End of study	40.0 ± 13.7	64.7 ± 14.3	56.0 ± 23.4	29.7 ± 21.1
α-Tocopherol (μmol/l)				
Baseline	24.4 ± 8.6	22.7 ± 4.1	26.1 ± 4.9	23.9 ± 5.3
End of run-in	24.3 ± 8.8	22.2 ± 5.0	25.5 ± 4.5	25.4 ± 5.8
End of study	56.7 ± 23.7*	22.6 ± 4.8	26.7 ± 6.0	24.4 ± 6.5
Lag time (min)				
Baseline	74 ± 16	56 ± 19	69 ± 18	81 ± 21
End of run-in	74 ± 16	63 ± 15	71 ± 24	86 ± 23
End of study	114 ± 26*	67 ± 18	101 ± 27*	80 ± 23
C-RP (mg/l)				
Baseline	4.5 (0.2–20.3)	2.9 (0.5–19.2)	3.8 (0.5–17.4)	3.1 (0.5–19.5)
End of run-in	5.6 (0.5–23.9)	3.0 (0.5–18.0)	3.5 (0.5–16.2)	2.9 (1.0–10.6)
End of study	2.9 (0.1–14.1)†	3.1 (0.5–24.5)	4.1 (1.2–14.6)	3.1 (0.6–12.3)

Data are *n*, means ± SD, or medians (range). *$P = 0.001$ in repeated-measures analysis of variance (ANOVA) with baseline values as covariates and significantly ($P < 0.001$) different from within-group end of run-in values. †$P = 0.004$ in repeated-measures ANOVA with baseline values as covariates and significantly ($P < 0.01$) different from within-group end of run-in values.

were not receiving vitamin E (baseline, 6.2 mg/l; end of placebo, 4.9 mg/l; end of study, 5.3 mg/l; median $n = 23$). Concentrations of circulating adhesion molecules did not change significantly during the study (ICAM-1, $P = 0.893$; VCAM-1, $P = 0.997$).

CONCLUSIONS — These data indicate that short-term supplementation with tomato juice increases plasma lycopene levels nearly 3-fold and the intrinsic resistance of LDL to oxidation by ~42% in diabetic patients. The magnitude of these changes was similar to that reported previously in healthy subjects who consumed a tomato juice supplement in a preliminary study (25). Furthermore, the magnitude of the present increase in LDL resistance to oxidation during tomato juice consumption was comparable with the corresponding increase during supplementation with vitamin E. In addition, treatment with vitamin E markedly decreased plasma levels of C-RP, which is a risk factor for myocardial infarction.

The increase in LDL resistance to oxidation during consumption of tomato juice may be at least partly due to increased LDL content of lycopene. Enrichment of LDL with lycopene in vitro increases its resistance to copper ion oxidation (11). The 3-fold increase in plasma lycopene in the present study undoubtedly included an increase in LDL lycopene levels. In the blood, carotenoids are transported by lipoproteins and substantially by LDL (26). However, compounds in tomatoes (e.g., flavanoids and phenolics) other than lycopene may also contribute to the increased resistance to oxidation of LDL isolated from subjects during regular consumption of tomato juice. Vitamin C is usually added to commercial tomato juice, but in our data, this antioxidant alone is not responsible for the increased resistance of LDL to oxidation during consumption of tomato juice. The susceptibility of LDL to oxidation was unchanged in patients who were randomized to receive a substantial dose of vitamin C comparable with the amount of vitamin C in the tomato juice supplement. This finding is in line with the fact that vitamin C is water soluble and is not incorporated in LDL. It is also unlikely that ACE inhibitor therapy was solely responsible for the increase in LDL resistance to oxidation in patients consuming tomato juice in the present study. The number of patients receiving ACE inhibitors (which are reported as inhibiting oxidation of isolated LDL [24]) was comparable in the groups of patients treated with tomato juice and placebo, whereas LDL susceptibility to oxidation was clearly decreased in those receiving tomato juice but not in those receiving placebo. Furthermore, treatment with ACE inhibitors remained unchanged during the study. We cannot entirely exclude the possibility that there were changes in habitual diet that contributed to the increased LDL resistance to oxidation in patients during consumption of tomato juice. However, this intervention is relatively minor and would not be expected to greatly alter habitual diet in a way that markedly increases LDL resistance to oxidation.

Our data suggest that supplementation with high levels of vitamin E may decrease plasma C-RP levels in patients with type 2 diabetes. This decrease in plasma C-RP is unlikely to be due to regression to the mean. Plasma C-RP levels remained stable during the placebo run-in phase in the patients supplemented with vitamin E. Furthermore, plasma C-RP levels did not change appreciably during the study in patients with high baseline levels of C-RP (comparable with the corresponding levels in the vitamin E group) who were not receiving vitamin E. The decrease in plasma C-RP during supplementation with vitamin E may indicate an improvement in systemic inflammatory status. It is possible that vitamin E decreases the secretion of proinflammatory cytokines that promote the synthesis of C-RP in the liver. Devaraj and Jialal (10) have reported that dietary supplementation with a high dose of vitamin E in healthy subjects inhibits the release of interleukin (IL)-1β from isolated monocytes. The proinflammatory cytokine IL-1β stimulates the expression of IL-6, which in turn increases the synthesis of C-RP (7). The decrease in IL-1β secretion induced by vitamin E appears to be independent of its antioxidant properties and relies on a decrease in 5-lipoxygenase activity (27). Our data suggest that plasma C-RP levels may also be unaffected by increased antioxidant protection and greater intrinsic resistance of LDL to oxidation in patients with type 2 diabetes. In patients whose diets are supplemented with vitamin C and tomato juice, levels of ascorbate and lycopene are increased, respectively, and in those treated with tomato juice, LDL resistance to copper ion oxidation is also increased, but plasma C-RP remains unchanged.

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The increases in plasma total cholesterol and apo(b) levels in patients receiving vitamin E and vitamin C, respectively, must be interpreted with caution. These increases may not be clearly different from the corresponding changes in the placebo group because the 95% CIs for the changes overlap appreciably. Also, few, if any, published placebo-controlled studies have reported an increase in plasma cholesterol in humans, including individuals with type 2 diabetes (14,15), during vitamin E supplementation.

This study has limitations that must be considered. Numbers of patients in the treatment groups were relatively small. Thus, care should be taken in extrapolating the present findings to other populations. Also, the treatment period was comparatively short. However, the length of the supplementation period was sufficient to establish markedly increased levels of circulating antioxidants. Patients were taking a number of medications to control diabetes and hypertension or reduce the risk of a cardiovascular event. However, these treatments are characteristic of patients with type 2 diabetes and remained unchanged during the study.

In conclusion, this study indicates that a simple dietary change (namely, the daily consumption of 2 cups of tomato juice) markedly increases plasma lycopene levels and increases the resistance of isolated LDL to oxidation almost as effectively as a high dose of vitamin E in patients with type 2 diabetes. A few patients may be unable to tolerate tomato juice and may need to increase their dietary intake of lycopene-rich fruit and vegetables instead. Vitamin E supplementation also decreases plasma C-RP levels, suggesting a decrease in proinflammatory activity. According to epidemiological studies (7,9,28), these changes in plasma C-RP, lycopene, and LDL resistance to oxidation are consistent with reduced risk of CHD. However, clinical trial data are sparse, and recent trials that have tested the effect of vitamin E supplementation on the incidence of coronary events (29,30) do not support the use of vitamin E supplementation as an option for treatment of cardiovascular disease. Thus, our findings suggest that tomato products warrant further investigation as a potential strategy for reducing the risk of CHD in patients with type 2 diabetes.

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