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 efficaciously 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, chemotransmitters, 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 of 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.
Antioxidants and LDL oxidation in diabetes

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

In diabetic patients, antioxidant pro-
tection may be inadequate, and plasma lev-
els of some antioxidants including vitamin C and lycopene (13) are frequently low. Supplementation with vitamin E increases
isolated LDL resistance to copper ion oxida-
tion 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 inflam-
matory products in patients with type 2 diabetes. The present study was
therefore designed to compare the effects of
Supplementation with tomato juice, vita-
min E, and vitamin C on these factors in
patients with type 2 diabetes in a random-
ized placebo-controlled trial.

RESEARCH DESIGN AND
METHODS

Patients
Patients with type 2 diabetes under the age
of 75 years and with an HbA1c level <10% and a fasting plasma glucose level <11
mmol/l were recruited from the Diabetes
Clinic at Dunedin Hospital, from local gen-
eral practitioners, and by a newspaper
advertisement. Exclusion criteria included
presence of hepatic or renal disease, cigarette
smoking, use of dietary antioxidant supple-
ments, and treatment with insulin, lipi-
dowering drugs, or hormone therapy during
the preceding 6 months. Patients gave writ-
ten and informed consent before participa-
tion 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.
Patients were also instructed to return any unused
supplements, and compliance with the study
protocol was assessed during the study by
counting returned supplements.

Study design and protocol
The study was a randomized placebo-con-
trolled parallel trial. Randomization was car-
ried 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
(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 pharma-
cutical 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 vita-
m C that was chosen was comparable with
the estimated daily intake of 300 mg vitamin
C in the tomato juice supplement. The vol-
ume 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 pro-
ceeded to their assigned supplement for the
following 4 weeks. Blood samples, blood
pressure, and BMI were taken on 2 occa-
sions 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 con-
taining disodium EDTA, sodium fluoride, or
heparin. Blood was kept on ice for a maxi-
mum of 2 h before plasma was separated by
low-speed centrifugation at 4°C. Metaphos-
phoric 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 ultra-
centrifuging 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 Labora-
tories, 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 varia-
tion 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, Ger-
many). HDL cholesterol was measured in
the supernatant after precipitation of apo-
ipoprotein 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 com-
mercial kit (Boehringer Mannheim). HbA1c
was measured using a commercial kit (Gly-
cotest 2; Pierce, Rockford, IL). Concentra-
tions of VCAM-1 and ICAM-1 were mea-
sured in duplicate by an enzyme-linked
immunosorbent assay (ELISA) (R&D Sys-
tems, 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 mea-
sured 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-
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.

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.

Table 1 — Baseline characteristics of the patients

<table>
<thead>
<tr>
<th></th>
<th>Vitamin E</th>
<th>Vitamin C</th>
<th>Tomato juice</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>12</td>
<td>12</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td>Age (years)</td>
<td>56 ± 14</td>
<td>56 ± 9</td>
<td>63 ± 8</td>
<td>60 ± 6</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>6/6</td>
<td>6/6</td>
<td>10/5</td>
<td>10/3</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>5.8 ± 7.6</td>
<td>1.9 ± 1.3</td>
<td>4.9 ± 5.5</td>
<td>3.2 ± 2.4</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>31.5 ± 7.4</td>
<td>30.7 ± 6.3</td>
<td>30.9 ± 7.0</td>
<td>31.8 ± 4.1</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>89 ± 10</td>
<td>78 ± 27</td>
<td>87 ± 6</td>
<td>89 ± 14</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>151 ± 14</td>
<td>123 ± 40</td>
<td>147 ± 13</td>
<td>141 ± 22</td>
</tr>
<tr>
<td>Diet therapy alone (n)</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>HbA₁c (%)</td>
<td>6.7 ± 0.9</td>
<td>6.7 ± 1.0</td>
<td>6.0 ± 0.7</td>
<td>6.6 ± 1.7</td>
</tr>
<tr>
<td>Fasting plasma glucose (mmol/l)</td>
<td>8.4 ± 2.1</td>
<td>8.7 ± 1.5</td>
<td>8.2 ± 1.3</td>
<td>9.1 ± 2.4</td>
</tr>
<tr>
<td>Plasma total cholesterol (mmol/l)</td>
<td>5.65 ± 1.16</td>
<td>5.96 ± 1.02</td>
<td>5.87 ± 1.02</td>
<td>6.48 ± 1.14</td>
</tr>
<tr>
<td>Plasma HDL cholesterol (mmol/l)</td>
<td>1.14 ± 1.21</td>
<td>1.10 ± 1.25</td>
<td>1.01 ± 1.29</td>
<td>0.93 ± 1.17</td>
</tr>
<tr>
<td>Plasma triglycerides (mmol/l)</td>
<td>1.86 ± 1.68</td>
<td>1.75 ± 1.64</td>
<td>2.38 ± 1.36</td>
<td>2.70 ± 1.60</td>
</tr>
<tr>
<td>Serum apo(a) (g/l)</td>
<td>1.23 ± 1.17</td>
<td>1.17 ± 1.21</td>
<td>1.16 ± 1.25</td>
<td>1.11 ± 1.16</td>
</tr>
<tr>
<td>Serum apo(b) (g/l)</td>
<td>0.91 ± 1.48</td>
<td>0.84 ± 1.24</td>
<td>0.92 ± 1.29</td>
<td>1.09 ± 1.28</td>
</tr>
</tbody>
</table>

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

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

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

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-1)β 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.
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 to reduce the risk of a cardiovascular event. However, these changes 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-RR levels, suggesting a decrease in proinflammatory activity. According to epidemiological studies (7,9,28), these changes in plasma C-RR, 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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Antioxidants and LDL oxidation in diabetes

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