Natural antioxidants from tomato extract reduce blood pressure in patients with grade-1 hypertension: A double-blind, placebo-controlled pilot study

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Background Treatment of hypertension (HT) can reduce the risk for cardiovascular diseases. Tomato extract contains carotenoids such as lycopene, beta carotene, and vitamin E, which are known as effective antioxidants, to inactivate free radicals, and to slow the progression of atherosclerosis. The purpose of our study was to evaluate the effect of tomato extract on systolic and diastolic blood pressure in grade-1 HT, on serum lipoproteins, plasma homocysteine, and oxidative stress markers.

Methods This study is a single-blind, placebo-controlled trial. Thirty-one subject with grade-1 HT, without concomitant diseases, who required no antihypertensive or lipid-lowering drug therapy, who were recruited from primary care clinics, completed the trial. Subjects entered a 4-week placebo period, then an 8-week treatment period with tomato extract, 250 mg Lyc-O-Mato, and a 4-week control period with placebo.

Results Systolic blood pressure decreased from 144 (SE ±1.1) to 134 mm Hg (SE ±2, $P < .001$), and diastolic blood pressure decreased from 87.4 (SE ±1.2) to 83.4 mm Hg (SE ±1.2, $P < .05$). No changes in blood pressure were demonstrated during placebo periods. Thiobarbituric acid–reactive substances, a lipid peroxidation products marker, decreased from 4.58 (SE ±0.27) to 3.81 nmol/mg (SE ±0.32, $P < .05$). No significant changes were found in lipid parameters.

Conclusions A short-term treatment with antioxidant-rich tomato extract can reduce blood pressure in patients with grade-1 HT, naive to drug therapy. The continuous effect of this treatment and the long-term beneficial effect on cardiovascular risk factors still need to be demonstrated. (Am Heart J 2006;151:100.e1-100.e6.)

Essential hypertension (HT) is one of the most prevalent health problems in the developed world. It is an unequivocal risk factor for cardiovascular morbidity and mortality, although the exact underlying pathophysiologic mechanism of its development remains obscure.[1] A role for oxidative stress in the pathogenesis of HT has been suggested by both animal model and human-based studies.[2] Oxidative stress can inactivate nitric oxide, thus impairing endothelium-dependent vasodilatation. Furthermore, low-density lipoprotein cholesterol (LDL-C) oxidation promotes the pathogenesis of atherosclerosis, which is another important risk factor of cardiovascular morbidity.

Current international guidelines recommend weight control, reduced intake of salt, and reduced alcohol consumption, and possibly, increase of potassium as nutritional approaches to prevent and treat primary HT. In observational studies, significant inverse association of blood pressure (BP) with vegetarian diet rich in fibers, magnesium, potassium, calcium, and protein have been reported.[3]

Generally, the use of dietary food additives has gained increasing popularity for the past few years. Various studies demonstrated the ability of antioxidant vitamins of natural origin to improve vascular function. Tomato (*Lycopersicon esculentum*), together with tomato products, is an important dietary source of antioxidants such as α-tocopherol and the carotenoids beta carotene, phytoene, and phytofluene. Tomato is also the main dietary source of lycopene, the most potent in vitro antioxidant among the carotenoids.[4] Consumption of tomato juice caused a significant elevation of plasma lycopene as well as increased resistance of low-density lipoprotein (LDL) to oxidation in subjects with type 2 diabetes mellitus.[5] Dietary supplementation of fruits and vegetables has been

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linked to a rise in plasma vitamin antioxidant levels and to a reduction in BP values.[6] Galley et al[7] demonstrated significant reduction in systolic blood pressure (SBP) and increase in serum beta carotene, α-tocopherol, and urine nitrite levels after antioxidant vitamin supplementation. However, data on the effect of antioxidant supplementation on BP are insufficient, particularly regarding patients with grade-1 HT.

Our primary hypothesis was that treatment with capsules containing tomato extract, rich in natural antioxidants, would produce a reduction in BP values in patients with grade-1 HT. A single-blind, placebo-controlled trial was designed as a pilot study to assess the changes in BP, oxidative stress, and LDL oxidation in response to an 8-week treatment with Lyc-O-Mato, a tomato extract naturally rich in antioxidant carotenoids and vitamins.

Methods

Study population

Forty patients with grade-1 HT, aged 30 to 70 years, were recruited from primary care clinics and through advertisements published in the local newspapers. Grade-1 HT was defined as SBP between 140 and 159 mm Hg, diastolic blood pressure (DBP) between 90 and 99 mm Hg, or both, measured with the subject in the sitting position in at least 3 different occasions. Subjects treated for HT or dyslipidemia, who had any suspected allergy to tomato, carotenoids, or α-tocopherol, or taking vitamins and other food additives were excluded from the study. Smokers, persons with diabetes, and subjects with cardiovascular, gastrointestinal, hepatic, or malignant disease were excluded as well. All included subjects signed an informed consent, which was presented to them by the researchers after an explanation regarding the course of the trial. The local Helsinki ethics committee approved the study protocol.

Materials

Lyc-O-Mato, an encapsulated tomato extract, was supplied by LycoRed–Natural Products Industries Ltd, Beer Sheva, Israel. Each 250-mg capsule consists of 15 mg lycopene (6%), beta carotene (0.15%), phytoene, and phytofluene (1%); and 5 mg vitamin E (2%), phospholipids (15%), and phytosterol (0.6%) suspended in tomato oleoresin oil. LycoRed supplied an identical-looking placebo capsule as well.

Procedure

Allocated participants started a 2-week run-in period to confirm the diagnosis of grade-1 HT and entered the study if they met the inclusion and exclusion criteria. After a baseline visit, all participants went through a 4-week control period, in which they were asked to consume 1 placebo capsule a day. An 8-week treatment period followed, during which participants consumed 1 capsule of Lyc-O-Mato per day. During the last 4 weeks of the study, participants again consumed placebo. Participants were blinded to the different study periods and were instructed to take the capsules with the main meal of the day to improve absorption of ingredients. No other dietary supplements were allowed throughout the study, and participants were instructed to keep their usual dietary habits. At the baseline visit, a thorough physical examination was performed, and a comprehensive medical and dietary history was taken. Blood pressure, pulse rate, height, and weight were measured, and body mass index (BMI) was calculated. Follow-up visits were held every 2 weeks at the Hypertension Outpatient Clinic of the Soroka University Medical Centre and included a short clinical evaluation and dietary questionnaire; BP, pulse rate, and weight measurements; and BMI calculation. Blood pressure was measured after 10 minutes of rest in the sitting position using an Omron HEM-705CP electronic semi-automatic sphygmomanometer (Tokyo, Japan). Recorded BP was calculated as the average of 3 serial measurements if the difference between them were <8 mm Hg for SBP and <5 mm Hg for DBP. All measurements were taken in the same hour of the morning after a 10-minute rest and abstinence from food and caffeine for a minimum of 30 minutes, by a trained research nurse who was blind to the study periods and treatment.

A 24-hour ambulatory blood pressure monitoring (ABPM) was conducted twice, at baseline and at the end of the 8-week treatment period, using an Accutracker Dx ABP Monitor (Suntech Medical Instruments, Morrisville, NC).

Participants were supplied with 20 capsules of Lyc-O-Mato or matching placebo at each visit, and were asked to return the unused capsules at the next visit. Compliance was verified by counting the remaining capsules and by reinforcement at each visit.

Blood was drawn after an overnight fast 3 times in the course of the trial: at baseline, at the end of the first placebo period, and at the end of the intervention period. Serum concentrations of total cholesterol, high-density lipoprotein cholesterol, LDL-C, and triglycerides were measured. Lipoprotein(a), apolipoprotein B-100, and apolipoprotein A-I levels were determined by immunoturbidimetric method, using a Cobas kit (Roche Diagnostics GmbH, Mannheim, Germany). Plasma homocysteine levels were determined using a high-performance liquid chromatography system reagent kit (Bio-red Laboratories GmbH, Munich, Germany). Blood chemistries, including serum glucose, blood urea nitrogen, creatinine, uric acid, sodium, and potassium levels, were measured as well.

Additional plasma samples were stored at −70°C. Stored samples were then analyzed simultaneously for oxidative stress parameters; LDL oxidation was determined by measuring the amount of thiobarbituric acid–reactive substances (TBARSs) using spectrophotometric method. Serum vitamin E (α-tocopherol), beta carotene, and lycopene were assayed using a high-performance liquid chromatography. The enzyme activity of glutathione peroxidase (GPx) was measured by spectrophotometer. Reduced thiol levels were determined using a spectrophotometer assay, which measured the redox state of the blood.

Statistical methods

Results of descriptive statistics included mean ± SD unless mentioned otherwise. Paired data sets were compared using 2-tailed t test. P values of <.05 were considered to indicate statistical significance. Statistics and analyses were done using STATA software version 7.0 (Stata, College Station, TX).

Table I. Clinical characteristics and laboratory findings

	Baseline	After placebo	After treatment
BMI (kg/m^2)	29.5 ± 0.8	29.4 ± 0.8	29.2 ± 0.7
SBP (mm Hg)	145.0 ± 1.3	144.0 ± 1.1	134.0 ± 2*
DBP (mm Hg)	88.9 ± 1.4	87.4 ± 1.2	83.4 ± 1.2†
Total cholesterol (mg/dL)	213.03 ± 6.42	199.21 ± 6.54	207.41 ± 6.53
Triglycerides (mg/dL)	201.78 ± 15.80	177.70 ± 17.29	182.50 ± 18.04
HDL-C (mg/dL)	43.68 ± 1.57	41.29 ± 1.80	43.59 ± 1.83
LDL-C (mg%)	126.15 ± 6.03	121.85 ± 6.23	127.96 ± 6.00
Lipoprotein(a) (mg%)	34.06 ± 6.20	35.59 ± 6.60	32.67 ± 6.56
Apolipoprotein B-100 (mg%)	100.74 ± 4.00	102.93 ± 4.36	105.26 ± 4.60
Apolipoprotein A-I (mg%)	135.52 ± 4.64	133.41 ± 4.88	133.59 ± 4.39
Plasma homocysteine (μmol/L)	12.31 ± 1.29	11.52 ± 0.88	11.98 ± 0.94
Serum glucose level (mg/dL)	88.71 ± 2.21	88.61 ± 2.33	92.23 ± 2.52
Serum urea level (mg/dL)	30.60 ± 1.48	30.68 ± 1.70	31.50 ± 1.58
Serum creatinine level (mg/dL)	0.98 ± 0.03	0.96 ± 0.04	0.98 ± 0.03
Serum uric acid level (mg/dL)	5.66 ± 0.24	5.79 ± 0.23	5.87 ± 0.26
Serum sodium (mEq/L)	139.61 ± 0.52	138.35 ± 0.43	138.20 ± 0.36
Serum potassium (mEq/L)	4.42 ± 0.06	4.39 ± 0.05	4.48 ± 0.08
$CuSO_4$-induced LDL oxidation (AAPH-TBARS in plasma) (nmol/mg)	4.88 ± 0.26	4.58 ± 0.27	3.81 ± 0.32‡
Vitamin E–cholesterol	6.57 ± 0.24	7.28 ± 0.55	6.32 ± 0.28
Vitamin E (mg/L)	13.60 ± 0.59	14.70 ± 1.20	12.77 ± 0.60
GSH thiols (mU/mL)	9.39 ± 0.57	8.82 ± 0.77	8.95 ± 0.40
Cellular GPx (mU/mL)	6.54 ± 0.32	6.46 ± 0.30	6.11 ± 0.48
24-h BP monitor			
SBP overall average (mm Hg)	134.00 ± 2.44		128.53 ± 3.29
DBP overall average (mm Hg)	81.93 ± 1.40		78.59 ± 1.60
Average awake SBP (mm Hg)	137.44 ± 2.27		131.41 ± 3.41†
Average awake DBP (mm Hg)	84.56 ± 1.39		81.24 ± 1.76
Average asleep SBP (mm Hg)	119.56 ± 3.52		118.06 ± 3.96
Average asleep DBP (mm Hg)	71.68 ± 1.77		70.88 ± 2.89

Values are presented as mean ± SE (N = 31). *HDL-C*, High-density lipoprotein cholesterol; *GSH*, glutathione; *AAPH*, 2,2′-azobis (2-amidinopropane) dihydrochloride; *TBARS*, thiobarbituric acid-reactive substances.
*Significant difference from placebo ($P < .0001$).
†Significant difference from placebo ($P < .05$).
‡Significant difference from baseline ($P < .05$).

Results

Participants

Recruitment and allocation took place between March to August 2001. Thirty-four participants were included in the trial of whom 31 (91.1%) completed all study phases: 18 men and 13 women with a mean age of 48 (range 30-73) years. Three participants (8.9%) dropped out because of lack of compliance (n = 1) and complaints of dizziness (n = 1) and unspecific rash (n = 1), both during the first placebo period. Mean BMI remained constant during the course of the study (29.5 ± 4.3 at baseline and 29.2 ± 3.4 at the end of the intervention period) (Table I).

Table II. Blood pressure values

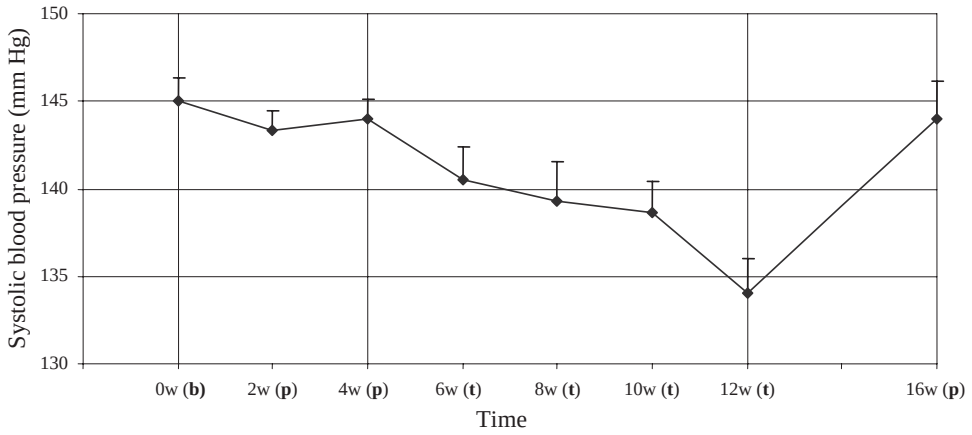
Time (phase)	SBP	DBP
Baseline	145.0 ± 1.34	88.9 ± 1.42
2 wk (placebo)	143.4 ± 1.13	88.7 ± 1.11
4 wk (placebo)	144.0 ± 1.08	87.4 ± 1.19
6 wk (treatment)	140.5 ± 1.84	85.4 ± 1.33
8 wk (treatment)	139.3 ± 2.27	85.6 ± 1.37
10 wk (treatment)	138.7 ± 1.79	85.0 ± 1.33
12 wk (treatment)	134.0 ± 2.01*	83.4 ± 1.22†
16 wk (placebo)	144.0 ± 2.14	85.2 ± 2.48

Values are in millimeters of mercury and are presented as mean ± SE (N = 31).
*Significant difference from placebo ($P < .0001$).
†Significant difference from placebo ($P < .05$).

Blood pressure

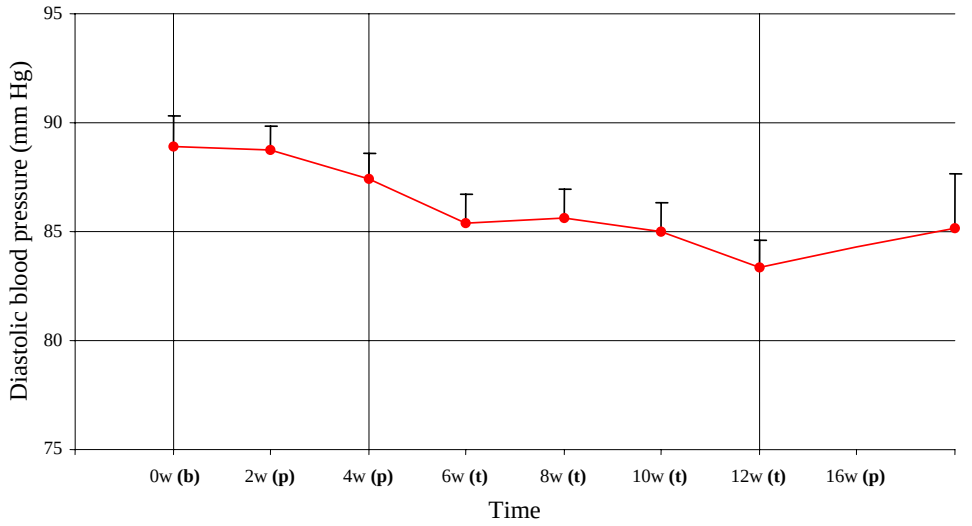
Mean SBP and DBP values at baseline were 145.05 ± 7.44 and 88.9 ± 7.9 mm Hg, respectively, and 144 ± 5.99 and 87.44 ± 6.8 mm Hg, respectively, at the end of the first placebo period (Table II, Figures 1 and 2). At the end of the intervention period, SBP decreased to 134.02 ± 10.83 mm Hg ($P < .0001$) and DBP decreased to 83.38 ± 6.6 mm Hg ($P = .003$). A significant reduction of SBP had been achieved as early as the sixth week of Lyc-O-Mato administration (−4.07 ± 12.15 mm Hg, $P = .038$), and significant reduction in DBP was demonstrated as early as the fourth week (−1.27 ± 3.62 mm Hg, $P = .029$). At the end of the final

Figure 1



Effect of tomato extract on SBP during the trial. Systolic blood pressure is represented for each meeting. Systolic blood pressure did not differ between baseline and the first placebo period, dropped by 134.02 mm Hg at the end of the treatment period ($P < .0001$), and rose back to baseline values at the end of the second placebo period. Data are presented as mean ± SE. *b*, Baseline; *p*, placebo; *t*, treatment.

Figure 2



Effect of tomato extract on DBP during the trial. Diastolic blood pressure is represented for each meeting. Diastolic blood pressure did not differ between baseline and the first placebo period, dropped by 83.38 mm Hg at the end of the treatment period ($P = .003$), and rose back to baseline values at the end of the second placebo period. Data are presented as mean ± SE.

placebo period, an increase of both SBP and DBP to 143.98 ± 6.41 and 85.16 ± 7.44 mm Hg, respectively, was observed in all subjects. Baseline 24-hour ABPMs of these newly diagnosed patients with grade-1 HT were mostly in the high-normal range. Only the baseline average SBP reached hypertensive values. These values showed a significant reduction to normal range at the end of the intervention period (from 137.44 ± 11.78 to 131.41 ± 14.04 mm Hg, $P = .02$), whereas an insignificant reduction has been found in overall (day and night) BP averages (Table I).

During the intervention period, lipid peroxidation products (AAPH-induced TBARS) declined from 4.58 ± 1.34 to 3.81 ± 1.58 nmol/mg ($P = .02$). Blood lipids, lipoproteins, and homocysteine were not significantly changed throughout the course of the trial. Changes in

vitamin E–cholesterol ratio, vitamin E, glutathione thiols, and cellular GPx levels were not significant.

Discussion

In this study, short-term, daily oral supplementation of carotenoid-rich tomato extract significantly decreased SBP and DBP and reduced levels of lipid peroxidation products. We particularly selected nonsmoking, recently diagnosed patients with grade-1 HT, receiving no antihypertensive or lipid-lowering pharmaceutical therapy, without significant cardiovascular risk factors other than HT. Patients who reported taking vitamins and other food additives were excluded from the trial, avoiding the potential bias arising from recruiting participants who are more health conscious than average. We accounted for a possible placebo effect by introducing 2 placebo periods: before and after the intervention. During the first placebo period, BP remained unchanged and raised back to the baseline values during the final placebo period. The reduction of BP observed in our study was not accompanied by changes in plasma concentrations of total cholesterol, lipoproteins, triglycerides, and BMI. Participants were advised and repeatedly reminded to maintain their current diet and lifestyle. Thus, our results are unlikely to be attributed to lipid or weight lowering, dietary changes, or enhanced physical activity.

To enhance the reliability of BP values measured during clinic visits, the subjects underwent 24-hour ABPM. As expected in newly diagnosed patients with grade-1 HT, baseline mean 24-hour ABPM values were in the borderline to mild HT range, with normal nighttime BP decline and hypertensive mean awake systolic level. The treatment with tomato extract caused a decline in all daytime averages; however because of the modest elevation to more than the normal level and the relatively small number of patients, only the awake SBP changes reached statistical significance.

Increased levels of reactive oxidative species compromise endothelial function and impair vascular dilatation, thus contributing to the development of HT.[8-10] Antioxidant vitamins such as carotenoids and vitamin E have been demonstrated to scavenge free radicals and lower levels of reactive oxidative species, thus may prevent oxidative damage to lipid membranes and LDL.[11] The carotenoid beta carotene is specifically carried by LDL particles and can quench singlet oxygen. Because oxidation of LDL with subsequent uptake by foam cells in the endothelium is a known contributor to the development of coronary heart disease through the development of atheroma, it has been proposed that carotenoids might prevent coronary heart disease.[12] Some researchers have demonstrated a link between the administration of antioxidants such as vitamin E, lycopene, and beta carotene, or their respective plasma levels, and the development of HT, atherosclerosis, and cerebral stroke.[13-16]

Our assumption is that the reduction in BP observed in the study was due to antioxidant activity of the tomato extract. This assumption is supported by finding a reduction in measured LDL oxidative products, which is attributable probably to an antioxidant-mediated inhibition of LDL peroxidation. In vitro data indicate a protective effect of tomato lycopene combined with beta carotene and vitamin E against LDL oxidation,[17] and in vivo supplementation of beta carotene demonstrated this protective effect as well.[18]

Our results concord with those from several studies examining the effects of vitamins, natural products, or dietary modifications on cardiovascular morbidity, BP, and antioxidant activity.[19-23] Ingestion of tomato juice increased plasma lycopene in healthy subjects[19] and reduced LDL oxidation in patients with type 2 diabetes mellitus.[5] A significant reduction of SBP in hypertensive patients was found after an 8-week supplementation of antioxidants to their antihypertensive drug therapy. Circulating levels of beta carotene and α-tocopherol increased in all subjects, and urine nitrite, which correlated to blood nitric oxide, increased in the hypertensive group.[7] Increased dietary intake of fruit and vegetables in highly selected populations raised plasma antioxidant concentrations.[23] In the DASH trial, increase in dietary fruits and vegetables, given for an 8-week period, reduced SBP and DBP by 2.8 and 1.1 mm Hg, respectively, more than the control diet.[3] In subjects who were encouraged to increase fruit and vegetables consumption, the SBP and DBP fell more than in the control group.

In the present study, tomato extract capsules were used. In these capsules, although containing natural tomato extract, concentrations of various antioxidants were known and standardized, providing a standard intervention for all subjects. Standardization of treatment enables researchers to better monitor patient's compliance to therapy and establish more accurate dose-response relations. Ease of administration and absence of side effects are some of the main characteristics of natural products such as the tomato extract capsules used in our study. It is well known that lack of compliance, in part due to side effects of antihypertensive drug therapy, is an important cause of treatment failure in hypertensive patients.[24]

Some studies, however, failed to demonstrate beneficial correlations between consumption of antioxidants and cardiovascular morbidity and mortality.[25-29] These studies were not designed to evaluate BP changes but were mainly secondary prevention studies conducted among high-risk populations.

The positive results in our pilot trial are encouraging. However, our relatively small study population comprised low-risk patients with grade-1 HT who were naive

to drug therapy. The course of therapy in our study was relatively short, and it is not clear whether the beneficial effect of tomato extract will persist with prolonged administration. The treatment in our trial was a primary therapeutic intervention, and it is reasonable to assume that these low-risk patients who have only minor or no vascular damage will be more responsive to the intervention than patients with higher-grade HT and more advanced vascular disease and multiple drug therapy. Reduction in BP from grade-1 HT range to high-normal range, such as achieved in our pilot study, is clinically significant. Maintaining patients in normotensive state and preventing the progression to higher-grade HT may postpone or even avert the need for an antihypertensive drug therapy. Studies with larger and more diverse populations examining the antihypertensive effect for longer periods are required to establish and define the role of this tomato extract as an antihypertensive agent.

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