Cardiovasc Drugs Ther (2009) 23:145–151
DOI 10.1007/s10557-008-6155-2

The Effects of Natural Antioxidants from Tomato Extract in Treated but Uncontrolled Hypertensive Patients

Esther Paran · Victor Novack · Yechiel Nir Engelhard · Inbal Hazan-Halevy

Published online: 4 December 2008

Abstract
Purpose To evaluate the effect of adding tomato extract to the treatment regime of moderate hypertensives with uncontrolled blood pressure (BP) levels.
Methods Fifty four subjects with moderate HT treated with one or two antihypertensive drugs were recruited and 50 entered two double blind cross-over treatment periods of 6 weeks each, with standardized tomato extract or identical placebo. Plasma concentrations of lycopene, nitrite and nitrate were measured and correlated with BP changes.
Results There was a significant reduction of systolic BP after 6 weeks of tomato extract supplementation, from 145.8 ± 8.7 to 132.2 ± 8.6 mmHg ($p < 0.001$) and 140.4 ± 13.3 to 128.7 ± 10.4 mmHg ($p < 0.001$) in the two groups accordingly. Similarly, there was a decline in diastolic BP from 82.1 ± 7.2 to 77.9 ± 6.8 mmHg ($p = 0.001$) and from 80.1 ± 7.9 to 74.2 ± 8.5 mmHg ($p = 0.001$). There was no significant change in systolic and diastolic BP during the placebo period. Serum lycopene level increased from 0.11 ± 0.09 at baseline, to 0.30 ± 01.3 μmol/L after tomato extract therapy ($p < 0.001$). There was a significant correlation between systolic BP and lycopene levels ($r = -0.49$, $p < 0.001$).
Conclusions Tomato extract when added to patients treated with low doses of ACE inhibition, calcium channel blockers or their combination with low dose diuretics, had a clinically significant effect—reduction of BP by more than 10 mmHg systolic and more than 5 mmHg diastolic pressure. No side-effects to treatment were recorded and the compliance with treatment was high. The significant correlation between systolic blood pressure values and level of lycopene suggest the possibility of cause–effect relationships.

Key words Treated hypertensives · Antioxidants · Tomato-extract · Lycopene

E. Paran (✉) · Y. N. Engelhard
Hypertension Unit, Soroka University Hospital,
Faculty of Health Sciences, Ben Gurion University of the Negev,
Beer Sheba 84101, Israel
e-mail: paran@bgu.ac.il

V. Novack
Division Medicine, Soroka University Hospital,
Faculty of Health Sciences, Ben Gurion University of the Negev,
Beer Sheba, Israel

I. Hazan-Halevy
Hypertension Research Laboratory and Department
of Biochemistry, Faculty of Health Sciences,
Ben Gurion University of the Negev,
Beer Sheba, Israel

Present address:
V. Novack
Trial Design & Development,
Harvard Clinical Research Institute (HCRI),
Boston, MA, USA

Introduction

Hypertension is the most common chronic disease, affecting nearly a billion people worldwide (World Health Organization. Integrated management of cardiovascular risk. Presented at: WHO meeting 2002 Geneva.) In the majority of those diagnosed as hypertensives their disease is of grade I–II according to JNCVII definition [1]. However even if the disease considered mild to moderate in most of the patients blood pressure (BP) is poorly controlled [2] on a single drug regime. Many require two or more drugs, in addition to "health promoting life style modifications". The compliance of patients with such recommendations is less than satisfactory, for a long line

of complex reasons and further decreases with the addition of each new drug [3, 4]. The median time to discontinuing drugs is 90 days, persistence varies with individual drugs, and adverse side effects are the prime culprit [5]. This is a reasonable conclusion, given that hypertension usually causes no symptoms and most antihypertensive drugs have sometimes uncomfortable side effects.

Dietary food additives have gained increasing popularity for the recent years. Various studies have demonstrated the ability of antioxidant vitamins of natural origin to improve vascular function. Regular dietary supplementation of fruits and vegetables has been linked to a rise in plasma vitamin antioxidant levels and a reduction in BP values [6].

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 [7]. In type 2 diabetic subjects consumption of tomato juice caused a significant elevation of plasma lycopene as well as increased resistance of low-density lipoprotein (LDL) to oxidation [8].

In a previous study we have shown a BP lowering property of tomato extract capsules in never treated grade I hypertensives [9].

To further evaluate the effect of tomato extract in hypertension, we conducted the present study involving grade I and II treated hypertensive patients.

The aim of this study was to evaluate the effect of adding tomato extract to pharmacologic treatment, in moderate hypertensives with uncontrolled BP levels, and to correlate this effect with plasma nitric oxide and serum lycopene levels.

Methods

Study population

Fifty-four subjects with moderate hypertension, aged 46–66 years, without concomitant diseases or medications, were recruited from the hypertension clinic of the Soroka University Hospital. They were included if they were treated with one of the following antihypertensive medications: low doses of angiotensin converting enzyme inhibitors (ACE, enalapril 10 mg), calcium channel blockers (CCB, amlodipine 5 mg), β blockers (atenolol 25 mg), or the combination of these drugs with low dose of diuretics (hydrochlorothiazide 12.5 mg); but their BP was not in the normal range on two different occasions (systolic blood pressure (SBP) between 140–159 mmHg or diastolic blood pressure (DBP) between 90–99 mmHg, or both), measured with the subject in the sitting position. Subjects with dyslipidemia, suspected allergy to tomato, carotenoids, or α-tocopherol were excluded from the study. Smokers, diabetics, subjects with cardiovascular, gastrointestinal, hepatic or malignant disease, were excluded as well.

Materials

Encapsulated tomato extract (Lyc-O-Mato®) and a matching placebo, were supplied from LycoRed—Natural Products Industries Ltd., Beer-Sheba, Israel. Each 250 mg Lyc-O-Mato®, capsule consists of 15 mg lycopene (6%), β-carotene (0.15%), phytoene and phytofluene (1%) and 5 mg vitamin E (2%), phospholipids (15%) and phytosterol (0.6%) suspended in tomato oleoresin oil. Both Lyc-O-Mato and placebo were provided in deep red colored soft-gel capsules of the same size and odor. The placebo capsules were filled with Soya oil and the shell matched the natural red color of the Lyc-O-Mato 15 mg. The capsules were swallowed by the patients without any possibility to identify their content.

Procedure

After a routine base-line evaluation, the study participants entered two double blind cross-over treatment periods of 6 weeks each, with standardized tomato extract or identical placebo. Participants were blinded to the different study periods, and were instructed to take one capsule, with the main meal of the day in order to improve absorption of ingredients. No other dietary supplements were allowed throughout the study and participants were instructed to keep their usual dietary and exercise 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 3 weeks at the hypertension outpatient clinic and included a short clinical evaluation, detailed dietary query, blood pressure, pulse and weight measurements and BMI calculation. Blood pressure was measured after 10 min rest in the sitting position using an Omron HEM-705CP electronic semi-automatic sphygmomanometer (Tokyo, Japan). Recorded blood pressure was calculated as the average of three serial measurements if the difference between them were less than 8 mmHg for SBP and 5 mmHg for DBP. All measurements were taken in the same hour of the morning following a 10 min rest and abstinence from food and caffeine for a minimum of 30 min, by a trained research nurse who was blind to the study periods and treatment.

At each visit, participants were supplied with 30 capsules and were asked to return unused capsules at the next visit. Compliance was verified by counting the remaining capsules and by reinforcement at each visit.

Plasma lycopene, nitrite and nitrate levels

Blood was drawn for the measurement of plasma lycopene, nitrite and nitrate levels at baseline, after 6 weeks of treatment and at the end of the study (12 weeks). The samples for the evaluation of plasma lycopene concentration were immediately placed on ice in the dark and the levels were measured as described before [10].

Total nitrite + nitrate (NO_2^- + NO_3^-), the stable end-products of NO, in plasma was measured using Greiss reagent [11]. Since very little or no NO_2^- is found in plasma, we did not attempt to differentiate between NO_2^- and NO_3^-. We report the results as the sum of NO_2^- and NO_3^-.

Ethics

All included subjects signed an informed consent, which was presented to them by the researchers following an explanation regarding the course of the trial. The study protocol was approved by the local Helsinki Ethics Committee.

Statistical analysis

Bivariate hypotheses involving continuous variables were tested with a *t* test for independent groups and paired *t* test was applied for analysis of the dependent samples. We used a repeated measures approach for analysis of more than two variables in the same patient over the span of the study. Correlation between continuous variables was assessed with Pearson test. Normality of the study data was tested with a one-sample Kolmogorov–Smirnov test to indicate the appropriateness of parametric testing. For tests of whether the distribution of categorical variables differed across study groups the χ^2 test was used. A Fisher exact test was applied when appropriate. To avoid spurious association between higher initial BP and the magnitude of BP reduction with tomato extract in evaluation of the treatment effect, we used Oldham's transformation [12, 13]. In brief, we correlated the mean of baseline BP and BP values after 6 week of tomato extract therapy with BP difference between two measurements.

We assessed the potential influence of the study period (before and after crossover) on the observed effect in BP change by testing an interaction term between treatment and period within linear regression model.

Continuous variables are expressed as mean ± SD, and categorical variables as percentages. All reported *p*-values are two-sided and $p < 0.05$ was considered significant.

Results

Of the 54 patients recruited to the study, four patients were not included as they did not meet the inclusion criteria, after baseline evaluation. All 50 patients enrolled, completed the study. There were no adverse effects reported during the entire study period.

Table 1 describes baseline characteristics of the patient population. Patients older than 65 years comprised 44% of the population. Mean SBP and DBP values at baseline were 144.0 ± 10.0 and 82.2 ± 7.8 mmHg respectively. Overall, 23/50 patients (46.0%) received two antihypertensive medications. Male patients were less likely be treated with diuretics and β-blockers than females— 7.7% vs. 31.8% ($p = 0.03$) and 19.2% vs. 40.9% ($p = 0.10$), respectively. There were neither differences between Group 1 (tomato extract→placebo) and Group 2 (placebo→tomato extract) patients in baseline values of SBP and DBP, nor in the rate of use of the different antihypertensive medications.

Figure 1a and b depict SBP and DPB in both groups during the study span. In Group 1 there was a significant reduction of SBP between baseline measurements and Visit 3 (6 weeks of tomato extract supplementation) from 145.8 ± 8.7 to 132.2 ± 8.6 mmHg (difference of 13.5 with 95%CI of 9.8 to 17.3 mmHg, $p < 0.001$). Similarly, there was a decline in DBP from 82.1 ± 7.2 to 77.9 ± 6.8 mmHg (difference of

Table 1 Baseline characteristics of the patients population

	All patients *N*=50	Group 1 tomato extract→placebo *N*=26	Group 2 placebo→tomato extract *N*=24	*p*-value
Age, years	61.4±8.9	59.2±9.4	63.7±7.9	0.08
Male gender, (%)	26 (52.0)	13 (50.0)	13 (54.2)	0.77
Systolic blood pressure, mmHg	144.0±10.0	142.5±11.0	145.8±8.7	0.25
Diastolic blood pressure, mmHg	82.2±7.8	82.2±8.5	82.1±7.2	0.95
Calcium channels blockers, (%)	17 (35.4)	8 (32.0)	9 (39.1)	0.61
β-Blockers, (%)	14 (29.2)	8 (32.0)	6 (26.1)	0.65
ACE inhibitors, (%)	32 (66.7)	14 (56.0)	18 (78.3)	0.10
Diuretics, (%)	9 (18.8)	5 (20.0)	4 (17.4)	0.82

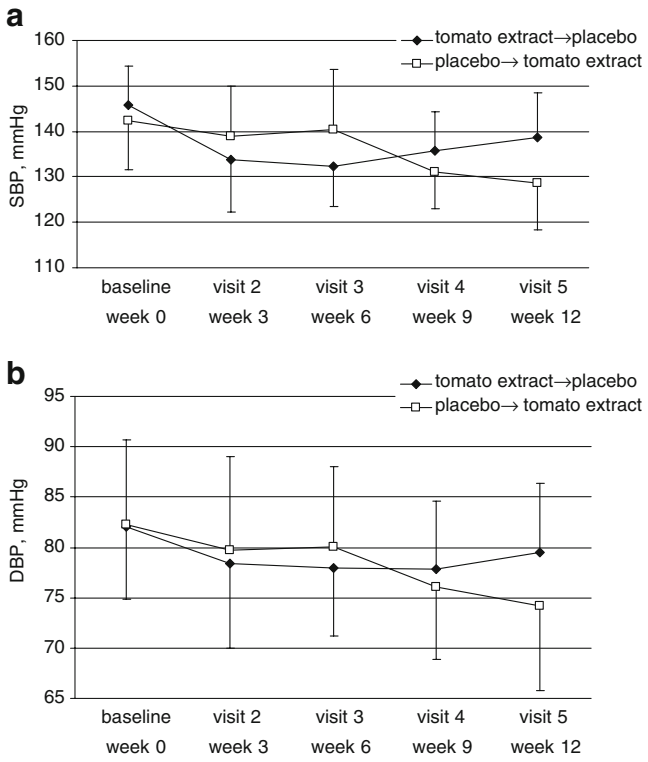

Fig. 1 **a** Systolic blood pressure during the study. **b** Diastolic blood pressure during the study. The mean (±SD) are given for each measurement. The crossover was performed after visit 3

4.2 with 95%CI of 1.8 to 6.5 mmHg, $p = 0.001$). At the same time there was no significant change in SBP and DBP of the patients from Group 2 (6 weeks of placebo supplementation) 142.5 ± 11.0 and 140.4 ± 13.3 mmHg ($p = 0.15$), 82.2 ± 8.5 and 80.1 ± 7.9 mmHg ($p = 0.22$) respectively. Following the crossover, patients in Group 1 were switched to 6 weeks of placebo treatment, which resulted in a mean SBP increment of 6.5 mmHg (95%CI 2.6 to 10.3 mmHg, $p = 0.002$). However, at the end of that 6 week period patients in Group 1 still had lower values of SBP as compared to their baseline values 138.7 ± 9.7 mmHg vs. 145.8 ± 8.7 mmHg ($p < 0.001$). Following the crossover to tomato extract supplementation, there was a significant decline in SBP in patients from Group 2—140.4 ± 13.3 to 128.7 ± 10.4 mmHg (difference of 11.7 with 95%CI of 7.5 to 15.9 mmHg, $p < 0.001$). Similarly, there was a decline in DBP from 80.1 ± 7.9 to 74.2 ± 8.5 mmHg (difference of 5.8 with 95%CI of 3.4 to 8.3 mmHg, $p = 0.001$).

A linear model with change in SBP or DBP as a dependent variable and the following covariates: treatment group, study period (before or after crossover) and interaction term treatment × period, showed that there was no significant interaction between two variables.

At baseline, weight and BMI did not differ between the groups: Group 1 (tomato extract→placebo) 76.8 ± 14.2 kg, and Group 2 (placebo→tomato extract) 83.6 ± 22.6 ($p = 0.20$, $p = 0.40$ respectively). Repeated measurements analysis showed that there were no significant changes in weight during the study in both groups: Group 1, maximal mean weight 76.8, minimal weight 76.2, $p = 0.06$, Group 2, maximal mean weight 83.6, minimal weight 83.2, $p = 0.08$.

To further evaluate the effect of tomato extract compared to placebo we combined the matching treatment periods for the two groups. Table 2 demonstrates the combined levels of lycopene; nitrate and blood pressure, assessed after 6 weeks of placebo treatment, compared to the result of 6 weeks tomato extract supplementation for the whole study population.

Mean SBP for the combined two groups on placebo was 139.4 ± 11.6 vs. 130 ± 9.6 mmHg on tomato extract ($p < 0.001$), while mean DBP dropped from 79.8 ± 7.3 to 76.0 ± 7.8 mmHg ($p < 0.001$), accordingly.

Figure 2a and b present linear association between baseline SBP and DBP values and the reduction of SBP and DBP after tomato extract treatment, combined for the two groups. After applying Oldham's transformation there was no correlation found neither between mean of baseline and post tomato extract SBP and SBP reduction—$r = 0.04$, $p = 78$, nor between mean of baseline and post tomato extract DBP and DBP reduction—$r = 0.003$, $p = 0.99$.

Although blood was drawn for the determination of lycopene levels from all the participants on three time points: baseline, visit 3 and visit 5 (Fig. 3), for technical reason, only in 22 patients all results were available: 9 in Group 1 and 13 in Group 2. In the two groups combined, the mean level of lycopene at baseline was 0.11±

Table 2 The effect of tomato extract vs. placebo supplementation on the serum nitrate and lycopene levels, and blood pressure

	Number of patients	Placebo	Tomato extract	95% CI of difference	*p*-value
Systolic blood pressure, mmHg	50	139.6±11.6	130.4±9.6	−12.1; −6.3	<0.001
Diastolic blood pressure, mmHg	50	79.8±7.3	76.0±7.8	−5.7; −1.9	<0.001
Lycopene, μmol/L	22	0.23±0.14	0.30±0.13	0.01; 0.13	0.02
Nitrate, μmol/L	43	10.4±3.5	12.0±4.4	0.35; 2.84	0.01

The combined results for all patients, according to the two treatment periods

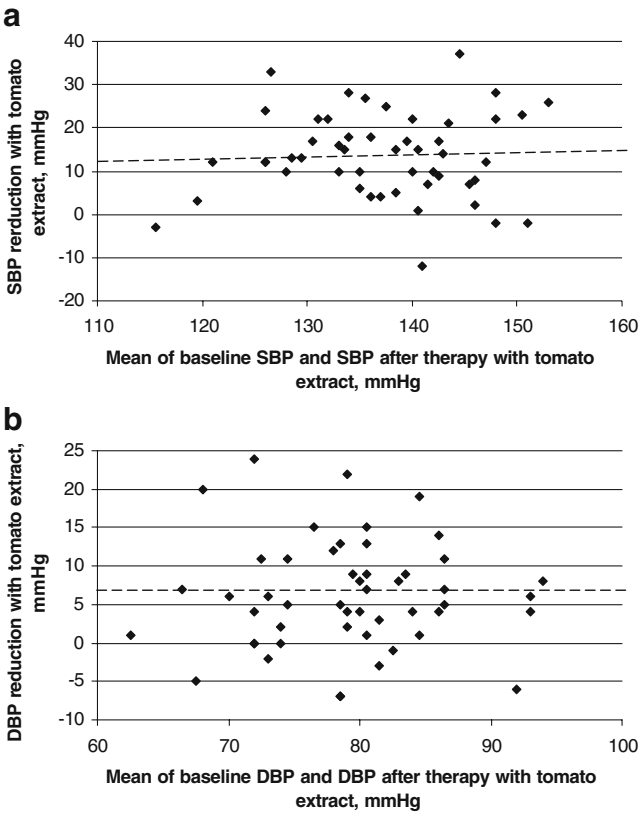

Fig. 2 **a** Reduction of the systolic blood pressure with tomato extract by the mean of baseline and after tomato extract systolic blood pressure (Oldham's transformation). *Line* represents linear regression function. **b** Reduction of the diastolic blood pressure with tomato extract by the mean of baseline and after tomato extract diastolic blood pressure

0.09 μmol/L, after 6 weeks of placebo treatment—0.23± 0.14 μmol/L and after 6 weeks of tomato extract supplementation—0.30±01.3 μmol/L (repeated measures, $p<0.001$) (Table 2). Of note, lycopene levels after 6 weeks of placebo treatment were significantly higher than the baseline both in Group 1 (0.23±0.11 vs. 0.10±0.06; $p<0.001$), as well as in Group 2 (0.22±0.17 vs. 0.11±0.11; $p=0.002$) and increased significantly while on tomato extract. Mean levels of nitrate at the baseline and after 6 weeks of placebo were 10.7±3.7 and 10.4±3.5 respectively; after 6-weeks of tomato extract supplementation the level increased significantly to 12.0±4.4 μmol/L (repeated measures, $p<0.001$).

Analysis of relationships between lycopene levels at three time points (baseline, placebo and tomato extract treatment) and levels of SBP and DBP showed, that there was a significant negative correlation between SBP and lycopene level ($r=-0.49$, $p<0.001$), while such an association was not found between DBP and lycopene levels ($r=-0.06$, $p=0.65$).

Discussion

In this present randomized placebo controlled cross-over study we assessed the effect of tomato extract supplementation in an established hypertensive population of patients with uncontrolled mild to moderate hypertension treated with one or two antihypertensive drugs. The core findings from this study are: (1) a significant decline both in systolic and diastolic blood pressures with tomato extract therapy and; (2) a significant increase in serum lycopene level after tomato extract therapy (3) a significant increase in serum nitrate level after tomato extract therapy.

The current study was designed as a second phase to our previous study, in which we have shown that short-term, daily oral supplementation of carotenoids-rich tomato extract in a dose equivalent to consumption of four medium tomatoes, significantly decreased SBP and DBP and reduced levels of lipid peroxidation products in nonsmoking, recently diagnosed patients with grade-1 hypertension, receiving no antihypertensive or lipid-lowering pharmaceutical therapy and without significant cardiovascular risk factors [9].

In the present study, no significant differences in the baseline characteristics between the two groups were observed and patients were advised and repeatedly reminded to maintain their current diet and lifestyle. Their

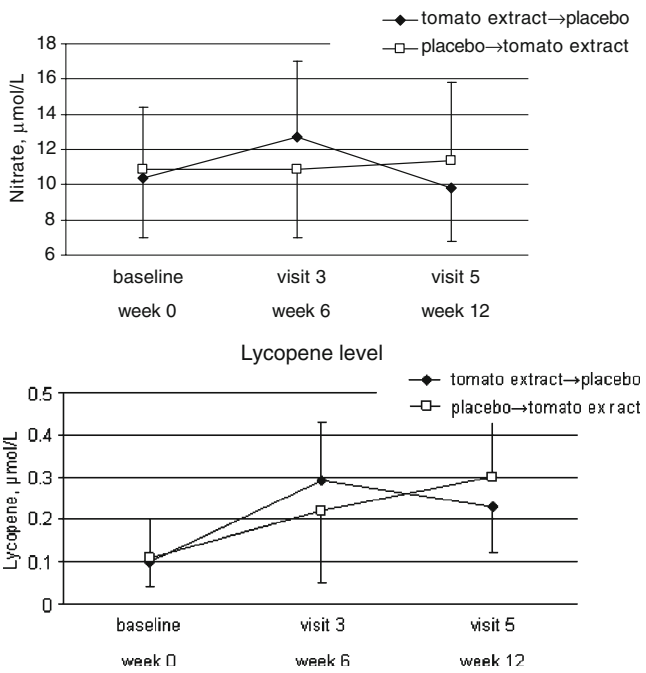

Fig. 3 Lycopene and nitrate levels at baseline, after first 6-weeks treatment period and after crossover and second 6-weeks period. The mean (±SD) are given for each measurement. The crossover was performed after visit 3. Lycopene levels were available in 22 persons: nine in Group 1 (tomato extract→placebo) and 13 in Group 2 (placebo→tomato extract). Nitrate levels were available in 43 persons: 20 in Group 1 and 23 in Group 2

body weight remained unchanged throughout the study, thus our results are unlikely to be attributed to weight lowering, and major dietary changes, or enhanced physical activity.

To evaluate the effect of tomato-extract addition to the treatment regime, we measured the plasma levels of lycopene, one of the main constituents of the tomato extract capsule. A significant increase in serum lycopene level after tomato extract therapy was detected. A much smaller but still significant increase of lycopene was observed on placebo treatment as well. We have no convincing explanation for this finding. Observing closely the change in BP during placebo period in Group 2 patients (placebo→tomato extract) no significant effect was observed, while during tomato-extract administration a good correlation between serum lycopene levels and BP reduction was recorded. In Group 1 (tomato extract→placebo) a significant elevation of plasma levels of lycopene well correlated with BP decline. However when these patients were switched to placebo, BP increased and plasma lycopene dropped significantly but never reached the baseline pre-treatment values. Although the half life of serum lycopene is about 14 days, its active metabolites and their varying tissue levels may be of importance [10, 14–16].

Tomatoes are a source of several antioxidant nutrients [17] as lycopene, beta-carotene, folate, potassium, vitamin C, flavonoids, and vitamin E. Many of these nutrients may function individually, or in concert, to protect lipoproteins and vascular cells from oxidation, the most widely accepted theory for the genesis of atherosclerosis. Several of theses substances have been shown to exhibit other cardio-protective functions, such as reduction of homocystein, platelet aggregation, and blood pressure levels. These findings have been supported by in vitro, in vivo, and many epidemiological studies that associate reduced cardiovascular risk with consumption of antioxidant-rich foods in general [6, 18] and beta-carotenes as lycopene in particular [19, 20]. The physiologic rationale is clear from many basic science studies, showing that these antioxidants act by scavenging free radicals as reactive oxidative species [21–23].

Dietary intervention trials on the impact of increased consumption of vegetables and fruits on blood pressure have demonstrated positive results [6, 24]. However, data from large prospective randomized clinical trials have failed to demonstrate beneficial cardiovascular or antihypertensive effects of antioxidants [25, 26]. There are many potential reasons for this failure, some relate to the antioxidants used: one or two synthetic vitamins with fixed dosage; others to the patients included in trials: mostly elderly patients after major CV event treated as a secondary prevention. Moreover, most of the trials were not designed to detect changes in BP.

The benefits of our study are in the use of an effective concentration of antioxidants in their natural formulation, tomato extract with all the nutrients of the tomato included, extracted in natural tomato oil. This substance has been already shown to reduce BP in naïve hypertensives [9]. None of the 50 patients included had any side-effect and the compliance with treatment was high.

Our study has several limitations. Due to the small sample size we were not able to assess the dose dependency between an increase of the serum lycopene level and a decrease in SBP or DBP. However, given the strong inverse linear relation between the lycopene levels obtained in different points of the study and SBP, one can argue that the observed decrease in SBP is the result of lycopene supplementation as an active ingredient of the tomato extract. In parallel, NO levels increased significantly, suggesting the mechanism of BP reduction, however they did not correlated to the increase in lycopene. The other ingredients included in the tomato extract as phytoene, and phytofluene may have an important effect on the BP, but our study was not designed to evaluate this kind of effect. During the placebo supplementation the serum lycopene levels were relatively high. This is possibly due to interpersonal variability, long half life and the probability that despite our attempts to minimize the alteration of the usual diet, some patients unawarely made some increase in their tomato intake. However, the reduction of SBP and DBP was recorded only during tomato extract supplementation. Thus most probably a mild increase of the dietary tomato intake is not sufficient for the blood pressure reducing effect.

The present study included a relatively short treatment period: 6 weeks of active treatment in each group. It gave us sufficient results to prove the BP lowering effect of the tomato extract but not enough time to argue for the possible use of it as an antihypertensive agent. There is a need for a long term study with larger number of patients to consider the future of the tomato extract as an effective addition to antihypertensive treatment.

The positive outcome of the study, the lack of side effects and the eagerness of the patients to use a food product instead of addition of another drug makes the future of the tomato extract promising.

References

1. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA 2003;289: 2560–72.
2. Van Wijk BL, Klungel OH, Heerdink ER, de Boer A. Initial non-compliance with antihypertensive monotherapy is followed by

complete discontinuation of antihypertensive therapy. Pharmacoepidemiol Drug Saf 2006;15:587–93.
3. Garfield FB, Caro JJ. Compliance and hypertension. Curr Hypertens Rep 1999;1:502–6.
4. Hassan NB, Hasanah CI, Foong K, Naing L, Awang R, Ismail SB, et al. Identification of psychosocial factors of noncompliance in hypertensive patients. J Hum Hypertens 2006;20:23–9.
5. Benson S, Vance-Bryan K, Raddatz J. Time to patient discontinuation of antihypertensive drugs in different classes. Am J Health Syst Pharm 2000;57:51–4.
6. John JH, Ziebland S, Yudkin P, Roe LS, Neil HA. Effects of fruit and vegetable consumption on plasma antioxidant concentrations and blood pressure: a randomised controlled trial. Lancet 2002;359:1969–74.
7. Gerster H. The potential role of lycopene for human health. J Am Coll Nutr 1997;16:109–26.
8. Upritchard JE, Sutherland WH, Mann JI. Effect of supplementation with tomato juice, vitamin E, and vitamin C on LDL oxidation and products of inflammatory activity in type 2 diabetes. Diabetes Care 2000;23:733–8.
9. Engelhard YN, Gazer B, Paran E. Natural antioxidants from tomato extract reduce blood pressure in patients with grade-1 hypertension: a double-blind, placebo-controlled pilot study. Am Heart J 2006;151:100.
10. Walfisch Y, Walfisch S, Agbaria R, Levy J, Sharoni Y. Lycopene in serum, skin and adipose tissues after tomato-oleoresin supplementation in patients undergoing haemorrhoidectomy or peri-anal fistulotomy. Br J Nutr 2003;90:759–66.
11. Miranda KM, Espey MG, Wink DA. A rapid, simple spectrophotometric method for simultaneous detection of nitrate and nitrite. Nitric Oxide 2001;5:62–71.
12. Gill JS, Zezulka AV, Beevers DG, Davies P. Relation between initial blood pressure and its fall with treatment. Lancet 1985;1:567–9.
13. Oldham P. The interpretation of numerical data. Measurement in medicine. London: London English Universities Press; 1968. p. 148–52.
14. Clinton SK. Lycopene: chemistry, biology, and implications for human health and disease. Nutr Rev 1998;56:35–51.
15. Stahl W, Schwarz W, Sundquist AR, Sies H. Cis–trans isomers of lycopene and beta-carotene in human serum and tissues. Arch Biochem Biophys 1992;294:173–7.
16. Rock CL, Swendseid ME, Jacob RA, McKee RW. Plasma carotenoid levels in human subjects fed a low carotenoid diet. J Nutr 1992;122:96–100.
17. Willcox JK, Catignani GL, Lazarus S. Tomatoes and cardiovascular health. Crit Rev Food Sci Nutr 2003;43:1–18.
18. Morris CD, Carson S. Routine vitamin supplementation to prevent cardiovascular disease: a summary of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med 2003;139:56–70.
19. Rissanen TH, Voutilainen S, Nyyssonen K, Salonen R, Kaplan GA, Salonen JT. Serum lycopene concentrations and carotid atherosclerosis: the Kuopio Ischaemic Heart Disease Risk Factor Study. Am J Clin Nutr 2003;77:133–8.
20. Gianetti J, Pedrinelli R, Petrucci R, Lazzerini G, De Caterina M, Bellomo G, et al. Inverse association between carotid intima–media thickness and the antioxidant lycopene in atherosclerosis. Am Heart J 2002;143:467–74.
21. Pickering TG. What should we advise our patients about taking antioxidants? J Clin Hypertens 2003;5:231–3.
22. Griendling KK, Sorescu D, Lassegue B, Ushio-Fukai M. Modulation of protein kinase activity and gene expression by reactive oxygen species and their role in vascular physiology and pathophysiology. Arterioscler Thromb Vasc Biol 2000;20:2175–83.
23. Heitzer T, Schlinzig T, Krohn K, Meinertz T, Munzel T. Endothelial dysfunction, oxidative stress, and risk of cardiovascular events in patients with coronary artery disease. Circulation 2001;104:2673–8.
24. Conlin PR, Chow D, Miller ER 3rd, Svetkey LP, Lin PH, Harsha DW, et al. The effect of dietary patterns on blood pressure control in hypertensive patients: results from the Dietary Approaches to Stop Hypertension (DASH) trial. Am J Hypertens 2000;13:949–55.
25. HOPE-TOO results: vitamin E supplements do not protect against cancer or cardiovascular disease. Nat Clin Pract Cardiovasc Med. 2005;2:233.
26. Czernichow S, Bertrais S, Blacher J, Galan P, Briancon S, Favier A, et al. Effect of supplementation with antioxidants upon long-term risk of hypertension in the SU.VI.MAX study: association with plasma antioxidant levels. J Hypertens 2005;23:2013–8.