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Tomato paste supplementation improves endothelial dynamics and reduces plasma total oxidative status in healthy subjects

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ABSTRACT

Consumption of tomato products is linked to beneficial outcomes through antioxidant and anti-inflammatory mechanisms. The aim of this study was to determine whether a 14-day period of tomato paste supplementation would improve endothelial function. Nineteen volunteers (mean age, 39 ± 13 years; 8 men/11 women) were studied in a randomized (exposure sequence), single-blind (operator), crossover design. The study consisted of a supplementation arm (70 g tomato paste containing 33.3 mg of lycopene) and a control arm, during which no tomato paste was added to their regular diet. Volunteers maintained their regular diet during study arms. Two-week washout periods preceded each arm. Flow-mediated dilatation (FMD) measured by brachial artery ultrasonography was used as an estimate of endothelial function at day 1 (acute response) and day 15 (midterm response). Plasma lipid peroxides were measured with a photometric enzyme-linked immunosorbent assay as an index of total oxidative status. Tomato supplementation led to an overall FMD increase compared with the control period ($P = .047$ for repeated-measures 3 × 2 analysis of variance). At day 1, FMD was not significantly increased ($P = .329$). By day 15, tomato supplementation resulted in an increase in FMD by 3.3% ± 1.4%, whereas at the control arm, FMD declined by –0.5% ± 0.6% ($P = .03$); magnitudes of change are absolute FMD values. Total oxidative status decreased at the end of the supplementation period compared with baseline values ($P = .038$). Daily tomato paste consumption exerts a beneficial midterm but not short-term effect on endothelial function. Further studies are warranted to explore the effects of tomato paste on endothelial dilation in different age groups and comorbidities.

1. Introduction

Several lines of evidence highlight the role of lycopene as an antioxidant. Abundant in tomatoes, lycopene is the most potent singlet oxygen quencher among carotenoids [1]. Moreover, a number of in vitro studies point to additional anti-inflammatory properties, thus spurring research into its potential role in primary prevention [2]. Nevertheless,

Abbreviations: ANOVA, analysis of variance; CVD, cardiovascular disease; FMD, flow-mediated dilatation; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NMD, nitroglycerin-mediated dilatation; TOS, total oxidative status.

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although lycopene plays a clearly beneficial role in the prevention of neoplasias, epidemiologic studies report equivocal results regarding its association with cardiovascular disease (CVD) risk [3–5].

The discrepancy between bench and bedside results can be addressed by assessing early, subclinical manifestations of atherosclerosis. Carotid intima-media thickness, a structural arterial marker, has been inversely linked to lycopene concentrations [6,7]. Trials of short-term supplementation have assessed the impact of lycopene consumption on functional arterial markers such as endothelial function [8] and circulating biomarkers [9], with inconsistent results.

The hypothesis of the present study was that a short period of diet supplementation with a tomato-based product would exert a beneficial effect on endothelial function. Nineteen volunteers were studied in a randomized, single-blind, crossover design. Volunteers received a 2-week-long period of tomato paste supplementation and a control procedure with intercalated washout periods. Flow-mediated dilatation (FMD) was used as a marker of endothelial function at baseline and at days 1 and 15 of the supplementation and control arms of the study.

2. Methods and materials

2.1. Study population and design

The study population consisted of 19 young, healthy volunteers (age, 39 ± 13 years; 8 men). All were free from CVD, hypertension, diabetes mellitus, dyslipidemia, or family history of premature vascular disease. Seven participants were smokers. Women were examined during the follicular phase of the menstrual cycle; none used oral contraceptives. The study protocol was approved by the Research Ethics Committee of Hippokration Hospital, Athens Medical School, and all subjects gave written informed consent.

The study was conducted in a randomized (sequence of exposure), single-blind (operator), crossover design (each subject received both the intervention and control treatments). It consisted of 2 study arms, the tomato paste supplementation arm and the control arm; during the control arm, the volunteers consumed no supplement. Participants were asked to maintain their regular daily dietary pattern for the duration of each study arm; tomato paste was provided in addition to their regular diet during the supplementation arm. Each arm was preceded by a 2-week washout period, during which participants abstained from all lycopene-containing products. Compliance to dietary instructions was evaluated at the end of the study; when participants were asked to report the number of servings of tomato paste they had consumed during the supplementation arm and to return empty cans.

Subjects were studied on 3 different occasions for each arm. During the supplementation arm, they were evaluated at baseline, 24 hours after the ingestion of a single dose of tomato paste (short-term response), and at day 15, after the daily ingestion of a dose of tomato paste for 2 weeks (midterm response). Time points for measurements were based on previously published data on lycopene pharmacokinetics in humans [10,11]. Volunteers visited our department at the same time points during the control arm. Subjects abstained from smoking and caffeine/alcohol intake for at least 12 hours before each session. A baseline fasting blood sample was drawn for glucose and lipid profile determination; additional blood samples were drawn at days 1 and 15 of the supplementation period for total oxidative status (TOS) determination. Glucose was measured using the hexokinase method; total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides were measured using enzymatic colorimetric methods (Abbott ARCHITECT System; Abbott Diagnostics, Abbott Park, Ill). Low-density lipoprotein (LDL) cholesterol was calculated using the Friedewald formula. Total oxidative status was determined by measuring total lipid peroxides in plasma with a photometric enzyme-linked immunosorbent assay (PerOx TOS/total oxidative capacity kit; Immundiagnostik AG, Bensheim, Germany).

During the supplementation arm, the participants consumed a commercially available tomato paste (70 g) in the morning after an overnight fast. Products from a single batch were used. The lycopene content of this tomato paste (tomato paste double concentrated 28%; Kyknos SA, Nafplion, Greece) has been previously measured by high-performance liquid chromatography by the manufacturer and was found to be 33.3 mg [12]. The supplied tomato paste also contained 1307 IU of vitamin A, 40.25 mg of vitamin C, 784 μg of β-carotene, 10.5 g of sugar, 11.27 g of total carbohydrate, 2.94 g of protein, 2.45 g of fiber, and 253 kJ of energy (data provided by the manufacturer).

2.2. Measurement of endothelial function of the brachial artery

Flow-mediated dilatation is used as an estimate of endothelial function and was measured by high-resolution vascular ultrasound (Agilent Sonos 5500, Hewlett-Packard, Andover, Mass) according to guidelines [13]. Briefly, endothelium-dependent FMD was assessed by measuring the changes in the diameter of the brachial artery for 2 minutes after reactive hyperemia for 5 minutes. *Flow-mediated dilatation* was defined as the maximum percentage change in brachial artery diameter compared with baseline; that is, FMD = [(postocclusion diameter − resting diameter)/resting diameter] × 100. Reactive hyperemia was calculated as the percentage change of brachial artery blood flow [14]. Nitroglycerin-mediated dilatation (NMD), that is, the endothelial-independent vasodilatation after a sublingual application of 400 μg of nitroglycerin spray, was also assessed at the end of each period. Analyses were conducted offline by 2 different investigators blinded to treatment. The repeatability coefficient for FMD in our unit is 2.06%. It has been previously calculated as defined by the British Standard Institution, according to the following formula: repeatability coefficient = $2 * \sqrt{(\sum di^2/N)}$, where N is the sample size and di is the difference between the 2 measurements in a pair.

2.3. Statistical analyses

Sample size calculations were based on the data from our unit. The SD of FMD for subjects with characteristics similar to those of our study population was 2.4% [15]. We hypothesized that tomato supplementation would result in an absolute