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Dietary supplementation with tomato-juice in patients with metabolic syndrome: A suggestion to alleviate detrimental clinical factors

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ABSTRACT

Lycopene, a carotenoid, is known for its antioxidant properties. Little is known, though, about the relationship of dietary tomato-juice intake and risks factors, like inflammation, insulin resistance and hyperlipidemia, implicated in metabolic syndrome. In the present study, we examined whether supplementation with tomato-juice has any implication on the risk status of patients with metabolic syndrome. A comparative study was conducted in 27 individuals diagnosed with metabolic syndrome. Fifteen of them were instructed to use commercially available tomato-juice as refreshment 4 times a week over a period of two months and twelve individuals served as the control group. Several parameters reflective of the metabolic syndrome were monitored both in the group supplemented with tomato juice and in the control group (ADMA for entdothelial function, TNF-α and IL-6 for inflammation, FIRI for insulin resistance). There was a significant improvement in the inflammation status and the endothelial dysfunction of the tomato-juice supplemented patients. At the same time, insulin resistance improved and a pronounced decrease in LDL was recorded, along with a slight increase in HDL. The results of the present study suggest an alleviating effect of tomato-juice with regard to risk factors associated with metabolic syndrome.

1. Introduction

Metabolic syndrome (MS) is a summation of a number of metabolic derangements associated with vascular endothelial dysfunction and oxidative stress and is widely regarded as an inflammatory condition, accompanied by an increased risk for cardiovascular disease (Ford et al., 2002; Rayssiguier et al., 2010; Rizvi, 2012; Vaidya et al., 2011). It is characterized by a compilation of cardiovascular and pro-thrombotic risk factors, such as insulin resistance, impaired glucose tolerance, dyslipidemia, obesity and elevated blood pressure. MS represents a combination of synergistic vascular pathologies that generally lead to an accelerated atherogenic state.

Endothelial dysfunction with low nitric oxide (NO) bioavailability has been implicated in insulin resistance and hypertension (Stühlinger et al., 2002). Asymmetric dimethyl arginine (ADMA) is linked to the impairment of endothelial NO-dependent function, by inhibiting endogenous nitric oxide synthetase in a concentration dependent manner, and has been associated with cardiovascular diseases (Boger et al., 1998; Palomo et al., 2011). The pathophysiology of insulin resistance involves pro-inflammatory cytokines, altered adipokines and endothelial dysfunction (Rentoukas et al., 2011; Tsarouhas et al., 2011). Moreover, dyslipidemia is a major risk factor for development of several obesity-related diseases. Among successful strategies that have been shown to improve endothelial function are statins, which lower cholesterol and improve NO

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Table 1
Nutritional evaluation of tomato juice (canned, salt added) (average values of microconstituents per 100 g). Nutrient data are provided free of charge by the USDA National Nutrient Database for Standard Reference and the Danish Food Composition Databank, version 7.0, 2008 (http://www.foodcomp.dk/).

Content per 100 g	Unit	Content
Vitamins		
Vitamin A	IU	259–450
β-carotene eq.	μg	214–425
Vitamin C	mg	51.5–68.7
Vitamin E (tocopherol)	mg	0.390–1.30
Vitamin K	μg	2.3–7.9
Niacin	mg	0.7
Vitamin B6	mg	0.1
Folate	μg	6.0–20.0
Pantothenic acid	mg	0.3
Choline	mg	6.8
Phenols	mg GAE	20.5–33.1
Minerals		
Calcium	mg	7.66–18.0
Iron	mg	0.180–1.18
Magnesium	mg	7.10–12.7
Phosphorus	mg	17.1–33.0
Potassium	mg	181–266
Sodium	mg	84.5–300
Zinc	mg	0.2–0.3
Copper	mg	0.1
Manganese	mg	0.066–0.160
Selenium	μg	0.3
Nickel	μg	1.60–11.4

* GAE: gallic acid equivalent.

production, angiotensin-converting-enzyme (ACE) inhibitors that affect suppression of endothelin production, which is mediated via angiotensin, and anti-oxidants, such as vitamins E and C (Lele, 2007).

Growing evidence from epidemiological studies has indicated that lycopene, the major carotenoid in tomato known for its antioxidant activities on the cellular level (Kelkel et al., 2010), might be more important than other carotenoids in preventing or reducing atherosclerosis and cardiovascular diseases (Kohlmeier et al., 1997). Processed tomato products, such as commercially available tomato juice, are the primary dietary lycopene source in western countries (Story et al., 2010). These products have been reported to possess equal antioxidant properties, even reducing oxidative DNA damage (Harms-Ringdahl et al., 2012). The lycopene content of tomato juice samples reported in the literature has been found to be quite similar with an average value of 2.79 ± 0.211 mg lycopene/100 ml (Jacob et al., 2008; Sanchez-Moreno et al., 2006). Furthermore, tomato juice contains several useful microconstituents and dietary fibers of important health benefits (Table 1) (Sanchez-Moreno et al., 2006; Tyssandier et al., 2004) and therefore, lycopene should not be regarded as exclusively responsible for any beneficial effects observed following tomato juice consumption. In rats viscous fibers can reduce the adiposity and hepatic steatosis that accompany a high-fat diet, and increase metabolic flexibility, regardless of fermentability (Brockman et al., 2014). In addition, low vitamin C has been found to be associated with obesity (García et al., 2013), while vitamin C supplementation led to lowering glucose levels and increased SOD and GSH enzyme activity that can probably reduce insulin resistance by enhanced lowering oxidative stress parameters (Rafighi et al., 2013).

Biomonitoring data in patients with MS have consistently shown lower carotenoid concentrations compared with individuals without MS (Beydoun et al., 2012; Li et al., 2013). A higher total carotenoid intake, beta-carotene and lycopene, was associated with a lower prevalence of MS and with lower measures of adiposity and serum triglyceride concentrations in middle-aged and elderly men (Sluijs et al., 2009). Furthermore, results indicate that chronic lycopene treatment might be useful in preventing diabetic vascular complications associated with endothelial dysfunction. In animal models chronic lycopene treatment attenuated endothelial dysfunction by reducing oxidative stress or by inducing a hypoglycemic effect (Bayramoglu et al., 2013; Zhu et al., 2011). Other studies suggested that lycopene decreases hypertension in humans (Engelhard et al., 2006).

In the present study, the effect of tomato-juice supplementation in some detrimental clinical parameters of patients with MS, such inflammation, endothelial dysfunction, dyslipidemia and insulin resistance, was investigated.

2. Materials and methods

2.1. Study population

The demographic and other characteristics of the population study are presented in Table 2. Patients were classified based on the presence of MS at baseline using the American Heart Association/National Heart, Lung and Blood Institute (AHA/NHLBI) definition (Grundy et al., 2005): triglycerides ≥150 mg/dL; high-density lipoprotein cholesterol (HDL) < 40 mg/dL in males or <50 mg/dL for females; blood pressure (BP) ≥ 130/85 mm Hg or treatment with antihypertensive medications; fasting blood glucose ≥100 mg/dL or treatment with oral hypoglycemic drugs or insulin injection; and waist circumference ≥102 cm for men and ≥88 cm for women. Patients who had 3 of 5 criteria were regarded as suffering from MS. Twenty-seven (27) patients with MS, who were being treated on a regular basis at the General Hospital of Karditsa, Greece, at the "Amalia Fleming" General Hospital in Athens, Greece, and at the private practice office of their attending cardiologists, fellow-researchers of the "Amalia Fleming" General Hospital, volunteered to participate in the study. The subjects underwent detailed cardiological evaluation at baseline. They were instructed to follow their usual eating habits during the days before the experiment. Fifteen of them were advised to use commercially available tomato-juice (Table 3) once a day as refreshment 4 times a week over a period of two months. The control group continued their regular eating and supplementation habits not using any lycopene-rich diet sources. Written informed consents were obtained from all participants. The research ethics committee of the "Amalia Fleming" Hospital approved the procedures. The Declaration of Helsinki (2000) and the applicable national standards as they relate to the involvement of human subjects in research were enforced. No external funding was received for this study.

2.2. Data collection and analyses

In the morning and after supine rest of at least 30 min, fasting venous blood samples were drawn from all patients, at baseline and at the end of the study period, centrifuged within 30 min and stored at −20 °C. Glucose was measured enzymatically with the hexokinase method. Total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL) and low-density lipoprotein cholesterol (LDL) were measured enzymatically, with final measurements at 520 nm and 583 nm, respectively, for HDL and LDL. For all the above assays, the COBAS INTEGRA 800 automated system by Roche Diagnostics Corp (Indianapolis, IN, USA) and all relevant diagnostic reagents were used. Analysis for ADMA was performed using an ADMA-ELISA kit (DLD Diagnostica GmBH, Hamburg, Germany). TNF-α and IL-6 were measured using the IMMULITEH 1000TNF-α and IMMULITEH 1000IL-6 assays (Siemens Medical Solutions Diagnostics, Llanberis Caernarfon, UK). Serum insulin levels were measured using a human immunoradiometric assay (TOSOH ST Insulin AIA-PACK) (TOSOH Bioscience, Belgium). The Fasting Insulin Resistance Index (FIRI), which is derived from fasting plasma insulin and glucose levels and has been validated against the hyperinsulinemic-euglycemic clamp (AlZadjali et al., 2009) was used as an empirical insulin resistance (IR) index. FIRI has previously been applied in our laboratory published studies (Tsarouhas et al., 2011) and a database from control population has been developed. Among the various surrogate markers for insulin resistance (i.e. HOMA-I, FIRI etc.), no superiority of one marker over the other is reported in the literature (Gupta and Jain, 2004; Ikeda et al., 2001). The following formula was used: FIRI = fasting glucose (mmol/l) × fasting insulin (mU/l)/25. Based on the range of normal values for glucose and the reference values for serum insulin found for the healthy individuals (Tsarouhas et al., 2011), a FIRI value of 2.94 ± 1.41 was determined as the upper limit of normal.

Tomato juice analysis. Standards of lycopene (>90%, from tomato) and β-carotene (>97%, UV) were purchased by Sigma-Aldrich. Extraction of the tomato juice commercial product was extracted in triplicate according to a previously used method, with minor modifications (Sanchez-Moreno et al., 2006). HPLC analysis was conducted as described elsewhere (Seybold et al., 2004). Results are summarized in Table 3.

Statistical analysis. All results are presented as mean values ± SD. Statistical analyses were performed with SPSS version 14 (SPSS Inc., Chicago, IL, USA). Normality of the data was tested using the Kolmogorov–Smirnov test in order to use parametric testing. Significant differences between means for the same parameters were investigated with repeated measures ANOVA and paired *t*-test analyses. Indepen-