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Effect of pistachio diet on lipid parameters, endothelial function, inflammation, and oxidative status: A prospective study

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Abstract

Objective: Recent studies have suggested that nuts have favorable effects beyond lipid lowering. We aimed to investigate effect of the Antep pistachio (*Pistacia vera L.*) on blood glucose, lipid parameters, endothelial function, inflammation, and oxidation in healthy young men living in a controlled environment.

Methods: A Mediterranean diet was administered to normolipidemic 32 healthy young men (mean age 22 y, range 21–24) for 4 wk. After 4 wk, participants continued to receive the Mediterranean diet but pistachio was added for 4 wk by replacing the monounsaturated fat content constituting ≈20% of daily caloric intake. Fasting blood samples and brachial endothelial function measurements were performed at baseline and after each diet.

Results: Compared with the Mediterranean diet, the pistachio diet decreased glucose ($P < 0.001$, $-8.8 \pm 8.5\%$), low-density lipoprotein ($P < 0.001$, $-23.2 \pm 11.9\%$), total cholesterol ($P < 0.001$, $-21.2 \pm 9.9\%$), and triacylglycerol ($P = 0.008$, $-13.8 \pm 33.8\%$) significantly and high-density lipoprotein ($P = 0.069$, $-3.1 \pm 11.7\%$) non-significantly. Total cholesterol/high-density lipoprotein and low-density lipoprotein/high-density lipoprotein ratios decreased significantly ($P < 0.001$ for both). The pistachio diet significantly improved endothelium-dependent vasodilation ($P = 0.002$, 30% relative increase), decreased serum interleukin-6, total oxidant status, lipid hydroperoxide, and malondialdehyde and increased superoxide dismutase ($P < 0.001$ for all), whereas there was no significant change in C-reactive protein and tumor necrosis factor-α levels.

Conclusion: In this trial, we demonstrated that a pistachio diet improved blood glucose level, endothelial function, and some indices of inflammation and oxidative status in healthy young men. These findings are in accordance with the idea that nuts, in particular pistachio nuts, have favorable effects beyond lipid lowering that deserve to be evaluated with prospective follow-up studies.

Keywords: Pistachio; Endothelium; Lipid; Inflammation; Oxidation

Introduction

Epidemiologic studies have shown that frequent nut consumption decreases the risk of coronary heart disease (CHD). Compared with people who consumed nuts less than one time per week, people who ate nuts at least five times per week showed a 50% reduction in risk [1–4]. Nuts are rich in monounsaturated fatty acid (MUFA) and polyunsaturated fatty acid (PUFA), which are known to have favorable effects on the lipid profile [5]. However, the potential benefits of the nuts on decreasing CHD are not limited to their effects on lipid parameters. Nuts are also a good source of

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dietary fiber, vitamins, micronutrients, antioxidants, amino acids (e.g., arginine), and plant stenols [5].

The majority of the nut studies were performed with walnuts, almonds, and peanuts. Thus far, to our knowledge, only three studies have been conducted in humans investigating the effects of pistachio nuts, which were performed as outpatient dietary intervention trials [6–8]. Investigators are more focused on the favorable effects of nuts beyond their effects on lipid parameters. Endothelial dysfunction is an early key event in the atherosclerotic process that predicts future CHD development [9,10]. Endothelial function measurement can be non-invasively performed. A recent study has demonstrated that substituting walnuts for MUFA in a Mediterranean diet improved endothelium-dependent vasodilation (EDV) in hypercholesterolemic subjects as a measurement of endothelial function [11]. Like the walnut, the pistachio is a good source of L-arginine, which is a precursor of endogenous vasodilator nitric oxide. To our knowledge, there are as yet no data regarding the effect of a pistachio diet on endothelial function.

Inflammation and oxidation play an important role in the pathogenesis and progression of CHD. Some studies have shown that nuts have favorable effects on inflammation and oxidative status; however, our knowledge about the impact of pistachios on inflammatory and oxidative balance is limited. In this study we therefore investigated the effect of an Antep pistachio (*Pistacia vera L.*) diet on lipid parameters, endothelial function, inflammation, and oxidative status in healthy young men living in a controlled environment, which has not been studied previously.

Materials and methods

Study population

To our knowledge, previous nut studies were organized as outpatient dietary modification studies. Although all of the previously published studies have reported good compliance of the participants to the administered diet, we believe that subjects living in a controlled environment would provide a better sample population in a dietary intervention study. After providing the required legal permissions, we performed the study in the vocational police education school of Gaziantep, Turkey. In the vocational police education school of Gaziantep, all students were living in a controlled environment and eating in the same place. Sleeping and waking hours and daily activities of the students were similar. They were not allowed to go outside the school borders and they were not provided any additional food other than that served during meal times, except unlimited water.

Thirty-three healthy students (mean age 22 y, range 21–24) were included in the study. All enrolled subjects were free of acute or chronic medical disorders and were of normal body habitus. All subjects underwent a detailed medical history and physical examination by the investigator physicians. Exclusion criteria were smoking any amount, history of eating nuts frequently (more than once a week), a history of a food or nut allergy, regular use of any drugs including vitamin supplements, and a history of any known disease. Subjects with concomitant inflammatory diseases such as infections, recent surgical procedures, or dyslipidemia were also excluded from the study. Participants were requested to abstain from coffee products and alcohol consumption during the recruitment period. The study protocol was approved by the ethical committee of Gaziantep University and all participants gave informed consent. Participants were offered free pistachios but no monetary compensation.

Protocol

Before the study, students were eating the same kind of regular diet (total energy from protein 20%, carbohydrate 47%, and fat 33%) prepared in the school kitchen. Although they were eating the same kind of food, the amount was not standardized for each student. They were allowed to eat as much as they wanted if the food remained. To overcome the disparities across the food intakes of the participants (amount, calories, proportions of protein, fat, carbohydrate, etc.), we accepted the recruitment period as a run-in period. A Mediterranean-type diet was administered for 4 wk. After 4 wk, the participants continued to receive the Mediterranean-type diet but pistachio was added by replacing the MUFA content constituting ≈20% of daily caloric intake. Because diet-induced lipoprotein changes stabilize in less than 4 wk, we planned the diet periods as 4 wk [12]. The protocol description was summarized in Table 1.

The Mediterranean-type diet was composed of natural food stuff. It was rich in vegetable and fish, whereas red meat, fat products, and egg products were limited. The pistachio diet was similar to the Mediterranean-type diet, but pistachio partly replaced MUFA-rich foods. Prepackaged, roasted unsalted pistachios (60 to 100 g) were administered as an appetizer during the second 4-wk period. In the pistachio diet, pistachio contributed ≈20% of total energy and replaced 32% of the energy obtained from MUFAs in the control diet

Table 1
Protocol description in summary

Weight, blood pressure, laboratory and endothelial function measurements	→	33 healthy young men living in a controlled environment	
		Mediterranean diet	
		↓	4 wk
Weight, blood pressure, laboratory and endothelial function measurements	→	Pistachio was added to the Mediterranean diet by replacing 32% of energy obtained by monounsaturated fatty acid	
		↓	4 wk
Weight, blood pressure, laboratory and endothelial function measurements	→	32 participants finished the protocol	

(Table 2). The pistachio diet was equivalent to the Mediterranean diet in total calory intake and proportions of carbohydrate and protein intakes; however, saturated fatty acid and PUFA intakes were lower ($P = 0.02$ and $P < 0.001$, respectively) and MUFA and fiber intakes were higher ($P < 0.001$ and $P < 0.001$, respectively). According to the data provided by the Pistachio Investigation Institute, Gaziantep, the composition of 100 g of pistachio was 18.3 g of protein, 52.7 g of fat (saturated fatty acid 6.7 g, MUFA 36.2 g, and PUFA 9.8 g), 20 g of carbohydrate, and 7.4 g of fiber.

During the study period a registered dietitian supervised mealtimes and ensured the complete intake of the respective meals. The components of the food during the study period were prepared and served by a food company (Tam Sofra Inc., Gaziantep, Turkey) under the supervision of the registered dietitian. The participants ate their breakfast, lunch, and dinner in the same field. Leftover foodstuffs were collected and weighed by the dietitian to determine compliance. Any deviations from the study protocol were recorded and reviewed by the investigators during the study.

Fasting blood sample collection, endothelial function, body weight, and blood pressure measurements were performed three times (during the run-in period, after 4 wk [4 wk after the Mediterranean-type diet], and after 8 wk [4 wk after pistachio diet administration]). Because the school program and the activities of the participants were preplanned for the entire education year, there was no change in daily activities of the participants during the study period.

Endothelial function measurement

Endothelial function measurements were performed by the same examiner who was unaware of the stage of the study. Each subject was studied in the morning hours (08:00 to 10:00) after fasting >8 h before the examination. Studies were performed in a quiet, semi-dark, temperature-controlled room (20–25 °C) with the subject lying in a supine position. Images were obtained using a commercially available device (Vivid 7, GE Vingmed Ultrasound AS, Horten, Norway) with a 12-MHz linear array transducer. According to the power calculation, to provide 80% power at 5% significance to detect a 2% mean absolute difference in EDV and endothelium-independent vasodilation as significant, 25 subjects would need to complete the study.

The measurements were performed as previously described [13]. The brachial artery was imaged longitudinally, 2 to 5 cm above the antecubital crease. An occluding cuff placed proximally on the forearm was inflated to a pressure of 200 mmHg for 5 min and rapidly deflated to induce reactive hyperemia. Brachial artery scans were obtained 30 s before cuff inflation (first baseline), at 60 to 90 s after cuff deflation to assess EDV, after a 10-min rest (second baseline), and 3 min after 0.4 mg of sublingual glyceryl trinitrate to evaluate endothelium-independent vasodilation. Arterial diameter was measured with ultrasonic calipers at end diastole, incident with the R wave on the electrocardiogram. Three cardiac cycles were analyzed for each scan, and measurements were averaged. Reliability of the measurements was qualified by having them remeasure a random sample of 15 subjects.

Table 2
Comparison of nutritional status of subjects during the Mediterranean and pistachio diets

Variable	Mediterranean diet	Pistachio diet	P
Total calories (kcal/d)	1966 ± 224	1983 ± 241	>0.1
CHO (% energy)	48.7 ± 3.2	49.2 ± 2.8	>0.1
Protein (% energy)	17.1 ± 1.5	16.8 ± 1.7	>0.1
Fat (% energy)	33.5 ± 2.2	33.1 ± 1.9	>0.1
SFA	5.9 ± 1.1	4.8 ± 1.4	0.02
MUFA	13.3 ± 1.6	20.2 ± 2.3	<0.001
PUFA	14.2 ± 1.3	7.1 ± 1.0	<0.001
Fiber (g)	6.4 ± 2.1	11.3 ± 2.4	<0.001

CHO, carbohydrate; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid.

Laboratory measurements

Venous blood samples of the participants were collected from the antecubital vein while patients rested in a supine position after an overnight fast. Serum and ethylenediaminetetra-acetic acid plasma samples were stored at −80 °C and analyzed at the end of the study period. Total cholesterol (TC), high-density lipoprotein (HDL), and triacylglycerol (TG) levels were determined by enzymatic–colorimetric methods. Low-density lipoprotein (LDL) was calculated by the Friedewald formula. Oxidized LDL was calculated by a monoclonal antibody–based immunoassay. Apolipoproteins (Apo) Al and B were determined by turbidimetry. Homocysteine was determined by fluorescence polarization immunoassay.

High-sensitivity C-reactive protein (hs-CRP) was measured by chemiluminescent immunometric assay. Interleukin-6 and tumor necrosis factor-α were determined by enzyme-linked immunosorbent assay. Total oxidant status (TOS) was determined as previously described [14]. Serum lipid hydroperoxide level was determined by the ferrous ion oxidation–xylenol orange method. Malondialdehyde (MDA) was measured by a standard high-performance liquid chromatographic method. Superoxide dismutase (SOD) levels were performed by a commercially available SOD kit. All laboratory analyses were done in duplicate.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation and categorical data are expressed as percentages. Two-tailed *t* test for paired samples was used to compare changes in outcome variables in response to diets. The differences between the compositions of the Mediterranean and pistachio diets were tested with unpaired *t* test or chi-square test. Because hs-CRP was highly skewed, a logarithmic transformation was used to obtain a normal distribution before analysis. Values were then transformed back and reported in their original form for presentation. Two-tailed $P < 0.05$ was considered statistically significant. All statistical studies were carried out with SPSS 11.5 (SPSS Inc., Chicago, IL, USA).

Results

Of the 33 participants initially included into the study, 1 subject had to undergo a urologic operation; therefore, 32 subjects (mean age 22 y, range 21–24) completed the protocol. Table 3 presents body weight, blood pressure, glucose, and lipid parameters of the participants at baseline and at the end of each diet. Body weight and blood pressure of the participants remained unchanged during the study. Compared with the Mediterranean diet, the pistachio diet caused significant decreases in glucose levels ($P < 0.001$, $-8.8 \pm 8.5\%$). Pistachio produced significant decreases in LDL ($P < 0.001$, $-23.2 \pm 11.9\%$), TC ($P < 0.001$, $-21.2 \pm 9.9\%$), and TG ($P = 0.008$, $-13.8 \pm 33.8\%$) and a non-significant decrease in HDL ($P = 0.069$, $-3.1 \pm 11.7\%$; Fig. 1) when compared with the Mediterranean diet. There were significant reductions in ApoA1 and ApoB levels and ratios of TC/HDL and LDL/HDL ($P < 0.001$ for all), whereas oxidized LDL and homocysteine levels and the ApoB/ApoA1 ratio remained unchanged (Table 3).

Suitable brachial artery endothelial function measurements were available for all 32 subjects who completed the study. The pistachio diet produced significant improvement in the EDV ($P = 0.002$, 30% relative increase), whereas endothelium-independent vasodilation remained unchanged when compared with the Mediterranean diet (Table 4, Fig. 2).

The pistachio diet caused significant decreases in serum interleukin-6, TOS, lipid hydroperoxide, and MDA and an increase in SOD ($P < 0.001$ for all), whereas there were no significant changes in hs-CRP and tumor necrosis factor-α levels when compared with the Mediterranean diet (Table 5).

Discussion

In this 8-wk dietary intervention trial, we demonstrated that a pistachio diet had favorable effects on glucose level, lipid parameters, endothelial function, and some indices of inflammation and oxidative status in healthy young men.

Most of the nut studies were performed with walnuts, almonds, and peanuts. Thus far, to our knowledge, only three studies have been conducted in humans investigating the effects of pistachio nuts, which were performed as outpatient dietary intervention trials [6–8]. Therefore, we believe that our study is unique in its design because it was conducted in a population living in a controlled environment. Previous studies about the effect of pistachio on lipid parameters have shown favorable effects [6–8]. Edwards et al. [6] demonstrated that 3 wk of a pistachio diet caused significant decreases in TC, TC/HDL ratio, and LDL/HDL ratio and a significant increase in HDL in moderately hypercholesterolemic patients. TG and LDL levels remain unchanged. Kocyigit et al. [7] reported that 3 wk of a pistachio diet caused significant decreases in TC, TC/HDL ratio, and LDL/HDL ratio and a significant increase in HDL in normolipidemic healthy volunteers. TG and LDL levels remained unchanged. Sheridan et al. [8] reported that 4 wk of a pistachio diet caused significant decreases in TC/HDL ratio and LDL/HDL ratio but a significant increase in HDL in subjects with moderate hypercholesterolemia. TC, LDL, and TG remained unchanged. In our study we demonstrated significant decreases in glucose, TC, TG, LDL, TC/HDL ratio, and LDL/HDL ratio in normolipidemic healthy young men. Although there was a trend of a decrease in HDL level, it was not statistically significant. The present study is the first demonstrating a decrease in LDL and TG levels with a pistachio diet. In addition, the three previous pistachio studies were associated with an increase in HDL, whereas the present study showed a non-significant decrease. One interesting result of the present study is the significant decrease in blood glucose

Table 3
Body weight, blood pressure, glucose, and lipid parameters at baseline and at the end of each diet

Variable	Baseline	Mediterranean diet	Pistachio diet	*P*
Weight (kg)	69.3 ± 4.9	69.7 ± 5.0	69.5 ± 5.1	>0.1
Systolic BP (mmHg)	117 ± 8	119 ± 8	117 ± 6	>0.1
Diastolic BP (mmHg)	73 ± 8	74 ± 7	73 ± 7	>0.1
Glucose (mg/dL)	91 ± 8	92 ± 8	84 ± 6	<0.001
TC (mg/dL)	199.6 ± 41.8	190.7 ± 30.1	149.4 ± 26.5	<0.001
TG (mg/dL)	91.2 ± 39.7	112.1 ± 45.5	91.1 ± 38.1	0.008
HDL (mg/dL)	43.3 ± 9.7	43.5 ± 9.2	41.7 ± 7.38	0.069
LDL (mg/dL)	142.0 ± 37.4	124.5 ± 24.5	95.0 ± 23.2	<0.001
Oxidized LDL (ng/mL)	355.1 ± 109.9	331.4 ± 95.6	346.2 ± 82.7	>0.1
TC/HDL	4.86 ± 1.0	4.40 ± 0.8	3.78 ± 0.7	<0.001
LDL/HDL	3.39 ± 0.9	2.88 ± 0.7	2.30 ± 0.6	<0.001
ApoA1 (g/L)	1.24 ± 0.17	1.34 ± 0.18	1.20 ± 0.20	<0.001
ApoB (g/L)	0.65 ± 015	0.64 ± 0.14	0.57 ± 0.15	<0.001
ApoB/ApoA1	0.53 ± 0.15	0.49 ± 0.13	0.48 ± 0.14	>0.1
Homocysteine (μmol/L)	10.7 ± 3.2	10.6 ± 3.8	11.0 ± 3.7	>0.1

Apo, apolipoprotein; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol; TG, triacylglycerol.

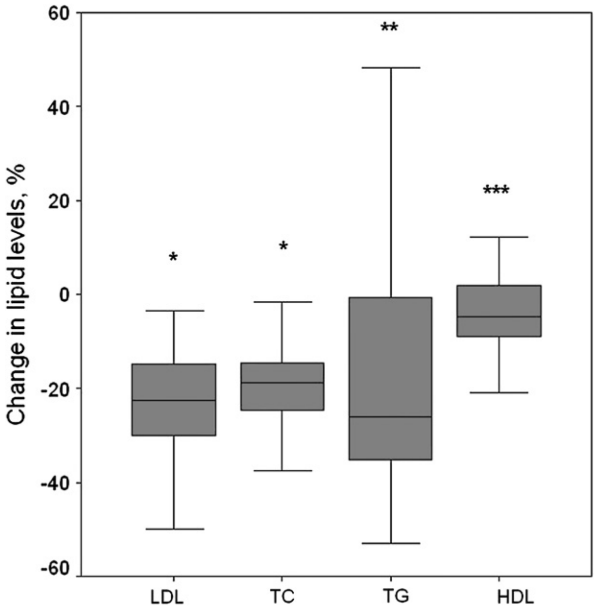

Fig. 1. A pistachio diet resulted in significant reductions in LDL (* $P < 0.001$, $-23.2 \pm 11.9\%$), TC (* $P < 0.001$, $-21.2 \pm 9.9\%$), and TG (** $P = 0.008$, $-13.8 \pm 33.8\%$) and a non-significant reduction in HDL (*** $P = 0.069$, $-3.1 \pm 11.7\%$) when compared with the Mediterranean diet. HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol; TG, triacylglycerol.

level with the pistachio diet, which warrants further studies especially in the diabetic population.

It is known that a diet rich in MUFA has favorable effects on CHD risk profile and pistachio is an excellent source of MUFA [15,16]. Dietary fiber intake is associated with a lower risk of CHD and fiber content was high in the pistachio diet [17–19]. These might explain the favorable effects of pistachio on lipid parameters. Most nut studies were performed based on an isoenergetic diet with a control group so that nuts were replaced with MUFA content constituting ≈15–20% of daily caloric intake. In our recent report, in an experimental model of rats, consumption of pistachio as 20% of daily caloric intake had beneficial effects on lipid parameters and LDL oxidation that were blunted when pistachio intake was increased to 40% of daily caloric intake [20]. Therefore, pistachio intake as 20% of daily caloric intake seems reasonable. Blood pressure and body weight of the participants did not change during the study and this was compatible with the data of previous nut studies.

Although it has been documented that a pistachio diet has favorable effects on lipid parameters, investigations have found that their cardioprotective effect has some other mechanisms beyond their hypolipidemic effects. Endothelial dysfunction is an early key event in the atherosclerotic process that predicts future CHD development [9,10]. The effect of pistachio on endothelial function has not been studied previously. In a recent study, substituting walnuts for MUFA in a Mediterranean diet resulted in an improvement in EDV in hypercholesterolemic adults [11]. In the present study, we demonstrated that a pistachio diet resulted in an improvement in EDV in normolipidemic healthy young men similar to a walnut diet. Although the specific mechanism is unknown, several possible mechanisms can be proposed. First, cholesterol lowering as in the present cohort is known to improve endothelial function [21]. Second, the high L-arginine content of pistachios might contribute to the improvement in EDV, which is a precursor of endogenous vasodilator nitric oxide [22]. Third, the favorable effects of a pistachio diet on inflammatory and oxidative statuses, which were demonstrated in the present study, and the fiber, vitamin, micronutrient, and phytosterol content of pistachio might improve EDV.

Inflammation and oxidation play an important role in the pathogenesis and progression of atherosclerosis. To date, there are no data about the effect of pistachio on inflammatory parameters. A pistachio diet did not cause significant changes in hs-CRP and tumor necrosis factor-α levels. However, there was a significant decrease in interleukin-6 level, which is also

Table 4
Brachial endothelial function at baseline and at the end of each diet

Variable	Baseline	Mediterranean diet	Pistachio diet	*P*
Baseline artery diameter (mm)	3.22 ± 0.23	3.26 ± 0.25	3.26 ± 0.24	>0.1
EDV (%)	7.19 ± 1.65	7.86 ± 2.28	10.29 ± 2.76	0.002
EIDV (%)	13.53 ± 3.20	13.33 ± 3.41	14.65 ± 2.43	>0.1

EDV, endothelium-dependent vasodilation; EIDV, endothelium-independent vasodilation.

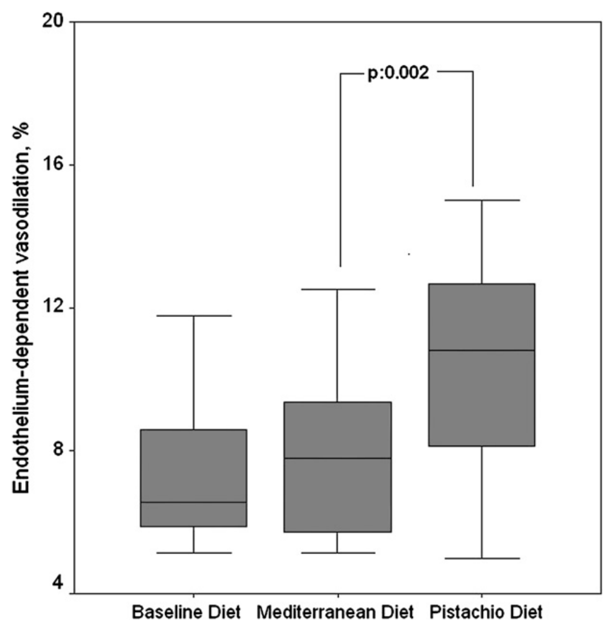

Fig. 2. Endothelial-dependent vasodilation in brachial arteries of 32 men. A pistachio diet produced a significant improvement in endothelial-dependent vasodilation (30% relative increase) when compared with the Mediterranean diet.

Table 5
Markers of inflammation and oxidation at baseline and at the end of each diet

Variable	Baseline	Mediterranean diet	Pistachio diet	*P*
hs-CRP (mg/dL)*	1.27 (0.90)	0.93 (0.34)	0.85 (0.72)	>0.1
IL-6 (pg/mL)	1.44 ± 1.02	1.14 ± 0.66	0.79 ± 0.65	<0.001
TNF-α (pg/mL)	8.6 ± 6.0	8.4 ± 5.6	9.0 ± 5.7	>0.1
TOS (μmol H_2O_2 equivalent/L)	9.34 ± 1.13	11.45 ± 3.48	8.58 ± 0.73	<0.001
LOOH (μmol/L)	6.33 ± 0.60	7.85 ± 1.88	5.48 ± 0.56	<0.001
MDA (nmol/L)	64.4 ± 3.9	75.9 ± 15.8	58.6 ± 4.5	<0.001
SOD (U/mL)	1.08 ± 0.28	0.42 ± 0.28	1.55 ± 0.32	<0.001

hs-CRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; LOOH, lipid hydroperoxide; MDA, malondialdehyde; SOD, superoxide dismutase; TNF-α, tumor necrosis factor-α; TOS, total oxidant status.

* Median values are presented in parentheses. Data were logarithmically transformed before analysis.

an indicator of inflammation. In a recent paper, Kocyigit et al. [7] reported that a 3-wk pistachio diet had a favorable effect on oxidative stress. They found a decrease in MDA level and an increase in antioxidant potential. In the present study we did not find any difference in oxidized LDL level among diets; however, the pistachio diet caused not only significant decreases in lipid hydroperoxide and MDA levels, which are indices of oxidation and lipid peroxidation, but also a significant increase in SOD, which reflects antioxidant potential. Moreover, we found a significant decrease in TOS with the pistachio diet. Various components of oxidation and antioxidation might be affected in different ways, but measuring TOS rather than those individual variables might be more practical. Therefore, a decrease in TOS after a pistachio diet provides additional data that help us extend the beneficial effects of pistachios beyond lipid lowering.

In conclusion, in this 8-wk dietary intervention trial, we not only confirmed the previous findings about the beneficial effects of a pistachio diet on lipid parameters but also demonstrated that it caused improvements in blood glucose level, endothelial function, and some indices of inflammation and oxidative status in healthy young men living in a controlled environment. These findings are in accordance with the idea that nuts, in particular pistachio nuts, have favorable effects beyond lipid lowering that need to be tested with prospective follow-up studies.

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