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Effects of pistachios on the lipid/lipoprotein profile, glycemic control, inflammation, and endothelial function in type 2 diabetes: a randomized trial

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Abstract

Objective—The health benefits of regular nut consumption have been well-documented; however, effects on cardiovascular risk in diabetes are emerging. This study examined the effects of daily pistachio consumption on the lipid/lipoprotein profile, glycemic control, markers of inflammation, and endothelial function in adults with type 2 diabetes.

Materials/Methods—We enrolled 30 adults (40–74 years) with well-controlled type 2 diabetes (mean glycated hemoglobin 6.2%) in a randomized, crossover, controlled feeding study. After a 2-week run-in period, participants consumed nutritionally-adequate diets with pistachios (contributing 20% of total energy) or without pistachios for 4 weeks each, separated by a 2-week washout. We assessed fasting lipids/lipoproteins, glycemic measures (while fasted and during a 75g oral glucose tolerance test), inflammatory markers, and endothelial function after each diet period.

Results—Total cholesterol and the ratio of total to HDL cholesterol were significantly lower ($p < 0.05$) following the pistachio diet (4.00 mmol/L and 4.06, respectively) compared to the control diet (4.15 mmol/L and 4.37, respectively). Triglycerides were significantly lower ($p = 0.003$) following the pistachio diet (1.56 mmol/L) compared to the control diet (1.84 mmol/L). There

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Author contributions

The authors' responsibilities were as follows: SGW, JSU, PMKE designed the study. KAS and CEM were responsible for subject recruitment and data collection. KAS conducted sample analysis for inflammatory markers. KAS and SGW analyzed the data. All authors contributed to interpretation of the data. KAS drafted the manuscript and all authors critically reviewed and revised the manuscript. SGW had primary responsibility for final content. All authors read and approved the final manuscript.

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were no treatment differences in fasting glucose and insulin, but fructosamine was significantly lower ($p=0.03$) following the pistachio diet ($228.5 \mu\text{mol/l}$) compared to the control diet ($233.5 \mu\text{mol/l}$). Inflammatory markers and endothelial function were unchanged.

Conclusion—Daily pistachio consumption can improve some cardiometabolic risk factors in adults with well-controlled type 2 diabetes. Our findings support recommendations that individuals with diabetes follow healthy dietary patterns that include nuts.

Keywords

Pistachios; nuts; cholesterol; glycemia; inflammation; endothelial function

1. Introduction

The health benefits of regular nut consumption have been well-documented in both observational studies and clinical trials [1]. Frequent nut consumers are 19–29% less likely to experience cardiovascular events compared to infrequent consumers, and they have a 17% reduced risk of all-cause mortality [2, 3]. Daily nut consumption has been shown repeatedly to improve the lipid/lipoprotein profile [4] and may also benefit glycemic control [5], inflammation [6], and endothelial function [7].

Among individuals with type 2 diabetes, for whom cardiovascular disease is the leading cause of death [8], management of such cardiometabolic markers is vital to reducing risk. Numerous studies have shown that nutrition interventions are effective in managing type 2 diabetes, including following dietary patterns consistent with the Mediterranean diet, the Dietary Approaches to Stop Hypertension diet, vegetarian or vegan diets, a prudent diet, and a moderately low carbohydrate diet [9]. Nut consumption is an appealing non-pharmacologic approach to risk management in this population, particularly since concerns that nut consumption may promote weight gain and obesity have been refuted [10]. However, nut studies in populations with type 2 diabetes are limited. A few trials reported beneficial effects on the lipid/lipoprotein profile [11–15], and a recent meta-analysis concluded that daily nut consumption reduces fasting glucose and glycated hemoglobin (HbA1c) [16]. Two studies that assessed inflammatory markers following nut interventions reported mixed results [17, 18], and one study reported a significant improvement in endothelial function following 8 weeks of walnut consumption [14]. However, most trials (regardless of the population) have studied mixed nuts or walnuts, and the health benefits of other nuts, such as pistachios, are less clear.

The purpose of this study was to examine the effects of daily pistachio consumption on the lipid/lipoprotein profile, glycemic control, markers of inflammation, and endothelial function in adults with type 2 diabetes. This is a secondary analysis of data collected as part of clinical nutrition trial with the primary outcome being systemic hemodynamics, for which the main results have been published previously [19]. We hypothesized that a diet containing 20% of daily energy from pistachios would benefit multiple cardiometabolic risk factors over a 4-week treatment period compared to a pistachio-free control diet.

2. Methods

This study was registered at ClinicalTrials.gov (NCT00956735) and the protocol described previously [19]. All data were collected at the Clinical Research Center at The Pennsylvania State University between July 2009 and March 2013. Written informed consent was obtained from all participants, and approval for the study was granted by the Institutional Review Board of The Pennsylvania State University.

2.1 Subjects

Potential participants were recruited through campus and community advertisements (Figure) and were assessed for eligibility over the phone. Participants were required to have a self-reported diagnosis of type 2 diabetes, be 30–75 years of age (women had to be post-menopausal), and have a body mass index (BMI) of 18.5–45.0 kg/m². Exclusion criteria were insulin use, self-reported history of chronic disease other than type 2 diabetes, history of bariatric surgery, major surgery in the prior 6 months, nut or latex allergies, and use of tobacco, daily aspirin, anti-inflammatory medications, oral steroids, hormone replacement therapy, or anti-hypertensive medication. Individuals who met the phone screening criteria completed a clinic screen for blood pressure measurement, an electrocardiogram, and a fasting blood draw. Further exclusion criteria were blood pressure ≥160/100 mmHg, abnormal electrocardiogram, fasting triglycerides ≥5.65 mmol/L, or HbA1c ≥7.4%.

In January 2010, due to low enrollment, the criteria were revised to allow individuals taking a single drug for hypertension to participate, under the conditions that their personal physician provide written approval to temporarily discontinue anti-hypertensive monotherapy and that resting blood pressure remain below 160/100 mmHg for the study duration. In November 2010, after discovery of significant inflammation in a participant, (who, in the interest of safety, was withdrawn from the study and referred for follow-up care; Figure 1), the criteria were revised to exclude individuals with C-reactive protein (CRP)

≥10.0 mg/l. Thirty participants (50% female) completed the full study, and their baseline characteristics are presented in Table 1.

2.2. Intervention

We implemented a 2-period, randomized, crossover, controlled-feeding design, preceded by a 2-week run-in period with a standardized diet to determine baseline values. The treatment diets were assigned in a randomized, counterbalanced order determined by simple randomization (www.randomization.com). The study coordinator (KAS) generated the allocation scheme and assigned the participants to the intervention orders. Technicians who measured outcome variables were blinded to treatment assignments, but due to the nature of the dietary intervention, participants were aware of their treatment order assignment.

Participants were instructed to discontinue omega-3 fatty acid supplements 8 weeks prior to starting the study and all other dietary supplements 2 weeks prior to starting the study. All study foods were prepared in the Metabolic Kitchen at the Pennsylvania State University Clinical Research Center. For 3–5 days each week (depending on travel distance), participants ate one meal per day in the Metabolic Kitchen with the other meals prepared for

off-site consumption. At the end of each diet period (including the run-in period), participants completed testing to assess the lipid/lipoprotein profile while fasted, glycemic measures while fasted and during a 75g oral glucose tolerance test, inflammatory markers, and endothelial function. The diet periods were separated by brief compliance breaks lasting 1 to 4 weeks.

The nutrient composition of the experimental diets is presented in Table 2 and has been described previously [19]. Briefly, calorie levels for weight maintenance were assigned based on estimated metabolic rates [20] and monitored throughout the study. The run-in diet was designed to be nutritionally-adequate and provided dietary fat and cholesterol in amounts similar to a typical Western diet (36% total fat, 11.5% saturated fat, and 278 mg/day of cholesterol). The control diet was based on the American Heart Association's Therapeutic Lifestyle Changes diet (26.9% total fat, 6.7% saturated fat, 186 mg/day cholesterol) [21]. The pistachio diet was a modification of the control diet wherein low-fat or fat-free snacks (i.e., pretzels, string cheese, etc.) were replaced with roasted pistachios that provided 20% of daily energy (range: 59–128g). Therefore, the difference in nutrient composition between the pistachio and control diets reflected the nutrient composition of the pistachios (i.e., rich in total fat, monounsaturated fat, polyunsaturated fat, fiber, and potassium; Table 2). Half of the daily dose of pistachios was unsalted and incorporated into entrees and the other half was salted and eaten as snacks. The pistachio nuts were provided by the American Pistachio Growers (Fresno, CA) and grown in California. An independent laboratory (Covance, Madison, WI) analyzed the pistachio nutrient profile, and the pistachio diet composition presented in Table 2 reflects this analysis.

2.3. Assessment of metabolic parameters

At the end of each diet period, blood samples were collected in the fasting state (12 hours with nothing but water, 48 hours without alcohol, and 2 hours without vigorous exercise). Whole blood was drawn into vacutainers by trained clinicians and processed by research staff for separation of plasma and serum. Except for endpoints that required unfrozen samples, samples were portioned and stored at -80°C for batch analysis.

2.3.1. Lipids and lipoproteins—Serum lipids and lipoproteins were measured on 2 separate days at the end of each diet period. Total cholesterol and triglycerides were measured by enzymatic procedures (Quest Diagnostics, Pittsburgh, PA; CV <2% for both). HDL cholesterol was estimated according to the modified heparin-manganese procedures (CV <2%). LDL cholesterol was directly measured with a chromogenic reaction after removal of all non-LDL cholesterol (N-geneous LDL-ST-C; Quest Diagnostics; CV <3%).

2.3.2. Insulin sensitivity/resistance—Serum glucose and insulin were assessed in the fasting state and during a standard 75g, 2-hour oral glucose tolerance test. Following a 12-hour fast, nursing staff placed an intravenous catheter and obtained a fasting blood draw. Participants then consumed a 75g glucose solution, after which blood was drawn at 30, 60, 90, and 120 minutes. Serum fructosamine and HbA1c were also assessed from a single blood sample at the end of each diet period.

2.3.3. Inflammatory markers—Serum concentrations of high-sensitivity CRP were measured by latex-enhanced immunonephelometry (Quest Diagnostics, Pittsburgh, PA; assay CV <8%). Plasma concentrations of E-selectin, intracellular adhesion molecule (ICAM), and vascular cellular adhesion molecule (VCAM) were measured via enzyme-linked immunosorbent assays (ELISA) kits from DRG International (Springfield, NJ) in duplicate (assay CV <20%).

2.4. Assessment of vascular endothelial function

Simultaneous brachial flow-mediated dilation (FMD) and peripheral arterial tonometry (PAT) tests were performed to assess endothelial function. This testing took place in a quiet, dimly lit room at 22–24°C after a 12-hour fast with participants in the supine position. The procedure included a 10-minute pre-test acclimation period, a 5-minute recorded baseline period, a 5-minute occlusion period, and a 5-minute post-deflation period. During the occlusion period, ischemia was induced on the right forearm with a blood pressure cuff connected to an automated rapid cuff inflator set to 250 mmHg (Hokanson, Bellevue, WA). When the cuff was immediately deflated at the end of the occlusion period, reactive hyperemia (increased blood flow in response to the ischemia) occurred and was quantified by the FMD and PAT tests.

2.4.1. Flow-mediated dilation—The brachial artery above the elbow was scanned in a longitudinal section and continuous, cross-sectional images were recorded during baseline, occlusion, and post-deflation. Changes in arterial diameter were measured by external B-mode ultrasound imaging (Acuson Aspen equipped with a 10-mHz linear array transducer; Acuson, Mountain View, CA) by a single, well-trained sonographer. The images were gated by using R-wave detection so that the scans were assessed at end diastole. Automated edge detection software (Brachial Analyzer; MIA, Iowa City, IA) was used to quantify artery diameter continuously throughout the test. Resting diameters were the average of all images collected over 1-minute of the baseline recording. Peak artery diameter was determined as the largest diameter recorded in the first 2 minutes of the post-deflation period. Percent change in brachial diameter at peak dilation compared to baseline (%FMD) was calculated by 2 independent scorers, and average values are presented. If %FMD values differed by >2%, a third technician reviewed the scan.

Average flow velocity (m/s) across the cardiac cycle, maximal flow velocity, and velocity time integral across the cardiac cycle (m) were measured by using duplex pulsed Doppler during the resting baseline and immediately after cuff release. Flow (ml/min) was calculated using the following equation: velocity time integral $\times$ cross-sectional area of the vessel $\times$ heart rate.

2.4.2. Peripheral arterial tonometry—Relative changes in digital pulse wave amplitude before and after occlusion were assessed with the EndoPAT 2000 (Itamar Medical Ltd, Caesarea, Israel). Two flexible probes were placed on the index fingers of the right (occluded) and left (control) hands. The reactive hyperemia index (RHI) was calculated as the ratio of the average pulse wave amplitude during hyperemia (60 to 120 seconds of the post-deflation period) to the average pulse wave amplitude during baseline in the occluded

hand divided by the same values provided by the control hand, and then multiplied by a baseline correction factor. The Framingham RHI (F-RHI) is an alternative calculation that uses the period of 90 to 120 seconds after deflation, does not incorporate a baseline correction factor, and has a natural log transformation applied to the resulting ratio. Both RHI and F-RHI have been shown to correlate with cardiovascular risk factors [22]. Vascular stiffness was estimated by augmentation index (AI), and calculated from the shape of the pulse wave recorded by the probe during baseline. This measure can be standardized to a heart rate of 75 beats per minute (AI@75) to correct for the independent effect of heart rate. Both unadjusted and adjusted indices are reported.

2.5. Statistical Analyses

Treatment effects were tested per protocol (only participants completing the entire study were included in the analysis) using the mixed models procedure in SAS (v9.3, Cary, NC). Differences in baseline characteristics according to treatment order assignment were examined for all variables and uniformly non-significant (data not shown). For the outcome analyses, treatment diet (control or pistachio), diet period (first or second) and the interaction were entered as fixed effects; subject was a random effect. Diet by period interactions were uniformly non-significant (no evidence of carryover). All analyses were adjusted for age, sex, BMI, and the baseline (end of run-in diet) value. Alpha <0.05 was considered statistically significant. Residuals were inspected for normality visually and by assessment of skewness; ICAM required natural log transformation. The results are presented as the means $\pm$ standard errors unless otherwise noted.

3. Results

Participants exhibited a small but statistically significant decrease in weight from the baseline period to the end of both treatment periods ($p < 0.01$); however, there was no significant difference in participant weights following the pistachio and control diets. The mean weight at baseline was 90.6 ± 3.4 kg (BMI 31.2 ± 1.1), the mean weight following the pistachio diet was 89.8 ± 3.4 kg (mean BMI 31.0 ± 1.1), and the mean weight following the control diet was 89.9 ± 3.4 kg (mean BMI 31.0 ± 1.1).

Fasting lipids and lipoproteins are presented in Table 3. Total cholesterol and the ratio of total to HDL cholesterol were significantly lower following the pistachio diet (4.00 mmol/L and 4.06, respectively) compared to the control diet (4.15 mmol/L and 4.37, respectively). Triglycerides were significantly lower following the pistachio diet (1.56 mmol/L) compared to the control diet (1.84 mmol/L). There were no differences between treatments for HDL cholesterol and LDL cholesterol.

Glucose, insulin, and other markers of glycemic control are presented in Table 3. There were no differences between the control and pistachio diets for glucose or insulin in the fasting state or during the oral glucose tolerance test (estimated via area-under-the-curve [AUC] methods). Indices of insulin resistance (homeostatic model of assessment for insulin resistance; HOMA-IR) and insulin sensitivity (Matsuda index of insulin sensitivity; Matsuda) calculated from glucose and insulin levels were also similar between the diets.

Fructosamine was significantly lower following the pistachio diet (228.5 $\mu\text{mol/l}$) compared to the control diet (233.5 $\mu\text{mol/l}$), while HbA1c was similar following both treatments.

Measures of inflammation and endothelial function are presented in Table 4. There were no significant differences between treatments for any measures. There was a non-significant trend toward a difference in resting brachial diameter (prior to the induced ischemia), with a larger resting diameter observed after the pistachio diet than the control diet (4.56 mm vs 4.51 mm; $p=0.076$).

4. Discussion

In this randomized, controlled-feeding, clinical trial of adults with well-controlled type 2 diabetes, we found that a diet containing 20% of daily energy from pistachios resulted in lower total cholesterol, triglycerides, and fructosamine compared to a pistachio-free control diet. Other measures of glucose metabolism, inflammation, and endothelial function did not differ between treatments. These results indicate that daily pistachio consumption has cardiometabolic benefits even in well-controlled type 2 diabetes.

The effect on the lipid/lipoprotein profile that we observed following the pistachio diet is consistent with previous studies in non-diabetic populations. A pooled analysis of primary data from 25 nut studies found that daily consumption of 67g of nuts (which is the lower end of our range of 59–128 g/day) reduced total cholesterol by 10.9 mg/dl (0.28 mmol/L), the ratio of total to HDL cholesterol by 0.24, and triglycerides by 20.6 mg/dl (0.23 mmol/L) [23]. This pooled analysis included only studies with participants who were not taking lipid-lowering medication, whereas we observed a beneficial effect of pistachio nuts on the lipid/lipoprotein profile in a cohort where 43% were taking lipid-lowering medication and had average pre-treatment lipid levels that met current treatment goals for diabetes (LDL cholesterol <2.59 mmol/L, HDL cholesterol >1.03 mmol/L (women) or <1.29 mmol/L (men), and triglycerides <1.69 mmol/L [24]). These results indicate that pistachio consumption can additionally benefit the lipid/lipoprotein profile even in individuals who are in good diabetes control following a prescribed drug regimen.

We did not expect to observe a treatment effect of pistachios on HbA1c due to the short duration of the treatment periods (HbA1c is a measure of glycemia over the preceding 3 months; the present intervention lasted only 4 weeks). We anticipated but did not observe significant treatment effects of pistachios on glucose, insulin, or measures of insulin sensitivity in the fasting state or during an oral glucose tolerance test. We did observe a small but statistically significant reduction in fructosamine, which reflects average blood glucose during the preceding 2–3 weeks. This observation equates to a difference in average daily glucose of 0.22 mmol/L between the diets. While statistically significant, we acknowledge that the clinical significance of this modest reduction remains to be determined.

Previous research has shown that a single dose of pistachios reduces postprandial glycemia in healthy adults and adults with metabolic syndrome [25, 26]. Two recent meta-analyses have examined whether daily nut consumption for 3 weeks affected glucose and measures

of glycemic control in all participants [5] and those with type 2 diabetes [16]. Both analyses concluded that nuts significantly reduced fasting glucose compared to control diets, but, similar to the present study, Vigiouliouk and colleagues [16] reported no significant effect of nuts on insulin or insulin sensitivity in type 2 diabetes. However, two studies that examined pistachios reported positive results. Parham *et al.* [18] reported that 12 weeks of pistachio consumption (25g/day) significantly reduced fasting glucose by 0.89 mmol/L and HbA1c by 0.4% compared to a control group in 48 Iranian adults with type 2 diabetes. Hernandez-Alonso *et al.* [27] reported that 4 months of 57g/d of pistachios significantly decreased fasting glucose (−0.29 mmol/l), insulin (−14.2 pmol/L), and HOMA-IR (−0.69) in 54 Spanish adults with pre-diabetes, but did not affect HbA1c. We did not observe pistachio-induced changes in fasting glucose, insulin, or HOMA-IR despite evaluating a greater pistachio dose than these studies (20% of daily energy, range 59–128g/day). Our intervention period was substantially shorter (4 weeks), but the small reduction we observed in fructosamine suggests that alterations in glucose metabolism were occurring. Taken together these studies suggest that small effects of pistachios on glucose metabolism may indeed exist, but the clinical significance of these effects remains to be elucidated and may vary between populations.

Numerous studies have examined the effects of nut consumption on inflammation with variable results [28, 29]. Several studies have shown that walnuts reduce cellular adhesion molecules [30–33], and publications from the PREDIMED study have reported consistent reductions in inflammation following supplementation with mixed nuts (walnuts, almonds, and hazelnuts) [34–36]. Specific to pistachios, a study in young healthy males reported a significant reduction in interleukin-6 and no change in tumor necrosis factor- α or CRP after 4 weeks of treatment [37]. A longer study (12 weeks) in adults with type 2 diabetes reported no effect on CRP [18]. Interestingly, in a sample of adults with pre-diabetes, pistachio consumption for 4 months did not affect circulating measures of inflammation but did reduce lymphocyte gene expression of interleukin-6 [27], suggesting that pistachios may have a nominal effect on inflammation that was not detected in previous work. We found no effect on any markers of inflammation in the present study; however, we did not assess interleukin-6, which has been reduced by pistachios in the above-mentioned study [37], and also by almonds in another study of type 2 diabetes [17]. The variability among studies in participant demographics, type of nut(s) consumed, and markers of inflammation evaluated makes it difficult to draw conclusions about the role of nuts in inflammation. Collectively, it seems probable that there are beneficial effects of pistachios on inflammation that may vary by population.

Previous research of nuts and endothelial function has likewise been mixed, with some studies reporting improvements following walnut [33, 38, 39], hazelnut [40], or pistachio [37] consumption, and others reporting no effect [41–44]. A study of adults with type 2 diabetes reported a significant improvement in FMD after 8 weeks of walnut consumption compared to a walnut-free control diet [14]. In contrast, we observed no effect of pistachio consumption on endothelial function measured by FMD or EndoPAT in type 2 diabetes. These discrepant findings could be explained by the type of nut studied. Walnuts contain greater amounts of alpha-linolenic acid than pistachios (9.08g vs 0.25g per 100g of nuts) [45]. We have previously demonstrated that walnut oil improves endothelial function

(measured by EndoPAT) after a single meal compared to whole walnuts, defatted walnut meat, and walnut skins [46]. We also observed a significant increase in FMD following a diet (for 8 weeks) high in alpha-linolenic acid from walnuts compared to an average western diet in adults with dyslipidemia, while a diet rich in linoleic acid did not affect FMD [39]. Further studies are needed to determine whether specific nuts (such as walnuts) can improve endothelial function in type 2 diabetes, and to investigate the potential mechanisms underlying such effects.

Our study has a few limitations. Our sample included adults with well-controlled type 2 diabetes (mean HbA1c at baseline: 6.2%) and may not be generalizable to individuals with more advanced or uncontrolled diabetes. The treatment periods lasted only 4 weeks, whereas in other nut studies the experimental diets were provided for 8–12 weeks. This shorter treatment period, in combination with the favorable cardiometabolic profile of the participants at baseline, may have contributed to the small and/or non-significant findings. A longer period of exposure or greater baseline dysfunction may be necessary to detect significant effects. Because we used a study design in which all food was provided to study participants, our results are not applicable to free-living individuals on self-selected diets. Effectiveness studies are needed to evaluate whether nut consumption can manage diabetes in real-world settings where patients are encouraged to consume nuts but are not provided with them [9]. Importantly, the present results should be interpreted cautiously as they are secondary analyses of a study designed and powered for a primary outcome of systemic hemodynamics. However, our study does add further support to the literature that daily nut consumption can improve the lipid/lipoprotein profile, and provides a basis for further investigation to evaluate whether pistachios can improve blood glucose control, endothelial function, or inflammation in a population with diabetes who are at high risk of cardiovascular complications.

In conclusion, we have shown that daily pistachio consumption can improve the lipid/lipoprotein profile in adults with medicated, well-controlled type 2 diabetes in a clinically-meaningful way. Pistachios may also have a small beneficial effect on glucose control, although longer term studies are needed to better address this question. Our findings support recent recommendations that individuals with diabetes follow dietary patterns that include nuts to reduce cardiometabolic risk [47].

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Abbreviations

AI augmentation index

AI@75	augmentation index standardized to heart rate of 75 beats per minute
AUC	area under the curve
CRP	C-reactive protein
FMD	flow-mediated dilation
F-RHI	Framingham reactive hyperemia index
HbA1c	glycated hemoglobin
HOMA-IR	homeostatic model of insulin resistance
ICAM	intracellular adhesion molecule
PAT	peripheral arterial tonometry
RHI	reactive hyperemia index
VCAM	vascular cellular adhesion molecule

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Figure 1.
CONSORT diagram of recruitment and study completion.

* Of these, 2 developed intolerances to tomatoes and 1 experienced an allergic reaction to pistachios. It was confirmed that this participant reported no history of nut allergies prior to study enrollment, but during questioning that followed the allergic reaction, this participant stated he had not previously eaten pistachios. Reprinted from Journal of the American Heart Association volume 3 issue 4, Sauder et al., Pistachio nut consumption modifies systemic hemodynamics, increases heart rate variability, and reduces ambulatory blood pressure in well-controlled type 2 diabetes: a randomized trial, 2014, under the Creative Commons Attribution-NonCommercial license.

Table 1

Baseline characteristics of the participants

	Mean $\pm$ SD
% Female	50.0
Age <i>years</i>	56.1 $\pm$ 7.8
Body mass index <i>kg/m²</i>	31.2 $\pm$ 3.1
Resting systolic blood pressure <i>mmHg</i>	116.2 $\pm$ 13.6
Resting diastolic blood pressure <i>mmHg</i>	71.0 $\pm$ 5.4
Fasting glucose <i>mmol/L</i>	5.9 $\pm$ 21.6
HbA1c %	6.2 $\pm$ 0.5
<i>mmol/mol</i>	44 $\pm$ 6.0
Total cholesterol <i>mmol/L</i>	4.2 $\pm$ 1.0
LDL cholesterol <i>mmol/L</i>	2.5 $\pm$ 0.9
HDL cholesterol <i>mmol/L</i>	1.1 $\pm$ 0.3
Triglycerides <i>mmol/L</i>	1.6 $\pm$ 0.8
% Taking diabetes medication(s)	
None	16.7
One *	66.7
Two or more	16.7
% Taking statin therapy	43.3

HbA1c, glycated hemoglobin.

* Of these, 90% were on metformin only.

Table 2Nutrient composition of the diets and the pistachio nuts^{*}

	Run-In Diet	Control Diet	Pistachio Diet	Pistachio Nuts
Energy <i>kcal</i>	2100	2100	2100	415
Total fat <i>g (%)</i>	85.6 (35.8)	64.0 (26.9)	78.5 (33.2)	32.5 (70.5)
Saturated fat <i>g (%)</i>	27.5 (11.5)	16.0 (6.7)	15.9 (6.8)	3.9 (8.4%)
Monounsaturated fat <i>g (%)</i>	31.3 (13.1)	26.0 (10.9)	31.2 (13.1)	16.5 (35.7%)
Polysaturated fat <i>g (%)</i>	20.2 (8.4)	16.8 (7.1)	24.6 (10.4)	9.6 (20.7%)
Protein <i>g (%)</i>	85.0 (16.0)	95.6 (18.1)	88.5 (16.6)	17.6 (16.9%)
Carbohydrate <i>g (%)</i>	261.5 (48.2)	302.8 (55.1)	270.6 (50.7)	15.8 (15.2%)
Fiber <i>g</i>	23.4	31.2	35.6	7.1
Sodium <i>mg</i>	3791	3039	2553	155
Potassium <i>mg</i>	2338	3767	4045	595
Cholesterol <i>mg</i>	278	186	172	0

^{*} Values calculated using Nutrient Data System for Research (NDSR), 2009 and adjusted according to the nutrient analyses conducted on the study pistachios by an independent laboratory (Covance, Madison, WI).

Table 3**Lipid, lipoprotein, and glucose metabolism**

Variable	Baseline	Control	Pistachio	P*
Fasting				
Total cholesterol (mmol/L)	4.18 ± 0.05	4.15 ± 0.06	4.00 ± 0.06	0.048
HDL cholesterol (mmol/L)	1.12 ± 0.02	1.04 ± 0.01	1.06 ± 0.01	0.08
Total:HDL cholesterol	4.04 ± 0.07	4.37 ± 0.08	4.06 ± 0.08	0.0004
LDL cholesterol (mmol/L)	2.52 ± 0.04	2.43 ± 0.06	2.39 ± 0.06	0.45
Triglycerides (mmol/L)	1.59 ± 0.04	1.84 ± 0.10	1.56 ± 0.10	0.003
Glucose (mmol/L)	5.9 ± 0.6	5.9 ± 0.1	5.9 ± 0.1	0.67
Insulin (pmol/L)	45.7 ± 56.3	43.4 ± 3.1	41.2 ± 3.1	0.45
HOMA-IR	1.8 ± 0.6	1.7 ± 0.1	1.6 ± 0.1	0.49
Oral glucose tolerance test				
Glucose AUC (mmol·min/L)	594.9 ± 38.6	643.2 ± 26.2	631.5 ± 26.2	0.70
Insulin AUC (pmol·min/L)	25322.2 ± 7398.7	23495.1 ± 1654.8	23022.8 ± 1571.7	0.79
Matsuda Index	7.7 ± 1.2	7.3 ± 0.4	7.3 ± 0.4	0.59
Glucose control				
Fructosamine (μmol/l)	233.2 ± 6.2	233.5 ± 2.1	228.5 ± 2.1	0.034
HbA1c (%)	6.2 ± 0.1	6.1 ± 0.0	6.0 ± 0.0	0.14

Data are means ± standard error. HDL: high-density lipoprotein; LDL: low-density lipoprotein; HOMA-IR: homeostatic model of insulin resistance; AUC: area-under-the-curve; HbA1c: glycated hemoglobin.

* Statistical significance for comparison between Control and Pistachio diets by PROC MIXED in SAS; adjusted for age, sex, BMI, and baseline (run-in) values.

Table 4

Inflammation and endothelial function

Variable	Baseline	Control	Pistachio	P*
Inflammatory markers				
CRP (mg/l)	1.73 ± 0.53	2.16 ± 0.16	1.98 ± 0.16	0.24
ICAM (ng/ml)	112.6 ± 6.4	114.7 ± 5.4	112.1 ± 5.8	0.75
VCAM (ng/ml)	337.8 ± 19.7	334.3 ± 25.0	337.7 ± 21.2	0.70
E-selectin (ng/ml)	42.9 ± 3.6	49.5 ± 3.6	47.1 ± 3.6	0.17
Flow-mediated dilation				
Baseline diameter (mm)	4.49 ± 0.15	4.51 ± 0.04	4.56 ± 0.04	0.076
Peak diameter (mm)	4.72 ± 0.15	4.74 ± 0.04	4.78 ± 0.04	0.31
FMD (%)	5.28 ± 0.41	5.29 ± 0.47	4.89 ± 0.48	0.55
Baseline flow velocity (ml/min)	147.5 ± 9.1	160.5 ± 11.3	156.9 ± 11.3	0.75
Peak flow velocity (ml/min)	898.8 ± 40.9	931.9 ± 36.3	905.6 ± 36.7	0.44
Peripheral arterial tonometry				
RHI	2.28 ± 0.17	2.31 ± 0.09	2.26 ± 0.09	0.66
Framingham RHI	0.64 ± 0.11	0.60 ± 0.05	0.61 ± 0.05	0.94
AI	17.29 ± 5.18	13.29 ± 1.94	12.70 ± 1.94	0.76
AI@75	9.93 ± 5.06	5.57 ± 1.75	4.94 ± 1.75	0.74

Data are means ± standard error. CRP: C-reactive protein; ICAM: intracellular adhesion molecule; VCAM: vascular cellular adhesion molecule; FMD: flow-mediated dilation; RHI: reactive hyperemia index; AI: augmentation index; AI@75: augmentation index standardized to heart rate of 75 bpm. FMD calculated as: (peak – baseline)/baseline x 100.

* Statistical significance for comparison between Control and Pistachio diets by PROC MIXED in SAS; adjusted for age, sex, BMI, and baseline (run-in) values.