Olive Oil Polyphenols Decrease Blood Pressure and Improve Endothelial Function in Women with High-Normal Blood Pressure or Stage 1 Essential Hypertension

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[3]Abbreviations used: asymmetric dimethylarginine, ADMA; blood pressure, BP; coronary heart disease, CHD; C-reactive protein, CRP; hyperemic area, HA; ischemic reactive hyperemia, IRH; oxidized LDL, ox-LDL; perfusion units, PU; total cholesterol, TC.

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ABSTRACT

This study aims to examine the influence of a polyphenol-rich olive oil on blood pressure (BP) and endothelial function in twenty-four women with high-normal BP or stage 1 essential hypertension. We conducted a double-blind, randomized, crossover dietary-intervention study. After a homogenization period of 4 months (baseline values), two diets were used, one with polyphenol-rich olive oil (Diet A), the other with polyphenol-free olive oil (Diet B). Systolic and diastolic BP, serum or plasma biomarkers of endothelial function, oxidative stress, and inflammation, and ischemia-induced hyperemia in the forearm were measured at baseline and after 2 months on Diet A or Diet B. When compared to baseline values, only Diet A led to a significant ($P <$ 0.005) decrease in systolic (–7.91 ± 1.97 mm Hg) and diastolic (–6.65 ± 2.10 mm Hg) BP. A similar trend was found for serum asymmetric dimethylarginine (–0.092 ± 0.001 μmol/L, $P < 0.005$), oxidized LDL (–28.23 ± 8.51 μg/L, $P < 0.005$), and plasma C-reactive protein (–1.90 ± 0.52 mg/L, $P < 0.005$). Diet A also elicited an increase in plasma nitrites/nitrates (+4.69 ± 1.36 μmol/L, $P < 0.001$) and hyperemic area after ischemia (+345.5 ± 78.8 perfusion units/sec, $P < 0.001$). We concluded that the regular consumption of a diet containing polyphenol-rich olive oil decreases BP and improves endothelial function in women with high-normal BP or stage 1 essential hypertension.

Introduction

Endothelial dysfunction is one of the phenomena associated with the development of atherosclerosis and cardiovascular disease in patients with hypertension (1). It is mainly characterized by decreased bioavailability of NO (2) and increased levels of ox-LDL (3). One of the predominant mechanisms in NO inactivation is a perturbation of the L-arginine–NO pathway by oxidative stress leading to elevations of plasma ADMA, which in turn exacerbates oxidative stress (4). Both a pro-oxidant status and increased ADMA are common features of disease states associated with atherosclerosis (4, 5) and hypertension (6).

Food intake is an important factor affecting vascular reactivity. Short-term feeding trials have shown the potential for certain foods to improve endothelial function, either as isolated nutrients or as healthy food patterns (7). Several studies suggest that some antioxidant compounds in food may limit oxidative damage and restore endothelial function, thus slowing atherogenic development (8, 9). Polyphenol intake has been associated with low CHD mortality rates (10). Prior studies have reported that antioxidant and anti-inflammatory polyphenols in the diet improve endothelial function and lipid profile (11). The minor components in virgin olive oil, particularly the phenolic compounds, may contribute to the health benefits derived from the Mediterranean Diet. In experimental studies, the phenolic compounds of virgin olive oil showed strong antioxidant properties (12, 13).

Although there are a large number of studies linking the consumption of phenolic compounds with a decrease in vascular events, recent evidence suggests that the effects of food vary according to gender (14) and that women are underrepresented in biomedical studies (15). Moreover, most of the studies on polyphenol healthy properties are based on high-risk populations, thus underestimating the potential benefits to low-risk populations (16).

In this study, we enrolled young women with high-normal BP or stage 1 essential hypertension and hypothesized that consumption of polyphenol-rich olive oil would decrease BP and improve endothelial function. Additionally, we examined which variables are most predictive of BP values and endothelial function biomarkers.

PATIENTS AND METHODS

Patients and design. Prior to the study, the Human Investigation Review Committee of the Virgen del Rocio University Hospital approved all protocols, and all participants provided written informed consent. The study was conducted according to the guidelines of good clinical practice and principles expressed in the Helsinki Declaration by the World Medical Association.

The study was conducted as double-blind, randomized, crossover. We consecutively asked to enter the study to forty Caucasian women that were newly diagnosed with high-normal BP (a systolic pressure of 120-139 mm Hg or diastolic pressure of 80-89 mm Hg) or stage 1 essential hypertension (a systolic pressure of 140-159 mm Hg and diastolic pressure of 90-99 mm Hg). Six women refused to do so, and ten more abandoned after the first dietary intervention. Therefore, twenty-four women completed the study. Their average age was 26 years (range: 24-27 years) and BMI was 25.4 kg/m^2 (range: 23.5-27.1 kg/m^2). They had values of plasma TC between 3.88-4.14 mmol/L and TG between 0.51-0.56 mmol/L. All participants completed a comprehensive health-related questionnaire that included lifestyle information (i.e., physical activity, smoking habits, alcohol consumption, tea and coffee, and dietary habits), medical and family history (especially those related to premature cardiovascular disease), and the use of medications, nutritional supplements, and vitamins. The exclusion criteria included previous history of cardiovascular disease, any severe chronic illness, treatment with antihypertensive or lipid-lowering drugs, and current smoking habits.

Following a homogenization period of 4 months on a healthy diet (homogenization diet), women who met inclusion criteria ate a diet with polyphenol-rich olive oil (Diet A) or a diet with polyphenol-free olive oil (Diet B) for 2-months period and then immediately started the second dietary 2-months period of either the Diet B or the Diet A. A set menu plan, which contained the same basic foods referred for the Mediterranean Diet (17) and calories to the habitual diets, was provided to the participants. They were instructed to avoid the adherence to any special foods or supplements affecting BP, lipid metabolism or highly rich in polyphenols. The only difference between diets (homogenization diet, Diet A, and Diet B) was the type of dietary fat. Sunflower or corn oil was permitted for the homogenization diet, whereas a virgin olive oil rich in polyphenols and the same oil without polyphenols (refined olive oil) were provided for the Diet A and Diet B, respectively. During each dietary intervention period, participants consumed 60 mL of the corresponding dietary fat daily. This study design ensured that each participant consumed comparable energy from dietary fats and amounts of polyphenols from virgin olive oil on the Diet A. To increase compliance, highly motivated women were selected for the study and were given clear written and verbal instructions. The participants understood the importance of adhering to the diet. At the end of the two dietary periods, participants completed a 4-days diet record, which was used to analyze their nutrient intake and compliance. The aim was to minimize metabolic perturbations between test diets focusing on comparison of polyphenol-rich olive oil versus polyphenol-free olive oil. More than 20 different virgin olive oils were analyzed for the polyphenol content, which was measured by reverse-phase HPLC-diode array detection as previously described (18). We selected a virgin olive oil containing 564 mg/kg polyphenols. A portion of this virgin olive oil underwent oil refining at the Instituto de la Grasa (CSIC, Seville) to produce a polyphenol-free olive oil.

Data on brachial BP and IRH, and blood samples were obtained after the homogenization diet (baseline values) and after the Diet A or Diet B.

BP measurement. Brachial systolic and diastolic BP was measured using an automated oscillometric device (Omron M6 Comfort; Omron Healthcare Co) in the right arm, with participants lying in the supine position for 10 minutes by a trained observer. Three BP readings were taken at 2-minutes interval, and the mean was used for data analysis.

Assessment of endothelial function, oxidative stress, and inflammation biomarkers. Participants were required to fast and avoid heavy exercise 12 hours prior to the morning of the examination. Plasma and serum were obtained from blood samples, stored at –80 ºC, and analyzed at the Clinic Laboratory Service of University Hospital Virgen del Rocio. Details on analytical methods for each biomarker are provided below. NO via total plasma nitrites/nitrates was measured by a colorimetric assay (NO, Colorimetric Assay; Roche Applied Science) using a modular analyzer Power Wave XS® (Biotek®). Serum endogenous ADMA (ADMA-ELISA; DLD Diagnostika GmbH), ox-LDL (Human Ox-LDL ELISA Kit; Biomedica Medizinprodukte GmbH & Co KG), and plasma high-sensitivity CRP (CRP ELISA Kit; Immundiagnostik AG) were measured with enzyme immunoassays.

IRH measurement. Laser-Doppler linear Periflux System 5000 (Perimed SA) was used to measure IRH. The participant was taken into a quiet room at our Day Hospital with only the researcher and a nurse present. The room temperature was maintained at 22 ºC. The technique and possible symptoms were explained in detail. With the participant in the supine position and after a 15-minutes resting, the BP cuff was placed on the patient's arm, and the receptor probe was attached on the forearm at 15 cm from the wrist. The BP cuff was then inflated to 40 mm Hg above the systolic BP and maintained at this pressure for 4 minutes. During this period, the monitoring system showed how PU fell steadily to reach the biological zero. Afterwards, the BP cuff was rapidly deflated and how quickly PU rose above the pre-ischemic PU values was monitored. The data were recorded and stored using PeriSoft for Windows. The values of HA after the ischemia were automatically calculated. The same researcher to avoid variability performed all measurements.

Statistical analysis. We compared the changes after the Diet A or Diet B with respect to the homogenization diet (baseline values) using Student's t-test for paired samples. The Kolmogorov–Smirnov test was used to assess normality of distributions. When samples were not normally distributed, the Mann–Whitney U test was then used. Pearson correlations were computed to explore the linear relationship between variables at baseline and changes relative to baseline values in response to dietary intervention. Differences were considered to be significant when $P < 0.05$. Data are expressed as mean ± SEM. All calculations were performed with the SSPS 15.0 software for WINDOWS (SSPS Inc).

RESULTS

The participants reported 100% compliance in terms of polyphenol-rich (Diet A) and polyphenol-free (Diet B) olive oil intake. Body weight of participants changed minimally over the periods on different diets (homogenization diet, Diet A, and Diet B).

Systolic and diastolic BP decreased after Diet A (–7.91 ± 1.97 mm Hg and –6.65 ± 2.10 mm Hg, respectively) ($P < 0.005$), but were not affected after Diet B (–1.65 ± 2.32 mm Hg and –2.17 ± 2.24 mm Hg, respectively) ($P > 0.05$) compared with baseline values after the homogenization diet. Only after Diet A, all of the participants had a systolic BP of 140 mm Hg or less, and 22 of 24 participants had a diastolic BP of 90 mm Hg or less. Compared with the homogenization diet, plasma nitrites/nitrates were significantly increased and serum or plasma levels of ADMA, ox-LDL, and CRP were significantly decreased after Diet A (**Table 1**). Changes in these endothelial function, oxidative stress, and inflammation biomarkers did not differ between the homogenization diet and Diet B. The total hyperemic response (HA) after 4-minutes arterial occlusions was increased after Diet A (+345.5 ± 78.8 PU/sec; $P < 0.001$), but was not significantly affected after Diet B (+36.3 ± 74.9 PU/sec; $P > 0.05$) compared with after the homogenization diet.

A secondary objective of our study was to analyze which variables are predictive of a stronger response in terms of changes in systolic or diastolic BP and serum or plasma biomarkers. The decreases in systolic and diastolic BP, serum ADMA, ox-LDL, and plasma CRP and the increases in plasma nitrites/nitrates and HA after Diet A were not related to age or BMI. However, BP changes were strongly related to BP values at baseline, indicating that participants with higher BP at baseline were the participants with higher decreases in BP after Diet A (**Figure 1**). Similarly, changes in plasma nitrites/nitrates, serum ADMA, ox-LDL, and plasma CRP, and HA after Diet A were strongly related to values at baseline (**Figures 2A-2E**).

DISCUSSION

The present hypothesis-testing study in 24 women with high-normal BP or stage 1 essential hypertension investigated the potential of olive oil polyphenols to decrease BP and improve endothelial function in a double-blind, randomized, crossover setting. Our study was conducted comparing two olive oils, a polyphenol-rich olive oil (Diet A) and the same one underwent oil refining (polyphenol-free olive oil) (Diet B). The strength of this study is its design and that compliance with consuming test diets, including the dose of olive oil polyphenols (~30 mg/day) during Diet A, was high. This enabled us to isolate the effects of olive oil polyphenols without complications of additional nutrient differences. One of the most relevant findings was a marked decrease in systolic and diastolic BP after 2 months on Diet A. For the first time, we show that a daily low amount of polyphenols in olive oil had similar BP-lowering effects in early forms of high BP to those obtained by commonly-prescribed first-line drugs for established high BP (19), such as thiazides of 6 mm Hg, beta-blockers of 5 mm Hg, or angiotensin converting enzyme inhibitors of 8 mm Hg for systolic BP, and calcium channel blockers of 6 mm Hg or angiotensin II receptor blockers of 10 mm Hg for diastolic BP. These findings agree with our previous study on the effects of virgin olive oil in lowering BP in hypertensive women when compared to high-oleic sunflower oil (20) and have implications at a population level, because reductions of 5 mm Hg in systolic BP and 3 mm Hg in diastolic BP have been shown to predict reduced cardiovascular morbidity and mortality risk up to 20% (21). Recent human intervention studies also reported significant BP reductions after diets supplemented with polyphenols from orange juice in moderately overweight men (22) and blueberries in obese men and women with metabolic syndrome (23). However, while polyphenol-rich dark chocolate had BP-lowering effects in healthy overweight and obese subjects (24), these effects were not apparent in a population with BP in the prehypertensive range (25).

We found that Diet A increased plasma nitrites/nitrates and decreased serum ADMA. Nitrites and nitrates are NO metabolites and the nitrites/nitrates ratio results from the stepwise reduction of nitrate to nitrite to NO (26). ADMA is an endogenously produced molecule that inhibits NO synthesis (27). Therefore, our data conforms to the mechanistic studies linking NO and hypertension (28) and shows that olive oil polyphenols could ameliorate BP levels by improving the bioavailability of NO.

The state of hypertension is often associated with increased vascular oxidative stress and inflammation. For example, it is known that ox-LDL activates renin-angiotensin system and angiotensin II via its type 1 receptor activates ox-LDL receptor LOX-1 (29). CRP is also implicated in inducing endothelial dysfunction by a decline in NO synthase mRNA stability and uncoupling (30) and is considered a novel ligand for LOX-1 (31). After Diet A, we observed a decrease in serum ox-LDL and plasma CRP. Most likely, the antioxidant potency of olive oil polyphenols (32), mainly hydroxytyrosol and derivatives thereof, would be responsible for lowering lipoprotein oxidation. In humans, polyphenol metabolites from olive oil polyphenols can be incorporated into LDL (33). Many in vivo and in vitro studies have suggested that phenolic groups in polyphenols can form relatively stable phenoxyl radicals, thereby disrupting chain oxidation reactions (34). While this evidence of direct antioxidant effects of polyphenols remains to be firmly established (35), our study also suggests anti-inflammatory effects for Diet A, which links with recent findings of direct correlation between levels of ox-LDL and CRP (36). Several molecular pathways that converge in vascular inflammation have been shown affected by olive oil polyphenols, including the arachidonic acid pathway and NF-κB (37). These prototypical biological properties of olive oil polyphenols would contribute to an improvement in vasodilatation, as we observed by the increase in HA in response to arterial ischemia after Diet A, which is consistent with previous studies in healthy subjects (38) and hypercholesterolemic patients (39). Therefore, at least part of the mechanism by which olive oil polyphenols reduce BP includes an amelioration of endothelial function, a suppression of oxidative stress and inflammation, and thereby a restoring of vascular reactivity.

We found that BP-lowering effects of Diet A were greater in participants with higher BP at baseline. This may be of interest as we selected participants having a low cardiovascular risk (women with high-normal BP or stage 1 hypertension) and it is conceivable that BP-lowering effects mediated by olive oil polyphenols could be even more pronounced in severe hypertensive patients. After Diet A, reductions in the levels of nitrites/nitrates, ADMA, ox-LDL, and CRP were also correlated with starting serum or plasma values, thus the highest benefit was observed in participants with the worst baseline values. Identical trend was observed for changes in HA relative to baseline values after Diet A. These observations are probably due to physiological control of the response to olive oil polyphenols rather than to regression to the mean, because similar observations did not occur with another diet that was not Diet A. Furthermore, our data suggest that values for baseline BP, nitrites/nitrates, ADMA, ox-LDL, CRP, and HA are predictive indicators for the degree of change in response to olive oil polyphenols.

In conclusion**,** we report that the regular consumption of a diet containing polyphenol-rich olive oil can significantly decrease BP and improve endothelial function in women with high-normal BP or stage 1 essential hypertension. Our data also support the notion that benefits of olive oil polyphenols on BP and endothelial function would be most prominent on a background of hypertension and endothelial dysfunction.

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F.J.G.M., J.V. and P.S. designed research; R.M.L. and M.L.M. conducted research; R.M.H., A.F.C., L.J.J. and A.J.V.V. analyzed data and performed statistical analysis; P.S. wrote this manuscript; J.V. had primary responsibility for final manuscript. All authors read and approved the final manuscript.

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TABLE 1 Endothelial function, oxidative stress, and inflammation biomarkers in women with high-normal BP or stage 1 essential hypertension after 4 months on homogenization diet and changes after 2 months on Diet A (polyphenol-rich olive oil) or Diet B (polyphenol-free olive oil)[1]

		Changes from baseline	
Biomarker	Baseline	Diet A	Diet B
Nitrites/nitrates (µmol/L)	19.69 ± 1.01	+4.69 ± 1.36[a]	+0.83 ± 0.85[b]
ADMA (µmol/L)	0.82 ± 0.02	–0.09 ± 0.00[a]	–0.04 ± 0.01[b]
Ox-LDL (µg/L)	153.04 ± 7.12	–28.23 ± 8.51[a]	–6.93 ± 6.82[b]
CRP (mg/L)	1.56 ± 0.47	–1.90 ± 0.52[a]	–0.65 ± 0.56[b]

[1] Data are presented as mean ± SEM, $n = 24$. Means of change in a row with superscripts without a common letter differ, $P < 0.01$. Asymmetric dimethylarginine, ADMA; C-reactive protein, CRP; oxidized LDL, ox-LDL.

FIGURE LEGENDS

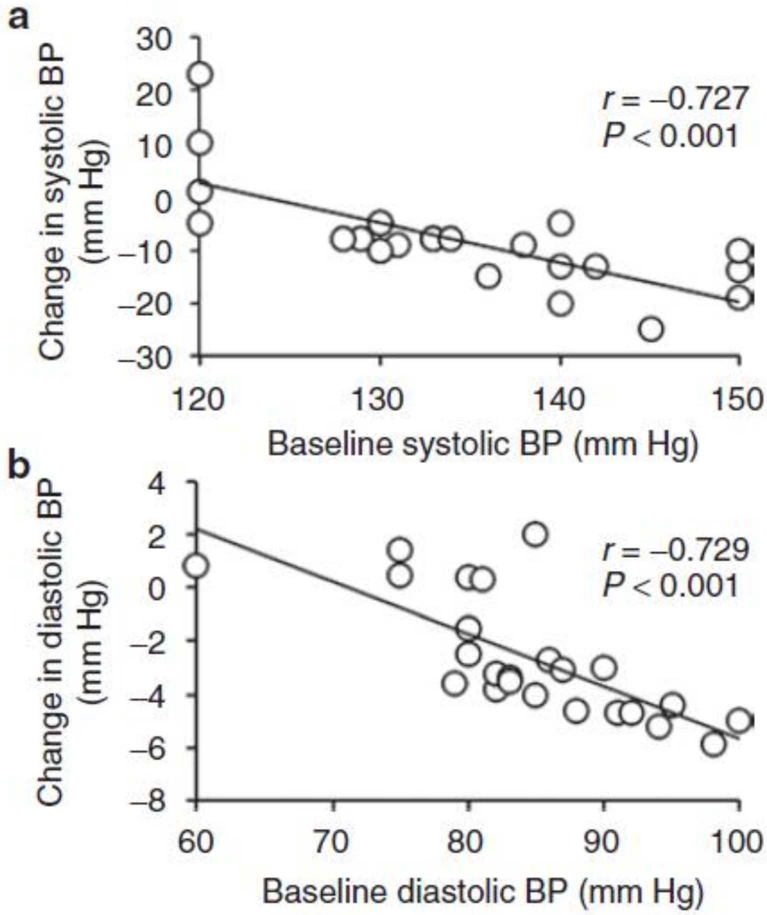

FIGURE 1 Changes in systolic (A) and diastolic (B) BP relative to baseline values in women with high-normal BP or stage 1 essential hypertension after 2 months on Diet A (polyphenol-rich olive oil). The line is the best-fit line, *n* = 24.

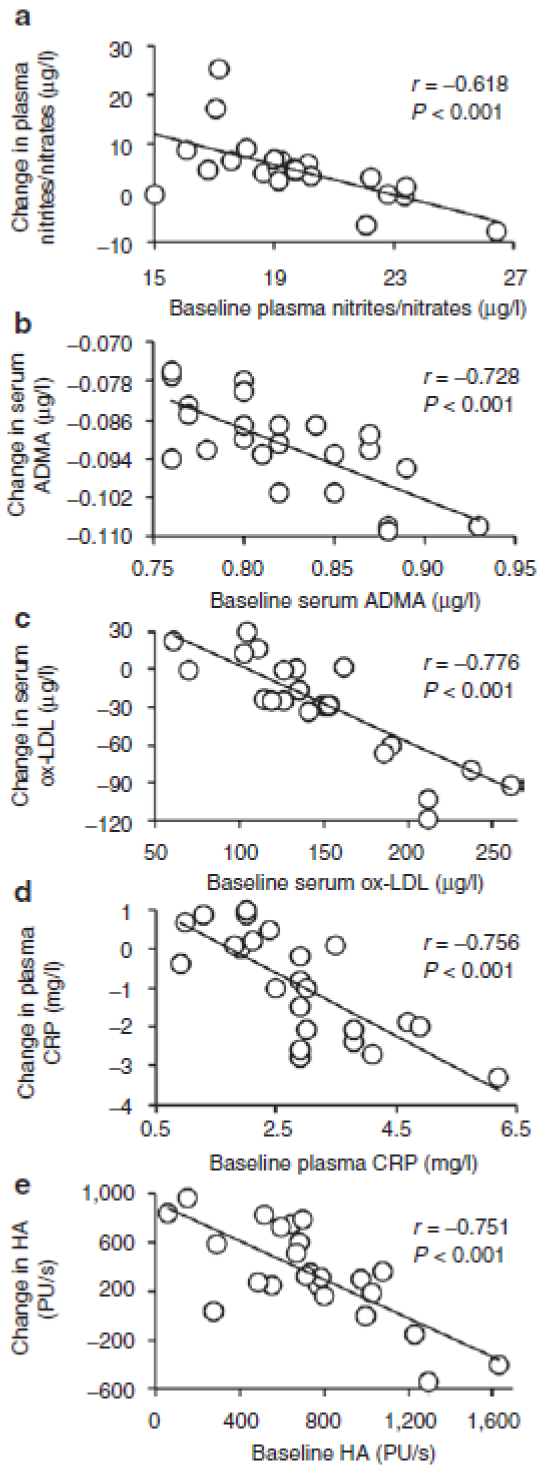

FIGURE 2 Changes in plasma nitrites/nitrates (A), serum ADMA (B), serum ox-LDL (C), plasma CRP (D), and HA (E) relative to baseline values in women with high-normal BP or stage 1 essential hypertension after 2 months on Diet A (polyphenol-rich olive oil). The line is the best-fit line, *n* = 24. Asymmetric dimethylarginine, ADMA; C-reactive protein, CRP; hyperemic area, HA; oxidized LDL, ox-LDL.