

Olive Oil and Reduced Need for Antihypertensive Medications

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Background: The blood pressure (BP) effects of changing the total fat intake and saturated-unsaturated fat ratio are still controversial, despite evidence that saturated fat-enriched diets are associated with higher BP levels. This double-blind, randomized crossover study evaluated a possible difference between antihypertensive effects of monounsaturated (MUFA) (extra-virgin olive oil) and polyunsaturated fatty acids (PUFA) (sunflower oil).

Methods: Twenty-three hypertensive patients were assigned randomly to MUFA or PUFA diet for 6 months and then crossed over to the other diet; effects were evaluated on the basis of daily antihypertensives needed.

Results: Diets high in MUFA and PUFA differed from the habitual diet for reduced total and saturated fats, whereas they differed from each other for MUFA (17.2% vs 10.5%) and PUFA content (3.8% vs 10.5%). Resting

BP was significantly lower ($P = .05$ for systolic BP; $P = .01$ for diastolic BP) at the end of the MUFA diet compared with the PUFA diet. Blood pressure responses during sympathetic stimulation with the cold pressor test and isometric exercise were similar. Daily drug dosage was significantly reduced during the MUFA but not the PUFA diet (-48% vs -4% , $P < .005$). All patients receiving the PUFA diet required antihypertensive treatment, whereas 8 of those receiving the MUFA diet needed no drug therapy.

Conclusions: A slight reduction in saturated fat intake, along with the use of extra-virgin olive oil, markedly lowers daily antihypertensive dosage requirement, possibly through enhanced nitric oxide levels stimulated by polyphenols.

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SEVERAL STUDIES were performed in the past 2 decades to detect the influence of dietary fat on blood pressure (BP). Despite evidence that BP increases concomitantly with increasing total fat and saturated-unsaturated fat ratio, debate continues as to whether changing dietary fat intake might be a non-pharmacological tool in the prevention or treatment of arterial hypertension.¹⁻⁵ Compared with a saturated fat diet, the Mediterranean diet, rich in olive oil, has been found to be associated with lower levels of serum lipids⁶ and BP.⁷ Accordingly, diets enriched with oleic acid, the main component of olive oil, have been shown to significantly reduce total and low-density lipoprotein (LDL) cholesterol and total triglyceride levels, while high-density lipoprotein (HDL) cholesterol levels remain unchanged or even slightly increased.^{8,9}

Aside from the high monounsaturated fatty acids (MUFA) content, the Mediterranean diet is characterized by the

presence of several components that might affect BP levels independently of each other. Previous observations have shown that an intake of vegetables and fruit, with the consequent increase in dietary potassium levels, might be responsible, per se, for the better BP control.¹⁰ More recently, the DASH (Dietary Approaches to Stop Hypertension) Collaborative Research Group found that a diet rich in fruit and vegetables, with low-fat dairy food and reduced total as well as saturated fat levels, significantly lowers BP.¹¹

On the other hand, evidence exists in the literature that vegetarians who consume large amounts of ω -6 polyunsaturated vegetable oils—only marginally contained in the Mediterranean diet—have lower BP values than nonvegetarians.^{12,13}

The aim of our controlled clinical trial was to compare the effects of 2 diets, one rich in MUFA and the other rich in polyunsaturated fatty acids (PUFA), on BP control in patients being treated for hypertension, on the basis of their daily drug

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PATIENTS AND METHODS

PATIENTS AND STUDY DESIGN

Twenty-three patients (10 male and 13 female; age range, 25-70 years) with mild-to-moderate essential arterial hypertension and without end-organ complications participated. The inclusion criteria were (1) BP levels of less than 165/104 mm Hg at entry, with stable values for at least 6 months before the study; (2) no change in antihypertensives or daily dosage for the previous 6 months; (3) no use of low-energy diets, hypolipidemic drugs, or oral contraceptives; and (4) stable weight for 6 months before the study.

Patients eligible for the study who had given their informed consent were entered in a 1-month run-in period and were seen twice at 2-week intervals. If, at the end of this period, their BP still met the entry criteria, they were randomly assigned to an MUFA or a PUFA diet group. Eleven patients were assigned to an MUFA dietary regimen (extra-virgin olive oil) and 12 to a PUFA-rich diet (sunflower oil) for 6 months; at the end of this period, patients were switched to the alternative treatment for 6 more months. To avoid seasonal influence on the pressor effects of the dietary regimens, randomization was performed on groups of 10 patients at a time. After randomization, patients were seen at 2-month intervals for a follow-up period of 1 year. We chose the extra-virgin type of olive oil because it differs from sunflower oil not only for its primary components (fatty acids), but also for other substances (the polyphenolic compounds).

BP MEASUREMENTS

Blood pressure and heart rate were measured every 2 months at rest and in the sitting position, between 8 and 10 AM, at least 12 hours after the last drug administration. Measurements

were made by one of us (S.R.) who was unaware of the patient's dietary treatment, using an automatic recorder (Sentron; Bard Biomedical Division, Bard Inc, Lombard, Ill). Patients rested for 10 minutes in the sitting position in a quiet and comfortable room, at 22°C; thereafter, systolic and diastolic BP were measured twice at 2-minute intervals, and the average of the measurements was used in the analysis.

Blood pressure was also measured at baseline, at the end of the first (6 months) and second (12 months) dietary regimen periods, and during sympathetic stimulation induced by means of the cold pressor test and handgrip. The cold pressor test was performed, after a 15-minute bed rest, by immersing 1 hand up to the wrist in ice-cold water for 2 minutes: BP and heart rate were measured twice before the test, at the first and the second minute of the test, and at the second and the fifth minute in the subsequent recovery phase. Isometric exercise was performed, after a 15-minute bed rest, by squeezing for 3 minutes a dynamometer at 30% of the maximal strength previously evaluated. Blood pressure and heart rate were measured twice before the test, at 1-minute intervals during the test, and twice in the recovery phase. The mean of BP and heart rate measurements at baseline, during the stress test, and in the recovery phase were calculated for statistical analysis of the tests.

Body weight was measured at each examination with a beam balance scale.

LABORATORY ASSESSMENT

Blood samples were taken by venipuncture after a 14-hour overnight fast, at least 30 minutes before BP measurements, at baseline and at 6- and 12-month follow-up,

dosage requirement. Diets were controlled not only for energy source but also for mineral components: sodium, potassium, and calcium.

RESULTS

The 23 patients who entered the trial all completed the 1-year study protocol. The 7-day food record showed that 20 patients were fully compliant with both diets, whereas 3 were not. These 3 patients followed a regimen with a lower total energy (approximately 5439 kJ) and carbohydrate intake, although their body weight was unchanged; however, since they had complied with the indications for the intake of MUFA or PUFA, they were still included in the final analysis. During the run-in period, total and saturated fatty acid content was 34% and 11%, respectively; these values were higher than during the experimental dietary periods, whereas total energy intake was unchanged. Experimental MUFA and PUFA diets were absolutely comparable for total energy, carbohydrate, protein, total and saturated lipid, and electrolyte content; they only differed for monounsaturated and polyunsaturated lipid composition and, thus, for monounsaturated-polyunsaturated lipid ratio. The number of daily servings of each food group was also similar (**Table 1**). Total daily electrolyte intake, including added salt, was

unchanged during the study, as shown by the mean 24-hour urine excretion of sodium (166 [29], 167 [32], and 169 [35] mmol) and potassium (56 [15], 55 [17], and 53 [14] mmol) at baseline, at the end of the MUFA diet, and at the end of the PUFA diet, respectively. This means that patients followed a diet containing approximately 10 g/d of sodium chloride, which is the same as that of a comparable population in the same geographic area.¹⁵

No one consumed spirits, and only 3 patients drank wine during meals (about 30 g/d of alcohol), without difference between diets.

Sex-related differences in dietary regimen were confined to total daily energy intake, which averaged 7950 (7799) kJ in men and 6276 (6230) kJ in women. Daily percentage of lipid intake decreased with age ($r = -0.406$; $P = .02$). Regarding sex-related differences in the characteristics of the study group, only body weight was significantly higher among men than among women (77.1 [4.7] vs 64.0 [7.7] kg; $P < .001$). The influence of age on the characteristics of the group was confined to systolic BP ($r = 0.530$; $P = .01$) and serum glucose level ($r = 0.356$; $P = .005$), both being positively related to age.

Body weight did not change in either treatment period, nor was any difference observed in lipid and carbohydrate metabolism variables (**Table 2**). Systolic (127 [14] vs 135 [13] mm Hg; $P = .05$) and diastolic BP (84

to determine serum glucose, total cholesterol, trygliceride, and HDL cholesterol levels.

Twenty-four-hour urine collections were provided by each patient at baseline and at the end of both intervention periods for the evaluation of sodium and potassium excretion.

DIETARY INTERVENTION

Participants were prescribed a well-balanced diet, with 8368 and 6276 kJ daily for men and women, respectively. The MUFA and PUFA diets were similar for daily content of protein (17%), carbohydrates (57%), total (26%) and saturated (5.6%) lipids, cholesterol (0.61 mmol), and fiber (35 g), and differed only for monounsaturated and polyunsaturated lipids. To minimize the between-diet differences in nutrients, patients were prescribed the same diet at the beginning of both intervention periods, but during the MUFA diet, they could use only olive oil as the source of added fat, whereas the PUFA diet allowed only sunflower oil. A dietitian (L.d'E.) suggested that oils be added after cooking. Men were told to add 40 g (about 4 spoonfuls) and women to add 30 g (about 3 spoonfuls) of oil. To reinforce the message, each participant was interviewed by the same dietitian at each 2-month visit, and compliance to dietary treatment was assessed using 7-day food records provided twice in the run-in and at each clinic visit during the 1-year follow-up. Foods were coded for computer analysis with a food composition table¹⁴; total daily salt intake, including the salt added to foods, was estimated from 24-hour urinary sodium excretion.

DRUG TREATMENT

The participants were asked to continue their habitual antihypertensive regimen during the run-in and the first 2

months of the trial. Thereafter, dosages were decreased in a stepwise fashion, provided that systolic BP was reduced by 5 mm Hg and/or diastolic BP was reduced by 3 mm Hg compared with the value at the previous clinic visit. When indicated, each drug was reduced by a half tablet daily. In patients receiving combination therapy, drug therapy was withdrawn in a stepwise fashion, according to a fixed sequence, in the following order: diuretics, followed by calcium antagonists and other vasodilators, angiotensin-converting enzyme inhibitors, and β -adrenergic blocking agents. The inverse sequence was followed in cases where drug therapy had to be increased or restored because of an increase in BP.

Drugs were prescribed by two of us (L.A.F. and L.G.), who were unaware of the patient's group assignment.

STATISTICAL ANALYSIS

Data were expressed as mean (SD), and differences between final values of both dietary regimens were analyzed using paired *t* test.

Results of the cold pressor test and isometric exercise were evaluated using 2-way analysis of variance, and the multiple comparisons were made using the Tukey test.

Actual pill consumption and percentage of reduction in pill consumption from baseline in both groups were evaluated using the Mann-Whitney *U* test. The comparison between the proportion of patients in both dietary regimens who had optimal BP control without drug treatment was performed using a χ^2 test for 2×2 contingency table. Confidence intervals (CI) are 95%.

The number of patients conferred a power of the study equal to 90% to detect a 40% difference between groups in the consumption of antihypertensives, with an α level of .05, and a β level of 0.1.

[8] vs 90 [8] mm Hg; $P = .01$) were significantly lower at the end of the MUFA than after the PUFA diet. Blood pressure levels during the 6-month periods are shown in **Figure 1**. No difference between dietary regimens was observed in BP response to sympathetic stimulation with the cold pressor or the handgrip test, during the tests or in the following recovery phase (**Figure 2**).

Daily dosage of antihypertensives was reduced by 48% (95% CI, -25% to -71%) during the MUFA diet and by 4% (95% CI, -24% to 17%) during the PUFA diet, this difference being statistically significant ($P = .005$). In particular, as shown in **Table 3** and **Table 4**, BP was controlled without any pharmacological treatment in 8 patients during the MUFA diet but in none during the PUFA diet ($P = .01$), with a correspondent decrease in the number of patients receiving monotherapy; accordingly, the total daily drug requirement was reduced during the MUFA diet (Table 4). Subanalysis of the 3 patients who drank wine showed similar results (-37% vs 4%, MUFA vs PUFA diet).

The analysis of the period effect did not show any treatment-period interaction, since olive oil was significantly more effective than sunflower oil in reducing antihypertensive dosage, independently of the sequence followed. In particular, when the MUFA diet was given first, drug dosage was reduced by 50% during the MUFA diet

and increased by 3.4% during the PUFA diet (mean difference, 53.3%). When the PUFA diet was prescribed first, drug dosage was reduced by 10.5% during the PUFA and by 47% during the MUFA diets (mean difference, 36.5%).

COMMENT

Many intervention studies in the last 2 decades have investigated the influence of dietary fat intake on BP regulation, mainly comparing the effects of diets with low or high fat intake and with a PUFA-saturated fatty acid ratio across a huge range, from 0.2 to 1. Some studies have shown a favorable effect of low-fat or high-PUFA diets in humans¹⁻³ and in animal models,¹⁶ whereas other observations have failed to detect this effect.^{5,17}

The pressure effects of ω -3 PUFA more recently have attracted the interest of several investigators, who have been able to demonstrate a significant BP reduction^{4,18,19} when diet was supplemented with a relatively high dose of these fats. Despite this evidence, however, there are still many doubts about the safety of fat-modified diets on BP regulation, because of the relatively little effect of ω -6 unsaturated fats on BP and the multiple adverse effects of high doses of ω -3 polyunsaturated fats.²⁰

A few studies have investigated the effects of oleic acid on BP. In a 6-week controlled trial performed in a

Table 1. Mean Energy, Nutrient Composition, and Consumption During MUFA and PUFA Diets*

	MUFA Diet	PUFA Diet
Components, mean (SD)		
Energy, kJ	6192 (1213)	6707 (1134)
Carbohydrates, %	55.1 (5)	54.7 (6)
Proteins, %	18.1 (1)	18.6 (2)
Lipids, %	26.6 (5)	26.6 (5)
PUFA, %	3.8 (2)	10.5 (2)†
MUFA, %	17.2 (3)	10.5 (3)†
Saturated fat, %	5.6 (1)	5.6 (2)
MUFA/PUFA ratio	5.7 (2.6)	1.1 (0.6)†
Cholesterol, mmol (mg)	0.495 (0.06) (19.1 [2.3])	0.514 (0.08) (19.9 [3.1])
Fiber, g	26.9 (9)	25.4 (7)
Food groups, No. of servings/d		
Fruits and vegetables	4.2	5.0
Bread, pasta, rice	4	4
Legumes (peas, beans, lentils)	0.3	0.4
Beef, pork, ham	0.71	0.56
Poultry	0.28	0.28
Fish	0.86	0.56
Eggs	0.14	0.18
Fat, oils	7.0	6.3

*Data are estimated using 7-day food record. MUFA indicates monounsaturated fatty acid; PUFA, polyunsaturated fatty acid.

†P<.001.

Table 2. Variables at the End of MUFA and PUFA Diets*

	Baseline	MUFA Diet	PUFA Diet
Body weight, kg	70.1 (9)	70.0 (9)	70.1 (8)
Body mass index, kg/m ²	26.2 (2)	26.0 (2)	26.0 (2)
Systolic BP, mm Hg	134 (17)	127 (14)†	135 (13)
Diastolic BP, mm Hg	90 (7)	84 (8)‡	90 (8)
Heart rate, beats/min	70 (9)	70 (5)	71 (6)
Cholesterol, mmol/L (mg/dL)	4.84 (1.16) (187.3 [44.9])	4.51 (1.09) (174.5 [42.2])	4.61 (1.03) (178.3 [39.8])
Triglycerides, mmol/L (mg/dL)	1.21 (0.68) (107.2 [60.2])	1.00 (0.41) (88.6 [36.3])	1.15 (0.65) (101.9 [57.6])
HDL cholesterol, mmol/L (mg/dL)	1.28 (0.26) (49.5 [10.0])	1.28 (0.31) (49.5 [12.0])	1.30 (0.26) (50.3 [10.0])
Serum glucose, mmol/L (mg/dL)	5.15 (1.00) (92.8 [18.0])	5.34 (0.22) (96.2 [4.0])	5.30 (0.28) (95.5 [5.0])

*BP indicates blood pressure; HDL, high-density lipoprotein. Other abbreviations are given in the first footnote to Table 1. Data are given as mean (SD).

†P=.05, compared with baseline and PUFA diet.

‡P=.01, compared with baseline and PUFA diet.

free-living sample of 57 normotensive volunteers from a healthy rural population of southern Italy, Strazzullo and coworkers⁷ found an increase in systolic and diastolic BP when olive oil was replaced with saturated fatty acids. More recently, Mensink and colleagues²¹ compared the effect of an olive oil-rich diet with that of a carbohydrate-rich diet in 47 (23 male and 24 female) healthy, normotensive subjects undergoing controlled feeding for 36 days and found no difference between groups. Finally in 1995, Thomsen and coworkers²² compared the effect of MUFA and PUFA diets on BP in a 3-week crossover study on 16 (10 male and 6 female) free-living patients with type 2 diabetes (mean age, 59 ± 7 years), showing a significant reduction in 24-hour as well as in daily BP when olive oil was given.

We compared the effects of olive oil rich in oleic acid (chain length [C], 18 carbon atoms, with 1 double bond [18:1]), and sunflower oil rich in linoleic acid (C 18:2) in free-living nondiabetic patients with arterial hypertension fairly well controlled with antihypertensives. To our knowledge, this is the first study investigating long-

term effects of MUFA or PUFA on BP. A 6-month treatment period was chosen to overcome the problem of a crossover effect of the previous treatment. In fact, although drug administration was similar after 2 months of either dietary regimen, a marked reduction in hydrochlorothiazide (-65 mg/d), nifedipine (-75 mg/d), and atenolol (-175 mg/d) dosage was observed after 4 months of olive oil intake, becoming even more marked at the end of the study. Moreover, tests for treatment-period interaction clearly demonstrated that olive oil was more effective in controlling BP values independently of the sequence. During the observation period, the variation in dietary components was lower than expected in a free-living population. As a matter of fact, the diet prescribed was similar in both treatment periods, with the only difference confined to the investigative factor, ie, extra-virgin olive oil vs sunflower oil. Moreover, patient compliance to the diet was strictly controlled by a dietitian, who reinforced the advice during the single interviews with the participant. The main result of our investigation was a straightforward reduction in antihyperten-

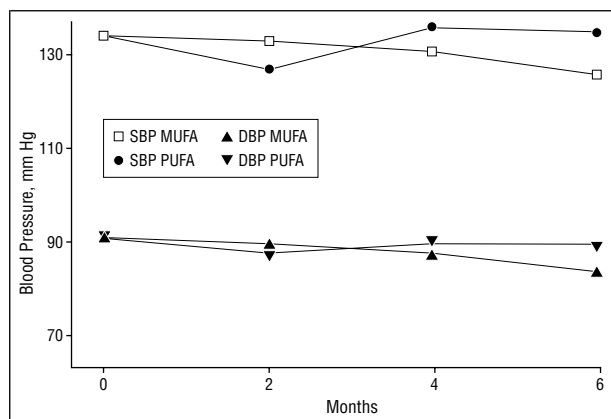


Figure 1. Resting systolic (SBP) and diastolic blood pressure (DBP) in 23 hypertensive patients during a 6-month intervention period with an olive oil– (MUFA) or sunflower oil–rich diet (PUFA).

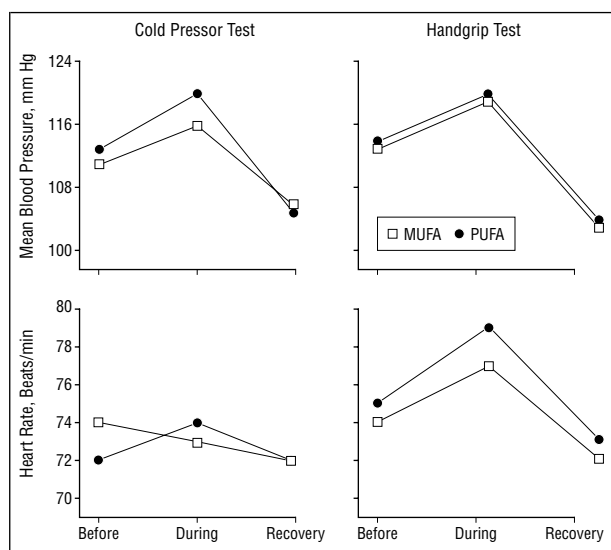


Figure 2. Blood pressure and heart rate during sympathetic stimulation with the cold pressor (left) and handgrip (right) tests in 23 hypertensive patients at the end of a 6-month intervention period with olive oil– (MUFA) and sunflower oil–rich diets (PUFA).

sive tablet consumption when patients were given olive oil, whereas drug consumption was only mildly affected by sunflower oil. At variance with experimental diets, free diets were higher in total (34.0% vs 26.6%; $P = .005$) and saturated (11.0% vs 5.6%; $P < .001$) lipid content. This is in line with results from epidemiological studies indicating that the rural habits of the traditional Mediterranean diet typical of southern Italy probably have changed since the original observations of the Seven Countries Study^{23,24} to resemble a more continental diet, ie, one richer in saturated fats.²⁵ A slightly favorable effect of unsaturated fat on serum lipid levels has also been detected, since we found a slight reduction in serum total cholesterol (-0.336 and -0.233 mmol/L [-13 and -9 mg/dL] during the MUFA and PUFA diets, respectively) and triglyceride levels (-0.215 and -0.068 mmol/L [-19 and -6 mg/dL] during the MUFA and PUFA diets, respectively). The between-group difference did not reach statistical significance. The magnitude of this effect was probably minimized by the characteristics of the patients, most of them

Table 3. Drug Therapy After MUFA and PUFA Diets*

	Baseline	MUFA Diet	PUFA Diet
No drug	2	8	0
Monotherapy	16	10	18
Atenolol	3	3	5
Nifedipine	7	5	8
Lisinopril	5	2	4
Doxazosin mesylate	1	0	1
Combination therapy	5	5	5
Atenolol and nifedipine	2	1	1
Lisinopril and hydrochlorothiazide	0	1	1
Atenolol and doxazosin	0	1	1
Atenolol, nifedipine, and hydrochlorothiazide	1	1	1
Atenolol, doxazosin, and hydrochlorothiazide	1	0	0
Lisinopril, nifedipine, and hydrochlorothiazide	1	1	1

*Abbreviations are given in the first footnote to Table 1. Data are given as number of patients.

Table 4. Daily Drug Consumption*

	Baseline	MUFA Diet	PUFA Diet
Atenolol	450	275	500
Nifedipine	420	220	380
Lisinopril	120	70	110
Doxazosin mesylate	8	4	8
Hydrochlorothiazide	75	31.5	75

*Data are given in milligrams per day. Abbreviations are given in the first footnote to Table 1.

having cholesterol and triglyceride levels within normal limits. The pressor effect of oleic acid is independent of weight loss and other possible confounding variables that might affect BP levels (ie, potassium level).¹⁰ The mechanisms behind the BP reduction induced by olive oil are not easily understood. It has been shown that insulin sensitivity increases when the polyunsaturated-saturated fat ratio in dietary intake increases. Accordingly, it has been shown that the decrease in the PUFAs of skeletal muscle phospholipids is associated with reduced insulin sensitivity.²⁶ We know that insulin resistance, and the consequent hyperinsulinemia, are well related to arterial hypertension; however, this does not seem a likely explanation for our finding. In fact, it would be difficult to explain why different fatty acids of the same chain length act differently on BP control, since insulin resistance is inversely related to total percentage of C 20-22 PUFAs.²⁶ The unsaturated fatty acids are also able to reduce serum levels of the vasoconstrictor thromboxane 2, which might influence BP regulation. Again, this does not seem a likely explanation for our finding, since oleic acid is not expected to influence this variable more favorably than polyunsaturated linoleic acid.

Other substances found in extra-virgin olive oil might play a key role in BP regulation. Although antioxidant polyphenols are completely absent in sunflower oil, there are as many as 5 mg of phenols in 10 g of extra-virgin olive oil.²⁴ Therefore, the men who participated in our study received 20 and the women received 15 mg/d of phenols, an amount similar to the total flavonoid intake

associated with a lower incidence of coronary heart disease in the Zutphen Elderly Study.²⁷ Oxidized LDL cholesterol particles are involved in the onset and progression of atherosclerotic lesions. They impair endothelium-mediated relaxation in isolated arterial segments²⁸ and the vasodilator responses in animals and humans.²⁹ In particular, oxidized LDL cholesterol suppresses nitric oxide production in cultured endothelial cells. It has been suggested that lipoproteins are relevant to the pathophysiologic features of hypertension and its pharmacological control³⁰; moreover, MUFA has been shown not only to increase HDL cholesterol levels more than PUFA,³¹ but also to produce oleate-enriched LDL cholesterol, which is more resistant to oxidative modifications.³² Polyphenols, which are responsible for the antioxidative activity of olive oil *in vitro*,³³ therefore might be involved in the better BP control observed and in the consequent reduction in the required daily drug dosage. This hypothesis is in keeping with a recent observation showing that oral antioxidant supplementation reduces BP, possibly via increased availability of nitric oxide,³⁴ although other authors have failed to demonstrate this effect.³⁵

In conclusion, our study indicates that dietary interventions based on the use of extra-virgin olive oil and a significant reduction in total and saturated fatty acid intake favorably affect BP control in pharmacologically treated hypertensive patients, significantly decreasing the required daily dosage of antihypertensives.

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