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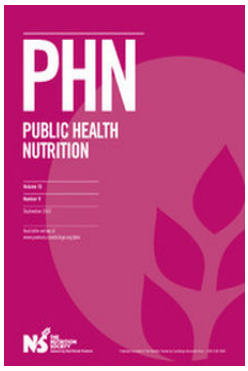

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Monounsaturated fatty acids, olive oil and blood pressure: epidemiological, clinical and experimental evidence

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Abstract

Diet has an important role in the prevention and treatment of hypertension. In early epidemiological studies, conducted mainly in the USA, monounsaturated fatty acids showed a deleterious association with blood pressure or no relationship at all. However, more recent studies, conducted in Mediterranean countries, have shed new light on this issue. In the present review we summarise the main results of epidemiological studies and feeding trials, and explain the possible mechanisms through which monounsaturated fatty acids, and specifically olive oil as the major dietary source of this type of fat in Mediterranean countries, could exert a favourable effect on blood pressure.

Keywords
Monounsaturated fatty acids
Olive oil
Hypertension
Mediterranean diet

Diet plays an important role in the primary prevention of hypertension (HT)[1,2]. Reduction of sodium and alcohol intake, an increase in potassium intake, and modification of the whole dietary pattern are the best-supported recommendations for the prevention of this disorder[3,4]. Based in an increasing amount of evidence, the classical Mediterranean dietary pattern has been proposed as a healthy choice for the prevention of cardiovascular disease[5]. Part of its beneficial impact can be mediated through a favourable effect on blood pressure (BP)[6]. A major characteristic of the Mediterranean diet is a high supply of energy coming from monounsaturated fatty acids (MUFA), mainly from olive oil.

Laboratory data and results from epidemiological studies and clinical trials are accruing to support the importance of MUFA, and more particularly of olive oil, in the prevention of HT. In the present paper, we review the effect of MUFA and olive oil on BP levels and their possible role in the prevention and treatment of HT. Initially, we describe the epidemiological evidence linking MUFA, olive oil and BP. Then, we summarise the results of controlled feeding studies and clinical trials. Finally, we point out the possible physiological mechanisms through which MUFA and olive oil can reduce BP and prevent the development of HT.

Dietary sources of MUFA

MUFA are fatty acids with a single double bond in the molecule. The most abundant MUFA in the diet is oleic acid (C18:1*n*−9). Table 1 shows the foods with the highest amounts of MUFA[7–9]. In Mediterranean countries, the main source of MUFA in the diet is olive oil. Other important dietary sources of MUFA are nuts and some types of meat. In the USA and Northern Europe, meat is one of the main sources of MUFA[10,11].

Virgin (non-refined) olive oil, besides its MUFA content, has important amounts of antioxidants and phytochemicals. However, when refined or heated to frying temperature in air, olive oil loses most of these non-lipidic natural compounds[12].

Additionally, new oil variants, rich in oleic acid, have been developed in recent decades. Thus, high-oleic-acid sunflower, soybean, safflower, corn and peanut oils are available on the market[9]. Along with the high amount of MUFA achieved in these oil variants, another characteristic is their increased amount of α-tocopherol.

Epidemiological evidence

Some epidemiological studies have assessed the relationship between types of dietary fat and incidence of HT or changes in BP (Table 2 [6, 13–20]). However, most of them have been conducted in the USA and Northern Europe, where overall MUFA consumption is only moderate and comes mainly from some types of meat, and hence is highly correlated with the intake of saturated fat. In fact, most epidemiological studies conducted outside Mediterranean countries have not found relevant associations between MUFA intake and the risk of HT.

An ecological analysis of NHANES III data (Third National Health and Nutritional Examination Survey) found a higher consumption of MUFA in regions with the highest mean BP[21]. Results from prospective studies show

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Table 1 Content of monounsaturated fatty acids (MUFA) in some foods

	MUFA (g/100 g)
Oils	
Olive oil	73.9
Sunflower oil	31.8
High-oleic-acid sunflower oil	83.6
Safflower oil	14.4
High-oleic-acid safflower oil	74.6
Corn oil	29.3
Soybean oil	24.3
Canola oil	58.9
Peanut oil	46.2
Foods	
Peanuts	23.4
Hazelnuts	42.2
Almonds	36.6
Lard	41.6
Butter	26.8

Sources: Moreiras *et al.*[7], US Department of Agriculture[8], and Martínez-Force and Garcés[9].

similar results. In nearly 60 000 US women included in the Nurses' Health Study, followed from 1980 to 1984, there was no relationship between total fat, saturated fat or unsaturated fat intake and the risk of HT[13]. A more recent analysis of the same cohort reached similar conclusions[14]. Similarly, the Health Professionals' Follow-up Study, analysing more than 30 000 US men who were followed for 4 years, did not find any association between BP and intake of saturated, polyunsaturated or *trans*-unsaturated fat[15]. In the Chicago Western Electric Company Study, a cohort with nearly 1800 men followed up over 8 years, intakes of total fat, saturated fatty acids (SFA), polyunsaturated fatty acids (PUFA) and MUFA were positively and significantly related to average annual change in systolic BP[16]. Results from the Multiple Risk Factor Intervention Trial showed an inverse association of BP with PUFA intake and with the dietary PUFA/SFA ratio, but the authors did not report any association between MUFA and BP[17]. Only one small cross-sectional study conducted in 76 middle-aged American men showed an inverse relationship between BP and MUFA intake as assessed from 3-day food records[18]. All these studies adjusted their analyses for potential confounding factors, including other dietary exposures. Also, the prospective design in most of them precluded a reverse causation bias; i.e. that changes in diet may be derived from the previous knowledge of BP levels.

On the contrary, the few epidemiological studies conducted in Southern Europe show very different results, suggesting a protective role for MUFA or olive oil. The high proportion that meat represents as a major source of MUFA in Western diets may have hindered the ability of epidemiological studies conducted in the USA and Northern European countries to find a protective effect of MUFA on HT. Southern European countries, where a substantial proportion of the population still follows the traditional olive oil-rich Mediterranean diet, are the ideal setting to ascertain this association, thus avoiding the strong correlation between MUFA and meat intake. Investigators from the Italian Nine Communities Study assessed the relationship between olive oil consumption and BP in almost 5000 middle-aged non-hypertensive individuals. Results showed a statistically significant inverse association, both for systolic and diastolic BP, and for both men and women when analysed separately, in spite of the moderate quality of the dietary assessment (researchers used a qualitative food-frequency questionnaire with only 35 items)[19]. In this same study, PUFA were associated with lower systolic BP but had no effect on diastolic BP.

In Greece, the cradle of the Mediterranean diet concept, a cross-sectional analysis of 20 343 EPIC (European Prospective Investigation into Cancer and Nutrition)

Table 2 Epidemiological studies assessing the relationship between monounsaturated fatty acids intake, olive oil consumption and hypertension

Study	Country	Study design	Participants	Main results
Studies conducted in non-Mediterranean countries				
Nurses' Health Study[13,14]	USA	Cohort	58 218 women aged 34–59 years	No effect on risk of HT
Health Professionals' Follow-up Study[15]	USA	Cohort	30 681 men aged 40–75 years	No effect on risk of HT
Chicago Western Electric Company Study[16]	USA	Cohort	1714 men aged 40–55 years	MUFA directly associated with increase in BP
Multiple Risk Factor Intervention Trial[17]	USA	Cohort	11 342 men aged 35–57 years	No effect on BP
Williams *et al.*[18]	USA	Cross-sectional	76 men aged 30–55 years	MUFA intake inversely associated with BP levels
Studies conducted in Mediterranean countries				
Italian Nine Communities Study[19]	Italy	Cross-sectional	4903 men and women aged 20–59 years	OO consumption inversely associated with BP levels
EPIC–Greece[6]	Greece	Cross-sectional	20 343 men and women aged 20–86 years	OO consumption and MUFA/SFA ratio inversely associated with BP levels
SUN Study[20]	Spain	Cohort	6863 men and women aged 20–80 years	OO associated with a reduced risk of HT among men but not among women

EPIC – European Prospective Investigation into Cancer and Nutrition; SUN – Seguimiento Universidad de Navarra; HT – hypertension; MUFA – monounsaturated fatty acids; BP – blood pressure; OO – olive oil; SFA – saturated fatty acids.

participants showed that the MUFA/SFA intake ratio was inversely associated with systolic and diastolic BP, after adjustment for potential confounders. Similarly, olive oil consumption was inversely associated with BP, even after adjustment for vegetable consumption[6]. For each 22 g increase in the daily consumption of olive oil, systolic and diastolic BP were 0.8 and 0.3 mmHg lower, on average, after adjustments were made for sex, age, education, body mass index, waist-to-hip ratio, energy intake, physical activity and vegetable consumption.

Another study that has assessed the relationship between MUFA, olive oil and BP is the SUN (Seguimiento Universidad de Navarra) Study. This cohort study has been specifically designed to assess prospectively the effect of a Mediterranean dietary pattern on HT, diabetes, obesity and cardiovascular disease[22]. In a baseline assessment of the first 8800 participants in this cohort, MUFA intake was associated with a lower prevalence of HT among those individuals with low fruit and vegetable consumption, while this effect was not apparent among those with higher fruit and vegetable consumption[23].

However, the three previous studies had a cross-sectional design, with their problems in establishing causal relationships. More recently, a prospective analysis of the SUN Study showed that olive oil consumption was inversely associated with the risk of developing HT among men[20], but no effect was observed among women. In this study, 5573 participants free of HT at baseline were followed up for a median of 28.5 months. Men in the highest quintile of olive oil consumption had a 50% reduction in the risk of incident HT compared with those in the lowest quintile of consumption, with a statistically significant linear trend ($P = 0.02$). This association was independent of other known risk factors for HT including relevant dietary factors. Among women, there was not a clear relationship probably due to a low number of incident cases of HT observed in the women of this cohort during that period. To our knowledge, this is the only study that has prospectively assessed the association between olive oil and the risk of HT. Information on diet and confounding factors was collected before the diagnosis of HT, and the analysis was adjusted for other factors potentially associated with the risk of HT. Its main drawback is the self-reported diagnosis of HT, although the validation study conducted in that population[24] and the high educational level of the study participants guarantee to a fair extent the validity of the outcome information.

Feeding trials

Since the late 1980s, several feeding trials have examined in a controlled environment the effect of MUFA and olive oil on BP. A summary of their main characteristics, including the source of MUFA and their overall results, is presented in Table 3[25–35]. In general, these studies were conducted in very controlled environments, with tight monitoring of the diets to which participants were allocated, leading to a sharp contrast between the dietary profiles of compared groups. Additionally, none of them was funded by the olive oil industry. Only two of them reported that the oils they used to feed participants were provided by oil companies[30,31].

One of the earliest studies was conducted in Italy on 57 normotensive volunteers aged 30 to 50 years. These individuals underwent a dietary intervention with a 70% increase in energy from SFA and a corresponding decrease in MUFA and carbohydrates. After 6 weeks, a significant increase in systolic and average BP was observed. BP reverted to baseline values when participants returned to their usual diet[36]. However, it was not possible to separate changes in BP derived from decreases in MUFA intake or from other dietary changes.

In a study conducted in Spain, 42 subjects were fed two different diets during 5-week periods. Diets differed in their fatty acid composition, while energy intake from carbohydrate, proteins and fat was held constant. Compared with a diet rich in SFA (17% of total energy intake), an olive oil-enriched diet (21% of total energy intake from MUFA) was associated with lower levels of mean BP[30]. A similar study, conducted in 41 male young volunteers, showed that a diet rich in MUFA (22% of total energy intake), from olive oil, had a beneficial effect on glucose metabolism and BP compared with a diet rich in SFA or carbohydrate[31].

Similarly, Thomsen *et al.* observed that an olive oil-rich diet (30% of total energy intake from MUFA) administered during 3 weeks significantly reduced systolic and diastolic BP compared with a PUFA-rich diet (27% of total energy intake) in a group of 16 normotensive type 2 diabetics[28]. This same group reported a beneficial effect of an olive oil-enriched diet compared with a high-carbohydrate diet[26]. Another study in 47 healthy normotensive volunteers showed a reduction of BP after a diet with a high amount of MUFA, from olive oil, compared with a diet rich in SFA. However, in this case, the MUFA diet did not perform better than a high-carbohydrate diet[25]. In women with gestational diabetes, MUFA (from high-oleic sunflower oil) intake prevented the BP increase in the third trimester of pregnancy compared with a diet rich in carbohydrates[34].

Ferrara *et al.* reported that a diet rich in extra virgin olive oil was associated with a reduced need for antihypertensive medication compared with a diet enriched in sunflower oil[32]. In this randomised cross-over trial, 23 hypertensive patients were assigned to each diet over periods of 6 months. Compared with the sunflower oil diet, the olive oil diet reduced significantly both systolic and diastolic BP (−8 mmHg and −6 mmHg, respectively). Daily drug dosage was significantly reduced during

Table 3 Feeding trials assessing the effect of monounsaturated fatty acids intake on blood pressure

Study	Participants	Design	Intervention	Main results
Mensink *et al.*[25]	47 healthy individuals (age range 18–59 years)	Randomised parallel trial	8-week OO-enriched diet vs. CHO diet	Both interventions decreased SBP and DBP significantly, but there were no differences between them
Rasmussen *et al.*[26]	16 type 2 diabetics (mean age 57 years)	Randomised cross-over trial	3-week intervention with 3-week wash-out period, MUFA diet (OO) vs. CHO diet	SBP and DBP significantly lower after MUFA diet than CHO diet
Passfall *et al.*[27]	10 hypertensive individuals (age range 40–61 years)	Double-blind randomised cross-over trial	6-week intervention with 4-week wash-out period, supplementation with OO (9 g) vs. fish oil (9 g)	DBP decreased after fish oil but not after OO. SBP without changes
Thomsen *et al.*[28]	16 type 2 diabetics (mean age 59 years)	Randomised cross-over trial	3-week intervention with 3-week wash-out period, MUFA diet (OO) vs. PUFA diet (grape-seed oil & margarine)	SBP and DBP were lower after MUFA diet than after PUFA diet
Ruiz-Gutiérrez *et al.*[29]	16 hypertensive women, (mean age 56 years)	Randomised parallel trial	4-week intervention with 4-week wash-out period, MUFA from VOO vs. MUFA from HOSO	Significant decrease in SBP and DBP after OO but not after HOSO
Lahoz *et al.*[30]	42 healthy individuals (age range 17–71 years)	Non-randomised cross-over trial	5-week intervention without wash-out period, SFA diet vs. MUFA diet (from OO) vs. *n*–3 PUFA diet vs. *n*–6 PUFA diet	SBP higher in SFA diet, no differences between MUFA and PUFA diets
Salas *et al.*[31]	41 healthy men (mean age 21 years)	Non-randomised cross-over trial	4-week intervention without wash-out period, SFA diet vs. MUFA diet (OO) vs. CHO diet	SBP and DBP higher during CHO diet than during MUFA or SFA diet
Ferrara *et al.*[32]	23 hypertensive individuals (age range 25–70 years)	Double-blind randomised cross-over trial	6-month intervention, VOO diet vs. SO diet	SBP and DBP lower after VOO than after SO. Reduced need for antihypertensive drugs after VOO
Appel *et al.*[33]	164 pre-hypertensives and hypertensives (older than 30 years)	Randomised cross-over trial	CHO-rich diet (similar to the DASH trial) vs. protein-rich diet vs. MUFA-rich diet	SBP and DBP lower after MUFA-rich diet compared with CHO diet, without differences between protein and MUFA diets
Lauszus *et al.*[34]	27 women with gestational diabetes (mean age 30 years)	Randomised parallel trial	Last 7 weeks of pregnancy, MUFA diet (from HOSO) vs. CHO diet	Higher increase of BP in the CHO diet than in the MUFA diet
Perona *et al.*[35]	31 hypertensive and 31 normotensive individuals (mean age 84 years)	Randomised cross-over trial	4-week intervention with 4-week wash-out period, VOO diet vs. SO diet	Normalisation of SBP after VOO in hypertensive individuals. No effect on DBP

OO – olive oil; CHO – carbohydrate; MUFA – monounsaturated fatty acids; PUFA – polyunsaturated fatty acids; VOO – virgin olive oil; HOSO – high-oleic-acid sunflower oil; SFA – saturated fatty acids; SO — sunflower oil; DASH – Dietary Approaches to Stop Hypertension; SBP – systolic blood pressure; DBP – diastolic blood pressure; BP – blood pressure.
None of the studies was sponsored directly by the olive oil industry. Lahoz *et al.*[30] and Salas *et al.*[31] received the oils from different companies.

the olive oil diet but not with the sunflower oil diet (approximately 50% vs. 4% reduction). This study suggests that olive oil can be used as a non-pharmacological approach in the treatment of HT.

More recently, the OmniHeart cross-over randomised trial compared the effect of three different diets on BP, a CHO-rich DASH (Dietary Approaches to Stop Hypertension) diet, a protein-rich diet and a MUFA-rich diet, in a group of 164 adults older than 30 years with pre-hypertension or stage 1 HT. After 6 weeks, the protein- and MUFA-rich diets produced higher reductions in BP than the CHO diet. However, there were no differences between the MUFA- and protein-rich diets[33].

It has been hypothesised that the effect of olive oil on BP is not only mediated through its MUFA content. Other compounds, such as the polyphenols present in virgin olive oil, can have a favourable effect. To assess this hypothesis, some studies have compared the effect of olive oil and high-oleic-acid sunflower oil on BP, both with a similar content in MUFA. Ruiz-Gutiérrez *et al*. reported a reduction in both systolic and diastolic BP after an olive oil-rich diet but not after a high-oleic-acid sunflower oil diet[29].

Not all studies have shown a beneficial effect on BP from MUFA or olive oil intake. For example, Perona *et al*. showed that a diet enriched with 60 g of virgin olive oil, compared with 60 g of sunflower oil, daily for 4 weeks, reduced systolic but not diastolic BP in a group of 31 hypertensives, with no effect on 31 normotensive individuals[35]. In the same way, fish oil but not olive oil was effective in the reduction of diastolic BP in a cross-over study on 10 hypertensive subjects (9 g fish oil or 9 g olive oil daily for 6 weeks)[27]. Another study conducted in 44 male mild hypertensives showed that systolic BP during psychophysiological stress was significantly lower after a diet enriched in sunflower oil (60 ml daily for 2 weeks), but not after olive oil or linseed oil supplementation (same amount for the same time)[37].

Canola oil is also rich in MUFA. Some animal studies have assessed its effect on BP. In general, the results do not show an important beneficial effect of this vegetable oil on BP[38,39]. On the contrary, rats fed diets rich in canola oil lived a shorter time than rats fed with PUFA-enriched diets[40,41]. To our knowledge, the only feeding trial conducted in human subjects did not find any significant effect for a diet enriched with canola oil on BP compared with a diet enriched with sunflower oil[42]. Similarly, with the exception of the studies that have used high-oleic-acid sunflower oil, there is no evidence in humans that MUFA-rich oils other than olive oil have a favourable impact on BP.

We can summarise this evidence as follows: although there are some inconsistencies, MUFA from vegetable sources, especially from olive oil in the context of Mediterranean diets, can be beneficial in the management of HT and probably may play a role in the primary prevention of this disorder.

Physiological mechanisms

The mechanisms through which MUFA and olive oil could modify BP levels are not completely clear. In the first place, although the number of studies is scarce, it seems that a high MUFA intake modifies membrane phospholipids in a way[43,44] that can, in turn, alter BP regulation and lead to lower levels of BP[29]. In fact, a recent study has shown that a molecule derived from oleic acid, 2-hydroxyoleic acid, has an impressive antihypertensive effect[45]. The authors of this study observed that the effect could be mediated through the modification of membrane proteins.

Results from the Pizarra Study[46] have suggested another explanation for the possible beneficial effect of MUFA on BP. In this study, the amount of polar compounds in cooking oil, resulting from the degradation of vegetable oils during the cooking process, was directly associated with BP levels. Interestingly, the utilisation of olive oil as cooking oil reduced the formation of these polar compounds. Moreover, olive oil consumption was directly associated with the MUFA content of plasma phospholipids. This, in turn, was inversely associated with BP levels.

Polyphenols present in olive oil, such as oleuropein, hydroxytyrosol, tyrosol and caffeic acid, have an important antioxidant effect. In rat leucocytes, these molecules have been shown to inhibit leukotriene B4 generation at the 5-lipoxygenase level and to reduce the generation of reactive oxygen species[47] – these later molecules causing endothelial dysfunction, a process that has been implicated in the pathophysiology of HT[48]. Finally, vascular response to a hypertensive stimulus was reduced in rats fed virgin olive oil but not high-oleic-acid sunflower oil, suggesting additional effects of olive oil beyond its MUFA composition[49]. These mechanistic findings of a beneficial effect due to the non-lipidic fraction of olive oil fit well with the epidemiological evidence that supports a major benefit associated not with all MUFA, but specifically with MUFA derived from olive oil (studies conducted in Mediterranean countries) and even more for virgin olive oil, rich in polyphenols.

Finally, several studies have assessed the effect of a MUFA-rich diet on endothelial function, mainly by way of evaluating flow-mediated dilation. Results regarding the acute postprandial effects of these diets have been inconclusive. MUFA intake worsened flow-mediated dilation[50] in some cases, had no effect[51,52] or improved endothelial function[53]. Interestingly, in the only study where MUFA had an acute adverse impact on endothelial function, this harmful effect was cancelled out when olive oil, as the source of MUFA, was consumed with foods (balsamic vinegar and salad), which is the usual way of olive oil consumption in Mediterranean countries[50]. Moreover, in the long term, diets rich in olive oil have shown an improvement in endothelial function compared with a high-carbohydrate diet[54] or a high-linoleic-acid diet[55].

In conclusion, there is laboratory and epidemiological evidence to suggest that MUFA, and particularly olive oil, could be components of a diet with some potential to be recommended for the prevention of HT. The results presented here suggest that adherence by the population at large to a Mediterranean dietary pattern, with an abundant supply of virgin olive oil, might reduce the overall prevalence of HT in Western societies, with important consequences for public health nutrition. None the less, results from prospective studies at a population level and primary prevention trials are needed before we can firmly recommend olive oil in the primary prevention of HT.

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