Olive Oil and Cardiovascular Health

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Abstract: The Mediterranean diet, in which olive oil is the primary source of fat, is associated with a low mortality for cardiovascular disease. Data concerning olive oil consumption and primary end points for cardiovascular disease are scarce. However, a large body of knowledge exists providing evidence of the benefits of olive oil consumption on secondary end points for the disease. Besides the classical benefits on the lipid profile provided by olive oil consumption compared with that of saturated fat, a broad spectrum of benefits on cardiovascular risk factors is now emerging associated with olive oil consumption. We review the state of the art concerning the knowledge of the most important biological and clinical effects related to olive oil and its minor components. The recent advances in human nutrigenomics associated with olive oil consumption will also be assessed. The wide range of benefits associated with olive oil consumption could contribute to explaining the low rate of cardiovascular mortality found in southern European–Mediterranean countries, in comparison with other westernized countries, despite a high prevalence of coronary heart disease risk factors.

Key Words: olive oil, phenolic compounds, monounsaturated, lipids, inflammation, oxidation, hypertension, gene expression

INTRODUCTION

Olive oil is the primary source of fat in the Mediterranean diet. A high degree of adherence to the traditional Mediterranean diet has been associated with a reduced risk of overall and cardiovascular mortality, cancer incidence and mortality, and incidence of Parkinson and Alzheimer disease.\(^1,2\) The most impressive benefits of this diet are, however, related to cardiovascular morbidity and mortality.\(^3\) Despite this, data concerning olive oil consumption and primary end points for cardiovascular disease are scarce. A reduction in the relative risk of having a myocardial infarction was associated to a high exposure to olive oil consumption in a Spanish case-control study.\(^4\) In a Greek cohort study, with a large sample size, the association between the ratio of monounsaturated (MUFA) to saturated (SFA) fatty acids, but not that of specific olive oil consumption, and cardiovascular and overall mortality was significant.\(^5\) However, a large body of knowledge exists providing evidence of the benefits of olive oil consumption on secondary end points for cardiovascular disease.

The beneficial effects of olive oil on cardiovascular risk factors are now recognized, but are often attributed only to the high levels of MUFA present in olive oil.\(^6\) Olive oil, however, is a functional food that, besides having a high-MUFA content, contains other minor components with biological properties.\(^6\) Virgin olive oil (VOO), rich in phenolic compounds, is a natural product obtained directly from the fruit by mechanical procedures. Other natural oils, such as those obtained from the Prunus cerasus pits (sour cherry)\(^7\) or the argan oil,\(^8\) have also been shown to have bioactive properties. Thus, a high oleic acid intake could not be the only responsible factor for the health properties of olive oil. We review the state of the art concerning the knowledge of the most important biological and clinical effects related to the intake of olive oil and its phenolic compounds, as well as the extent to which we possess evidence of their health benefits.

OLIVE OIL COMPONENTS

The major components of olive oil are the fatty acids, of which the MUFA oleic acid represents from 55% to 83% of the total fatty acids, polyunsaturated fatty acids (PUFA) from 4% to 20%, and SFA from 8% to 14%. The minor components of olive oil constitute from 1% to 2% of the total content of an olive oil. They are classified into 2 types: (1) the unsaponifiable fraction that could be extracted with solvents after the saponification of the oil and contains squalene and other triterpenes, sterols, tocopherol, and pigments and (2) the soluble fraction that includes the phenolic compounds.\(^6\)

The content of the minor components of an olive oil varies, depending on the cultivar, climate, ripeness of the olives at harvesting, and the processing system employed to produce the olive oils currently present on the market: extra virgin and virgin, olive oil (UE 1991), or pomace.\(^9\) VOOs are obtained from the olive solely by physical means under conditions that do not alter the oil. Extra virgin olive oils are VOOs with a free acidity, expressed as grams of oleic acid per 100 grams of olive oil, less than 0.8 g of VOO and with an acidity less than or equal to 3.3 (International Olive Oil Council Regulation/T.15/NC.n3.Rev2.Nov24, 2006) (=2 in Europe, European Regulation N. 1513/0) that are submitted to a
LIPIDS AND LIPOPROTEINS

The report of the First International Conference on Olive Oil and Health, held in Jaen, Spain, in 2004 highlighted the benefits of olive oil consumption on the lipid profile. By mixing virgin and refined olive oil, an ordinary olive oil (olive oil, UE 1991) is produced and marketed. After VOO production, the rest of the olive drupe and seed is processed and submitted to a refining process, resulting in pomace olive oil, to which a certain quantity of VOO is added before marketing.

Contradictory results have been the frame of the debate. The fact that increased and prolonged MUFA consumption both within and out of the Mediterranean diet with a sunflower-rich one. Postprandial oxidative stress is linked with postprandial lipemia and hyperglycemia. Contradictory results have been obtained on the in vivo antioxidant effect of phenolic compounds from olive oil in postprandial studies. In olive oil doses where oxidative stress occurs (equal to or greater than 40 mL), the in vivo lipid oxidative damage was inversely modulated in a dose-dependent manner with the phenolic content of the olive oil administered.

Oxidative stress associated with postprandial lipemia also contributes to endothelial dysfunction, which shifts hemostasis to a more thrombogenic state. In this sense, a VOO with a high content of phenolic compounds changes the postprandial hemostatic profile to a less thrombogenic state compared with a low phenolic content olive oil.

Concerning sustained olive oil consumption, controversial results were obtained in the studies performed in 2004. Recent results of the EUROLIVE (The effect of olive oil consumption on oxidative damage in European populations) study have provided definitive evidence of the in vivo antioxidant role of phenolic compounds from olive oil in humans. The EUROLIVE was a large, crossover, multicenter, clinical trial performed in 200 individuals from 5 European countries. Participants were randomly assigned to receive 25 mL/d of 3 similar olive oils, but with differences in their phenolic content, in intervention periods of 3 weeks preceded by 2-week washout periods in which olive oil and olives were avoided. Results of the study showed that all olive oils increased HDL cholesterol and the ratio between reduced and oxidized forms of glutathione and decreased triglycerides, total to HDL cholesterol ratio, and DNA oxidative damage.

Consumption of medium and high phenolic content olive oil decreased the LDL/HDL cholesterol ratio, and the in vivo plasma circulating oxidized LDL, serum uninduced conjugated dienes, and serum hydroxy fatty acids. The increase in HDL cholesterol and the decrease in lipid oxidative damage were observed in a dose-dependent manner of the phenolic content of the olive oil administered.

OXIDATIVE DAMAGE

Oxidized LDL is currently thought to be more damaging to the arterial wall than native LDL due to the ability of oxidized LDL to promote the atherosclerotic process. Elevated concentrations of circulating oxidized LDL are predictors for coronary heart disease development. The MUFA component, the oleic acid, and the phenolic compounds from olive oil have shown in vivo antioxidant activity both in experimental models and in human studies. The fact that phenolic compounds from olive oil are bioavailable in humans, even from low doses [25 mL (22 g)] of olive oil, reinforces their protective role in vivo.

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protective effect of olive oil on DNA oxidation related to its phenolic content.\textsuperscript{34} In a substudy with the Danish participants of the EUROLIVE, no changes on the etheno-DNA adduct formation, a lipid peroxidation–derived DNA damage, were observed among olive oils.\textsuperscript{35} Protective effects of olive oil phenols on in vivo DNA oxidation, measured as 8-oxo-deoxyguanosine in peripheral blood mononuclear cells (PBMCs) and in urine, were found in healthy male subjects in a short-term study in which participants were previously submitted to a very low antioxidant diet.\textsuperscript{36} In postmenopausal women, consumption of high-phenol extra virgin oil reduced the DNA oxidation, measured by the comet assay in peripheral blood lymphocytes, compared with low-phenol olive oil.\textsuperscript{37} Further studies are warranted to investigate the role of phenolic compounds of olive oil on the different biomarkers for DNA oxidation.

INFLAMMATION AND VASCULOPROTECTIVE EFFECTS

Oxidation and inflammation are an intertwined process. Free radicals, besides promoting oxidative damage, activate pro- and anti-inflammatory cytokines. Major and minor olive oil components have been shown to be protective against inflammation and endothelial activation.\textsuperscript{6} In animal models, a diet rich in olive oil suppressed the natural killer cell activity,\textsuperscript{38} and the expression of receptors for interleukin (IL)-2.\textsuperscript{39} In human studies, LDL-induced monocyte adhesion to endothelial cells was lower after MUFA consumption than after that of SFA or PUFA in healthy individuals.\textsuperscript{40} Human LDL enriched in oleic acid promoted less monocyte chemotaxis (52% lower) and reduced monocyte adhesion (77%) compared with linoleic-enriched LDL, when exposed to oxidative stress.\textsuperscript{41} Consumption of an oleic acid–rich diet for 2 months promoted a decrease in the expression of the intracellular adhesion molecule-1 (ICAM-1) in PBMC of healthy subjects.\textsuperscript{42} Inflammatory markers, such as the high-sensitivity C-reactive protein and IL-6, and cell adhesion molecules, such as ICAM-1, have been reported to decrease after both short-term (3 months)\textsuperscript{43} and long-term (2 years)\textsuperscript{44} consumption of olive oil–rich diets, such as the Mediterranean diet. In postprandial studies, however, no differences were obtained in plasma levels of proinflammatory cytokines after the ingestion of different breakfasts rich in olive oil, walnuts, or butter, neither versus the baseline nor among treatments.\textsuperscript{45} Although the protective mechanism of oleic acid–rich diets on inflammation has been attributed to a decrease in the LDL linoleic acid content, oleic acid is not the single responsible factor for the anti-inflammatory properties of olive oil. Olive oil minor components have been shown to have anti-inflammatory, antihypertensive, and antiendothelial activation properties in experimental studies.\textsuperscript{56} The olive oil phenolic compound named oleocanthal has been described as having similar properties to that of the anti-inflammatory molecule ibuprofen.\textsuperscript{47} The bioavailability of oleocanthal in humans from olive oil ingestion remains, however, to be elucidated. Several studies have examined the anti-inflammatory and vasculoprotective effect of olive oil phenolic compounds in humans (Table 1). In these studies, olive oil phenolics have been shown to be effective in reducing the eicosanoid inflammatory mediators derived from arachidonic acid, such as thromboxane B\textsubscript{2} and 6-keto-prostaglandin F\textsubscript{1a},\textsuperscript{48,49} and other inflammatory markers, such as high-sensitivity C-reactive protein or IL-6.\textsuperscript{52} Contradictory results have been obtained concerning the effect of olive oil phenolic compounds on cell adhesion molecules. A decrease of ICAM-1 and vascular cell adhesion molecule-1 serum levels at postprandial state after VOO when compared with refined olive oil ingestion has been reported.\textsuperscript{53} However, no differences in ICAM-1 levels were reported after sustained virgin or refined olive oil consumption.\textsuperscript{52} The anti-inflammatory role of olive oil and its minor compounds is promising, and further human studies are required to obtain full evidence.

Replacement of SFA by MUFA in the diet led to a decrease in blood pressure.\textsuperscript{54} An inverse relationship between arterial blood pressure and olive oil consumption has been reported in a large cross-sectional study.\textsuperscript{55} Data from EUROLIVE study showed a decrease in the systolic blood pressure in northern and central European participants after olive oil ingestion.\textsuperscript{56} Olive oil was more effective in reducing blood pressure, and the antihypertensive treatment, than PUFA-rich diets.\textsuperscript{57,58} VOO, but not high-oleic sunflower oil, reduced blood pressure in hypertensive women,\textsuperscript{59} suggesting a role for the minor olive oil components on blood pressure levels. Phenolic compounds from olive oil have been shown to be able to improve the endothelium-dependent vasodilation at postprandial state.\textsuperscript{50} Also, a decrease in the systolic blood pressure after high-phenolic olive oil consumption, in comparison with low phenolic olive oil, in hypertensive stable patients with coronary heart disease has been reported.\textsuperscript{61}

NUTRIGENOMIC EFFECTS

Besides their role as scavengers of reactive oxygen species and chain-breaking antioxidants, olive oil components can exert their health effects by acting at the genomic level, directly or through a decrease in reactive oxygen species, by modulating the expression of key genes for disease processes. Some of the gene expression–mediated mechanisms underlying the beneficial health effects of particular components of olive oil have been examined in experimental models. In endothelial cell models, oleic acid inhibited the expression of the vascular cell adhesion molecule-1 messenger RNA (mRNA) levels and the nuclear factor \alpha \beta\textsuperscript{52,63} Pomace olive oil, rich in unsaponifiables, upregulated the extracellular nitric oxide synthase expression in spontaneously hypertensive rat aortic rings.\textsuperscript{64} Also, an olive oil enriched with the unsaponifiable fraction upregulated the expression of obesity- and insulin sensitivity–related genes in Apo E–deficient mice.\textsuperscript{65} In agreement with the previously described cyclooxygenase-2 (COX-2) inhibitory activity of oleocanthal,\textsuperscript{47} a reduction in COX-2 expression in cell cultures, via inhibition of p38/cyclic adenosine monophosphate response element–binding protein phosphorylation, by olive oil phenolic compounds has also been reported.\textsuperscript{66} The COX-2-765C allele is associated with a low degree of inflammation in human studies. However, the polymorphism COX-2-765G>C has been reported as not modifying the anti-inflammatory effect of an olive oil–rich Mediterranean diet.\textsuperscript{67} In experimental studies, the antioxidant
In agreement with the previous reports concerning the protective effects of sustained olive oil consumption on lipid and DNA oxidative damage, some related genes such as lipoic acid synthase (LIAS), aldehyde dehydrogenase A1 (ALDH1A1), and genes corresponding to the DNA repair proteins such as the excision repair cross complementation group (ERCC5) and X-ray repair complementing defective repair in Chinese hamster cells 5 (XRCC5) were upregulated. Although further studies are needed, nutrigenomic responses could be key mechanisms to explain the benefits associated with olive oil consumption.

### Comments

On the basis of the information discussed above, olive oil–rich diets can be a useful tool against risk factors for cardiovascular disease. The benefits of olive oil consumption are beyond a mere reduction of the LDL cholesterol. Olive oil–rich diets increased HDL cholesterol and insulin sensitivity and decreased lipid and DNA oxidative damage. Moreover, oxidative lipid damage was inversely related to the phenolic content of the olive oil in a dose-dependent manner. Directly, or through a reduction in the oxidative status, dietary olive oil reduces the inflammatory and thrombogenic status, the endothelial dysfunction, and the blood pressure levels. Olive oil elicits changes in the expression of genes associated with the atherosclerosis process. The wide range of antiatherogenic effects associated with olive oil consumption could contribute

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**TABLE 1. Vasculoprotective and Anti-inflammatory Effects of Olive Oil Phenolic Compounds in Human Studies (Weeks)**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Subjects</th>
<th>Study Design</th>
<th>Intervention</th>
<th>End Points</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruiz-Gutiérrez et al</td>
<td>Hypertensive women (16)</td>
<td>Randomized, crossover, controlled</td>
<td>Virgin versus high-oleic sunflower oil (4 wk ad libitum; washout 4 wk, usual diet)</td>
<td>SBP DBP</td>
<td>Decrease with the phenolic content of the oil</td>
</tr>
<tr>
<td>Oubina et al</td>
<td>Postmenopausal women (12)</td>
<td>2 consecutive periods, no washout</td>
<td>VOO versus oleic acid-rich sunflower oil ad libitum</td>
<td>TXB2 in PRP TXB2 in urine 6-keto-PGF1α Serum TBX2</td>
<td>Lower in VOO No differences No differences Decrease with the phenolic content of the olive oil</td>
</tr>
<tr>
<td>Visioli et al</td>
<td>Hyperlipidemic patients (12 men and 10 women)</td>
<td>Randomized, crossover</td>
<td>Virgin versus refined olive oil (40 mL/d, 7 wk, washout 4 wk with usual diet)</td>
<td>Serum TBX2</td>
<td>Decrease at day 4</td>
</tr>
<tr>
<td>Fitó et al</td>
<td>Hypertensive men with CHD (n = 19)</td>
<td>Randomized, crossover, controlled</td>
<td>Virgin versus refined olive oil (3 wk, raw 50 mL/d; washout, 2 wk; refined olive oil for cooking in all the study)</td>
<td>Serum TBX2</td>
<td>Decrease with the phenolic content of the olive oil</td>
</tr>
<tr>
<td>Lèger et al</td>
<td>Patients with type I diabetes (5)</td>
<td>Linear intervention</td>
<td>Olive mill waste water (HT: 25 mg first day; 12.5 mg/d during 3 d)</td>
<td>Serum TBX2</td>
<td>Decrease at day 4</td>
</tr>
<tr>
<td>Bogani et al</td>
<td>Healthy men (12)</td>
<td>Randomized, crossover, postprandial</td>
<td>Virgin versus refined olive oil (50 mL with potatoes)</td>
<td>Plasma LTBA Plasma TBX2</td>
<td>Decrease with the phenolic content of the olive oil</td>
</tr>
<tr>
<td>Pacheco et al</td>
<td>Healthy (14) and hypertriglyceridemic (14) men</td>
<td>Randomized, crossover, postprandial</td>
<td>Fat meal with virgin versus refined olive oil, after 1 wk of each olive oil (50 mg/m² body surface)</td>
<td>Serum ICAM-1 and VCAM-1 area under curve</td>
<td>Decrease with the phenolic content of the olive oil</td>
</tr>
<tr>
<td>Fitó et al</td>
<td>Men with CHD (n = 28)</td>
<td>Randomized, crossover, controlled</td>
<td>Virgin versus refined olive oil (3 wk, raw 50 mL/d, washout, 2 wk; refined olive oil for cooking during all the study)</td>
<td>hs-CRP IL-6 Serum ICAM-1</td>
<td>Decrease with the phenolic content of the olive oil No changes</td>
</tr>
</tbody>
</table>

CHD, coronary heart disease; hs-CRP, high-sensitivity C-reactive protein; HT, hydroxytyrosol; SBP, systolic blood pressure; TXB2, thromboxane B2; VCAM-1, vascular cell adhesion molecule-1; 6-keto-PGF1α, 6-keto-prostaglandin F1α.

scavenger enzyme transcriptome response has been shown to be upregulated by olive oil phenolic compounds. They activated the mRNA transcription of glutathione-related enzymes in murine J774 A.1 macrophage-like cells. In agreement with this, olive oil feeding increased catalase and glutathione peroxidase expression in the islets of Langerhans in mice.

Few studies have analyzed the in vivo changes in gene expression associated with olive oil consumption in humans. In an ex vivo study, triglyceride-rich lipoproteins isolated from healthy volunteers after ingestion of a meal enriched with refined olive oil promoted a fewer atherogenic gene expression (Table 1).

On the basis of the information discussed above, olive oil–rich diets can be a useful tool against risk factors for cardiovascular disease. The benefits of olive oil consumption are beyond a mere reduction of the LDL cholesterol. Olive oil–rich diets increased HDL cholesterol and insulin sensitivity and decreased lipid and DNA oxidative damage. Moreover, oxidative lipid damage was inversely related to the phenolic content of the olive oil in a dose-dependent manner. Directly, or through a reduction in the oxidative status, dietary olive oil reduces the inflammatory and thrombogenic status, the endothelial dysfunction, and the blood pressure levels. Olive oil elicits changes in the expression of genes associated with the atherosclerosis process. The wide range of antiatherogenic effects associated with olive oil consumption could contribute
to an explanation of the low rate of cardiovascular mortality found in southern European–Mediterranean countries, in comparison with other westernized countries. The mechanisms by which olive oil exerts its beneficial effects merit deeper investigation. Further studies are required to obtain evidence of the benefits of olive oil consumption on primary end points for cardiovascular disease.

ACKNOWLEDGMENT

The CIBEROBN is an initiative of the Instituto de Salud Carlos III, Madrid, Spain.

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