Review

Olive oil in the primary prevention of cardiovascular disease

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Abstract

Ischemic heart disease is the leading cause of mortality worldwide. Many mechanistic reasons support that a high consumption of olive oil may provide a protection against myocardial infarction, the hallmark of ischemic heart disease. International comparisons are also consistent with this hypothesis. Surprisingly, there is not much evidence coming from analytical epidemiological studies about this issue. A case-control study conducted at the University of Navarra (Spain) found a strong inverse association between olive oil consumption and the risk of a first non-fatal myocardial infarction. Subsequently a large cohort in Italy and another case-control study conducted in Greece also found inverse associations. However, no complete consistency exists and further prospective studies and trials are being implemented in order to obtain more complete evidence.

1. Introduction

Globally, noncommunicable diseases will cause over three quarters of all deaths in 2030. The major noncommunicable conditions are cardiovascular diseases. Worldwide deaths from cardiovascular diseases are projected to rise from 17.1 million in 2004 to 23.4 million in 2030 [1]. Ischemic heart disease (IHD) was ranked as the first global cause of death in 2004 and it is unfortunately broadcasted to remain the first cause of death in 2030 [1]. As well as remaining the major cause of death in industrialized countries, the incidence and mortality from IHD are also rapidly growing in less developed countries. Acute myocardial infarction (AMI) constitutes a catastrophic manifestation of IHD and coronary atherosclerosis.

Unacceptable high absolute rates of mortality from AMI still exist in many developed countries. However, a surprisingly low incidence is found in several Southern European countries such as France, Spain, Greece, Italy or Portugal, as compared with Northern European countries or the US. This contrast partially contributes to explain the higher life expectancy in Mediterranean areas. The Mediterranean diet (Med-Diet) has been proposed as the major protective factor responsible for this advantage [2–5] although some inconsistencies still persist [6]. The classical Med-Diet is identified as the traditional dietary pattern found in olive-growing areas such as Crete, Greece, and Southern Italy in the late 1950s and early 1960s [7,8]. One of the most important characteristics of the Med-Diet is the abundant presence of olive oil, which is the characteristic culinary fat in these countries.
Cumulative evidence suggests that olive oil may have a profound influence on health [9,10]. More specifically, recent reviews have summarised the effects of olive oil on cardiovascular risk factors [11,12]. These reviews have emphasized the effects of some components of olive oil other than oleic acid, and are thus challenging the reasoning that olive oil is healthy only because it is a good source of monounsaturated fatty acids (MUFA) [10]. According to its biological effects, a strong protection by olive oil against AMI is expected to be found in analytical epidemiological studies assessing this relationship. Surprisingly, there is not much evidence coming from analytical epidemiological studies and research results with primary end points for cardiovascular disease are still needed [12].

In this paper we review the available evidence on biological mechanisms of olive oil as well as the epidemiological evidence to support a beneficial effect on cardiovascular risk factors. Afterwards, we summarise the state of the art concerning the role that olive oil may have in the primary prevention of cardiovascular disease.

2. Olive oil components and its biological mechanisms

The major components of olive oil represent the glyceride fraction, and oleic acid makes up 68–81.5% of the fatty acids [13]. The minor components are present in about 2% of oil weight and include more than 230 chemical compounds [13]. A group to be highlighted among these minor components are the phenolic compounds which can also be found in different fruits and vegetables. The most abundant lipophilic phenolic compound is α-tocopherol and there are also several hydrophilic phenolic compounds such as oleanuropein and hydroxytyrosol.

Different processing methods produce virgin, refined, and ordinary olive oil [13]. This classification is important to understand the variable composition of olive oil and consequently its potential health benefits. Virgin olive oil is obtained only by mechanical means that do not lead to alterations in the oil. When the acidity of virgin olive oil exceeds 3.0 degrees, this oil is refined with the use of chemical and physical filters. During this process the hydrophilic phenolic compounds are lost; therefore, these compounds are peculiar to virgin olive oil. Numerous studies are centred exclusively in virgin olive oil with the belief that these minor components have a cardiovascular protective effect [12]. An ordinary olive oil is obtained by mixing refined and virgin olive oil.

In comparison to saturated fatty acids, olive oil reduces low-density lipoprotein (LDL) cholesterol, and compared with carbohydrates, it maintains or even increases the levels of high-density lipoprotein (HDL) cholesterol. In addition, it is relatively resistant to oxidation and contains a large amount of antioxidants relative to its polyunsaturated fat content. Some polyphenol constituents of virgin olive oil (hydroxytyrosol and oleanuropein) are potent scavengers of superoxide radicals and inhibit LDL oxidation [14–16]. Moreover, the phenolic compounds can modify the composition of very low-density lipoprotein [17]. Olive oil has induced a reduction of atherosclerosis in animal models and may slow the development of coronary atherosclerosis, being associated with a reduced DNA synthesis in human coronary smooth muscle cells [18]. Olive oil also favourably affects postprandial factor VII activity, avoiding a prolonged thrombotic response to a high-fat diet. A beneficial effect of MUFA on von Willebrand factor, as well as other benefits of olive oil on the haemostatic system have also been suggested [19].

The preservation of the endothelial function is a key mechanism for the prevention of atherosclerosis. The available information about the effects of olive oil on the endothelial function also suggests a benefit. The vascular endothelium plays a key role in local vascular tone regulation and can be modulated by dietary fat. In a randomized trial a MUFA-rich Med-Diet improved the endothelium-dependent vasodilatory response suggesting that a Med-Diet rich in olive oil may be able to avoid the postprandial deterioration of endothelial function [20]. Another trial showed the antithrombotic and anti-inflammatory effect of extra virgin olive oil [21]. This anti-inflammatory activity had been previously supported by the discovery of oleocanthal, an olive oil phenolic compound, which inhibits COX-1 and COX-2 [22].

It is well known that the metabolic syndrome increases the risk of AMI. In a Spanish cohort of university graduates including initially healthy participants, a higher adherence to the classical Med-Diet was found to be associated with a lower risk of developing the metabolic syndrome after 74-month follow-up [23]. In a randomised clinical trial, participants receiving a Med-Diet education showed a reduction in the overall prevalence of the metabolic syndrome compared to participants who had been advised to follow a low-fat diet [24]. This protective outcome may be better explained by the overall effect of the Mediterranean dietary pattern than by the effect of a single component. In diabetic patients, olive oil improved the lipid profile and glycaemic control [25,26]. Moreover, two recent large cohort studies and a clinical trial have reported a strong protection of Med-Diets, rich in olive oil, against type-2 diabetes [27–29]. Another trial found that a Med-Diet delayed the need for antihyperglycemic drug therapy [30].

3. Olive oil and primary prevention of cardiovascular diseases

3.1. Available epidemiological evidence

No primary prevention trial has ever assessed the association between adherence to an olive-oil-rich Med-Diet and the incidence (and not only mortality) of a first IHd event. The pioneering results of the Seven Countries Study showed that coronary heart disease death rates were low in countries where olive oil was the main fat [31]. A very important cohort study found that a Mediterranean food pattern was protective against mortality from IHd [32]. However, they included only fatal IHd cases (54 coronary deaths) as the outcome. Subsequently other studies confirmed the protection of Mediterranean-type diets against overall mortality [33–37]. In any case, mortality from IHd is not only related to its incidence but also to the quality and timeliness of medical care. If the quality of medical care is associated with the adherence to a Med-Diet pattern, the use of mortality as outcome would lead to confounding [6].

A randomized secondary prevention trial conducted in France [38] showed an impressive protection provided by an experimental Mediterranean diet on the risk of death and re-infarction among survivors of a first acute myocardial infarction (AMI). Nevertheless, as the major element of the assigned diet was an experimental canola-oil based margarine and the diet simultaneously included a high intake of alpha-linolenic acid, fruit and vegetables, it was not possible to attribute its benefit to a single factor. In addition, no special consideration was given to olive oil, which is the major source of MUFA in Mediterranean countries. The fat composition of the experimental group in the Lyon Diet Heart Study was 30.5% of energy intake as total fat (12.9% MUFA). These values are far from the characteristic 35–40% total fat and 15–20% MUFA content present in the traditional Med-Diet. Some methodological caveats [39] have been raised on the Lyon Diet Heart Study, including the small number of observed primary events in the experimental and control groups (14 vs. 44).

A few studies have assessed the specific role of olive oil on the risk of clinical coronary events. A protective role for olive oil on mortality among patients with a previous AMI has been reported by the investigators of the large cohort of patients who partici-
pated in a previous trial. This study included 11,246 survivors of a myocardial infarction. Through a brief, non-validated questionnaire, the authors assessed the consumption of five food items, at baseline, and after 6, 18 and 42 months of follow-up. After 6.5-year follow-up the mortality odds ratio (OR) for the categories of olive oil consumption “often” and “regularly” compared with the “never or sometimes” category were 0.77 (95% CI 0.62–0.94) and 0.71 (95% CI 0.60–0.84), respectively [40].

In a recent case-control study (748 cases and 1048 controls) conducted in Greece, a protection was also found for the exclusive use of olive oil (Odds Ratio = 0.53 (95% CI: 0.34–0.71) against acute coronary syndromes [41]. However, the authors grouped the participants in three categories (no use; exclusive use; olive plus other oils or fats), and they apparently did not further quantify the amount of olive oil nor they adjusted for total energy intake.

Nevertheless, conflicting results have been also reported. A Greek case-control study reported no significant association of monounsaturated fatty acid intake with the risk of coronary disease [42]. Specifically for olive oil, a small randomized trial of corn oil and olive oil carried out more than 40 years ago found no benefit for olive oil and even an adverse significant effect for corn oil in 80 coronary patients after 2 years of follow-up [43]. Moreover, two Italian case-control studies did not find any association between olive oil consumption and non-fatal AMI. The first one, a case-control study in Italian women (287 cases/649 controls), reported no significant benefit for oil consumption [44]. The second case-control study (507 cases/478 controls) provided additional data showing no trend in risk with the consumption of olive oil [44,45].

3.2. The case-control study in the University of Navarra

In order to assess the potential role of olive oil for the primary prevention of CHD and to quantify the reduction in the risk of a first AMI that can be provided by a high olive oil intake, a hospital-based case-control study was conducted at the University of Navarra, Spain [46]. The case series was comprised by 171 patients (81% males, age <80 years) who suffered their first acute myocardial infarction. The control series included 171 age-, gender- and hospital-matched controls with a wide variety of conditions believed to be unrelated to diet. A previously validated semi-quantitative food frequency questionnaire (136 items) was used to appraise long-term dietary exposures. The same physician conducted the face-to-face interview for each case patient and his/her matched control. Conditional logistic regression modelling was used to take into account potential dietary and non-dietary confounders. The description of cases and controls is shown in Table 1.

Quintiles of olive oil intake defined according to the distribution among controls were compared regarding several potential nutritional and non-nutritional confounding variables (Tables 2 and 3).

Table 1

<table>
<thead>
<tr>
<th>Agea (years, mean)</th>
<th>Cases (n = 171)</th>
<th>Controls (n = 171)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40</td>
<td>6.48</td>
<td>6.49</td>
</tr>
<tr>
<td>40–64</td>
<td>6.53</td>
<td>6.60</td>
</tr>
<tr>
<td>≥65</td>
<td>6.65</td>
<td>6.63</td>
</tr>
</tbody>
</table>

Table 2

Distribution of potential non-nutritional confounding variables across quintiles of energy-adjusted olive oil intake among control subjects (n = 171).

<table>
<thead>
<tr>
<th>Quintiles of energy-adjusted olive oil intake</th>
<th>1</th>
<th>2–4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy adjusted olive-oil (g/day, mean)</td>
<td>3.6</td>
<td>22.5</td>
<td>54.1</td>
</tr>
<tr>
<td>Body mass index (kg/m², mean)</td>
<td>26.8</td>
<td>27.3</td>
<td>27.8</td>
</tr>
<tr>
<td>% white collar</td>
<td>18</td>
<td>28</td>
<td>24</td>
</tr>
<tr>
<td>% educational level higher than primary</td>
<td>18</td>
<td>30</td>
<td>21</td>
</tr>
<tr>
<td>% married</td>
<td>56</td>
<td>80</td>
<td>85</td>
</tr>
<tr>
<td>% smokers</td>
<td>18</td>
<td>21</td>
<td>35</td>
</tr>
<tr>
<td>% high blood cholesterol</td>
<td>15</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>% high blood pressure</td>
<td>29</td>
<td>33</td>
<td>21</td>
</tr>
<tr>
<td>% diabetes</td>
<td>6</td>
<td>5</td>
<td>18</td>
</tr>
<tr>
<td>Leisure-time physical activity (METSc-h/week, mean)</td>
<td>30.5</td>
<td>36.3</td>
<td>33.8</td>
</tr>
</tbody>
</table>

* Metabolic equivalents.

of olive oil in order to obtain a better protection. This possibility of IHD may think that they should increase their consumption. Furthermore, it is likely that subjects who perceive themselves at higher risk of coronary disease. Interestingly, a previous diagnosis of angina pectoris, a previous history of IHD or other prior diagnosis of major cardiovascular disease were exclusion criteria in this case-control study. This is important because an inverse association between olive oil and IHD has long been suggested. This belief is also held by the general public in Mediterranean countries. There-fore, recall bias does not seem to be a likely alternative explana-tion of the discordant findings between the case-control study conduced in Navarra [46] and other two case-control studies conducted in Italy [44,45], which did not find any significant association. Recall bias is a potential concern when the case-control design is used. But differential over-reporting would be more probable to exist among cases than among controls because cases are more likely to be aware of the role of nutrition as a determinant of IHD. Therefore, recall bias does not seem to be a likely alternative explanation of the findings of the Navarra case-control study. Moreover, when the assessment of exposure was done through different items in a comprehensive questionnaire, it would be more difficult that patients might consistently underestimate their exposure to olive oil. Although the in-hospital selection of controls facilitates a higher participation, it also imposes some caution in the interpretation of findings because the exposure may be related to the diseases caus-ing the hospital admission of controls. However, olive oil has not been found to induce the most frequent diseases usually present in the control series: any trauma or genitourinary disease or any com-

### 3.3. Limitations and inconsistencies in case-control studies: the need for further evidence

The results found in the case-control study conducted in Navarra suggest that olive oil consumption may substantially reduce the risk of coronary disease. Interestingly, a previous diagnosis of angina pectoris, a previous history of IHD or other prior diagnosis of major cardiovascular disease were exclusion criteria in this case-control study. This is important because an inverse association between olive oil and IHD has long been suggested. This belief is also held by the general public in Mediterranean countries. Therefore, it is likely that subjects who perceive themselves at higher risk of IHD may think that they should increase their consumption of olive oil in order to obtain a better protection. This possibility would introduce a selection bias in the case series. This could be a plausible explanation of the discordant findings between the case-control study conducted in Navarra [46] and other two case-control studies conducted in Italy [44,45], which did not find any significant association.

### Table 3

Distribution of potential nutritional confounding variables across quintiles of energy-adjusted olive oil intake among control subjects ($n = 171$).

<table>
<thead>
<tr>
<th>Quintiles of energy-adjusted olive oil intake</th>
<th>1</th>
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<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy adjusted olive-oil (g/day, mean)</td>
<td>3.6</td>
<td>22.5</td>
<td>54.1</td>
</tr>
<tr>
<td>Total energy intake (kcal/day, mean)</td>
<td>2882</td>
<td>2417</td>
<td>2778</td>
</tr>
<tr>
<td>Ethanol intake (g/day, mean)</td>
<td>16</td>
<td>16</td>
<td>27</td>
</tr>
<tr>
<td>% energy from fat (mean)</td>
<td>29</td>
<td>31</td>
<td>36</td>
</tr>
<tr>
<td>% energy from saturated fat (mean)</td>
<td>11</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>% energy from monounsaturated fat (mean)</td>
<td>12</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td>MUFA/SFA intake (mean)</td>
<td>1.18</td>
<td>1.59</td>
<td>2.02</td>
</tr>
<tr>
<td>% energy from trans-fatty acids (mean)</td>
<td>0.23</td>
<td>0.19</td>
<td>0.14</td>
</tr>
<tr>
<td>Glycaemic load (g/day, mean)</td>
<td>235</td>
<td>231</td>
<td>207</td>
</tr>
<tr>
<td>Total fibre intake (g/day, mean)</td>
<td>38</td>
<td>30</td>
<td>29</td>
</tr>
<tr>
<td>Folic acid intake (mcg/day, mean)</td>
<td>513</td>
<td>409</td>
<td>395</td>
</tr>
<tr>
<td>Vitamin B6 intake (mcg/day, mean)</td>
<td>3.3</td>
<td>2.6</td>
<td>2.5</td>
</tr>
<tr>
<td>Vitamin C intake (mg/day, mean)</td>
<td>320</td>
<td>262</td>
<td>233</td>
</tr>
<tr>
<td>Vitamin E intake (mg/day, mean)</td>
<td>8.7</td>
<td>7.4</td>
<td>7.5</td>
</tr>
</tbody>
</table>

### Table 4

Odds ratio (OR) (95% CI) of a first myocardial infarction according to olive oil intake (unadjusted for total energy intake).

<table>
<thead>
<tr>
<th>Quintiles of olive oil intake</th>
<th>p for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls/case (n)</td>
<td>32/36</td>
</tr>
<tr>
<td>Median intake (g/day)</td>
<td>7.2</td>
</tr>
<tr>
<td>Multivariate adjusted ORb (95% CI)</td>
<td>1 (Ref.)</td>
</tr>
<tr>
<td>Multivariate adjusted ORc (95% CI)</td>
<td>1 (Ref.)</td>
</tr>
</tbody>
</table>

### Table 5

Odds ratio (OR) (95% CI) of a first myocardial infarction according to energy-adjusted olive oil intake.

<table>
<thead>
<tr>
<th>Quintiles of energy adjusted olive oil intake</th>
<th>p for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls/case (n)</td>
<td>28/40</td>
</tr>
<tr>
<td>Median intake (g/day)</td>
<td>6.1</td>
</tr>
<tr>
<td>Multivariate adjusted ORb (95% CI)</td>
<td>1 (Ref.)</td>
</tr>
<tr>
<td>Multivariate adjusted ORc (95% CI)</td>
<td>1 (Ref.)</td>
</tr>
</tbody>
</table>

### Notes

1. Monounsaturated fatty acids/saturated fatty acids.
2. Multivariately adjusted for % energy derived from saturated fat, % energy derived from trans-fat, total fibre intake, folic acid intake, vitamin C intake, glycaemic load and ethanol intake (adding a quadratic term to account for non-linearity).
3. Additionally adjusted for % energy derived from saturated fat, % energy derived from trans fat, total fibre consumption, folic acid intake, vitamin C intake, glycaemic load and ethanol intake (adding a quadratic term to account for non-linearity).
4. Olive oil and cardiovascular health promotion

The development of new therapeutics and patient care strategies in the last twenty years have substantially reduced the morbidity and mortality related to AMI. However, the so-called cardiovascular disease (CVD) paradox shows that the prevalence of CVD is increasing despite a reduction in age-related CVD deaths [54]. The consequence of this trend will be a growing economic burden because of the increasing number of surviving patients and the expensive new technologies and treatments. The solution proposed to face this growing problem is the promotion of cardiovascular health and the primary prevention of CVD. Therefore, the implementation of preventive actions at the population level still remains a big as well as unmet challenge.

Among other cost-effective interventions, a good strategy has to do with the use of the Mediterranean diet as a nutrition education and health promotion tool [55]. In spite of its relatively high-fat content, there is an important advantage of the Med-Diet pattern in the promotion of vegetable consumption, because fat-free or low-fat dressings make vegetables much less palatable than the use of olive oil. The sautéing or stir-frying of vegetables with olive oil instead of dressings make vegetables much less palatable than the use of olive oil. The sautéing or stir-frying of vegetables with olive oil instead of

an individual’s overall food pattern [52]. Moreover, a prospective cohort study found that the intake of olive oil is associated with other healthy aspects of the diets as well as with higher educational levels [57]. Olive oil availability has experimented a significant increase during the last 40 years not only in Mediterranean regions but also in several non-Mediterranean countries, especially in Northern Europe [58]. At the same time, an undesirable departure from the traditional Med-Diet has been reported to have occurred in Southern European countries [59]. We hope that the expected results from prospective studies will reinforce the cardiovascular healthy consequences that an increased use of olive oil and Med-Diet pattern may have at the population level.

Contributors

Conception and design: Miguel Ruiz-Canela and Miguel A. Martínez-González; Financial support: Miguel A. Martínez-González; Data analysis and interpretation: Miguel A. Martínez-González; Manuscript writing: Miguel Ruiz-Canela and Miguel A. Martínez-González; Final approval of manuscript: Miguel Ruiz-Canela and Miguel A. Martínez-González.

Competing interest

There is no conflict of interest. There is no financial arrangement with any food company. All funding has been provided by the Spanish Ministry of Health and the Navarra Regional Government.

Provenance and peer review

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