Nutritional and health aspects of olive oil

This review describes the types of lipids in human diets and their possible implications for health and disease. The high oleate and significant linoleate contents of olive oil are important for nutrition; moreover, when olive oil is used for deep-fat frying, as in a typical “Mediterranean Diet”, then many of its desirable properties are retained and there is much less deterioration than for some other cooking oils. The health-promoting effects of olive oil have been cited anecdotally for many years. However, as highlighted in this review, the scientific basis for these effects is still unclear. In this review, particular attention is paid to obesity, cardiovascular disease, cancer and inflammatory diseases. There is good evidence that olive oil is protective in cardiovascular diseases. Its mechanism of action may involve effects on blood lipids, but other mechanisms, including effects on immune function, endothelial function and the coagulation pathways remain possible and are discussed. The effects of olive oil in obesity and cancer are less clear. Finally, many questions still remain about the potential health effects of the many non-lipid components of olive oil.

Keywords: Olive oil, monounsaturated fat, cardiovascular disease, cancer, health.

1 Olive oil as a source of dietary fat

1.1 Introduction

In recent years the general public has been much more conscious of the importance of dietary components (both beneficial and harmful) for general health. Within these components, fats have figured quite prominently - not least because of the increasing problems with obesity in many countries, particularly Western, is a particular example. Dietary advice often begins with the exhortation to reduce the total amount of fat consumed and to replace saturated with polyunsaturated fat. Such advice is given because in reducing fat intake it is expected that people will put on less weight and because of the widespread belief that polyunsaturated-rich margarines which are marketed as ‘healthy for your heart’ contain just as much fat as butter, or indeed, which foods contain high or low levels of fat. There is also a tendency to categorise a given fat as ‘good’ (e.g. polyunsaturates) or ‘bad’ (e.g. cholesterol) as well as to simplify a situation, such as grouping all saturated fats as equivalent. Similar misconceptions apply when people refer to the “Mediterranean Diet” as though there were just one.

The term “Mediterranean diet” reflects food patterns which have evolved around the Mediterranean Sea, where adult life expectancy is among the highest in the world and the rates of chronic disease (including coronary heart disease and some cancers) are among the lowest [2]. In fact there are many variants of the Mediterranean diet of which two are well recognised. The Italian variant is relatively low in total fat, with a moderate intake of olive oil, fruit and vegetables and a high intake of cereals, while the Greek variant is higher in total fat intake, but lower in cereal intake [2]. Whether these two variants are equivalent in terms of their health-promoting qualities is not clear, but a great deal of importance has been placed on the fact that olive oil, containing a high proportion of monounsaturated fat, is the principal source of cooking fat in these regions. A number of potential reasons have been put forward to explain why olive oil might be preferable over animal fats, some other plant-derived oils and, perhaps, even excessive amounts of dietary carbohydrates [2]; these will be explored in sections 2 and 3 of this review.

1.2 Lipids in foods

When considering the effect of olive oil as a component of an individual’s diet, one has also to take account of other constituents, especially the fats. The lipid in most human diets consists of a mixture of animal and plant fats. The overall composition will depend on the proportions of the latter and also on the exact nature of the fat. Some examples are given in Tab. 1.
As a generalisation, meats contain more stearate and arachidonate than other sources with arachidonate, having putative important nutritional consequences. Fish flesh is usually poor in fat (exceptions are the ‘oily’ fish such as sardines or herrings) but they and the storage (liver) oils are highly enriched in very long chain polyunsaturated fatty acids of the \( \text{n-3} \) family. Of these, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are the main constituents. Plant leaves contain structural lipids which are highly enriched in \( \alpha \)-linolenate but because of their low fat content and poor digestibility do not usually supply much total fat in the diet. On the other hand, plant oils are used widely for frying, as cooking ingredients and as spreads. With the exception of coconut and palm oils or cocoa butter, plant edible fats tend to be highly unsaturated. However, the main unsaturated fatty acids contained in a given plant oil can vary widely. Olive oil is the most highly enriched in oleic acid (hence, the latter’s name!) which varies from about 55-83% [3] depending on the cultivar and growing conditions. While the use of olive oil in Northern Europe may be limited, this region has seen increased production and use of cheap and easy-to-produce monounsaturated oils, such as rape-seed oil, which contains approximately 50% oleic acid. It is not known whether this monounsaturated oil shares the apparent health-promoting properties of olive oil.

1.3 Lipid modification in processing or use

In the context of general aspects of fats in the diet, a few brief words should be stated about possible modifications that can occur to oils after they have been obtained from the natural source. There are two types of modification that can occur – deliberate (during processing) or coincidental (during storage or cooking). Deliberate changes, which can be made, include catalytic hydrogenation to convert oils into lower melting spreads, interesterification (to modify the fatty acid content) and fractionation. During catalytic hydrogenation there are three main changes which can take place. The total number of double bonds in the fatty acid molecules are reduced, which is the desired aim. However, other changes include isomerisation of cis double bonds to the trans configuration and movement of double bonds to produce a series of positional isomers. These structural changes may have nutritional significance (see later). Interesterification and trans-esterification are used to change the physical properties of a lipid or to produce a modified lipid with particular characteristics (as in cocoa butter substitutes). There is some evidence that interesterification can change the way in which a fat is metabolised [4], although it is thought that such changes are relatively minor. As an alternative, the original oil can be fractionated by various physical methods to yield a series of products that will have different fatty acid compositions. This can be used to produce, for example, low cholesterol products from animal fats or spreadable fats from palm oil.

The main changes, which can occur to oils or fats subsequent to processing, involve various oxidative reactions. In the case of olive oil, the stages of pressing and malaxation allow broken tissue cells from the fruit to interact with the olive oil. Thus, degradative enzymes (acyl hydrolases) release fatty acids which are subjected to lipoxidation and further metabolism by the lipoxygenase pathway (see Sanchez and Harwood, pp. 564–573) to produce im-

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**Tab. 1. The different fatty acid patterns of various foods.**

<table>
<thead>
<tr>
<th>Fatty acid [% total]</th>
<th>C16:0</th>
<th>C18:0</th>
<th>C18:1</th>
<th>C18:2</th>
<th>C18:3</th>
<th>C20:4</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beef muscle</td>
<td>16</td>
<td>11</td>
<td>20</td>
<td>26</td>
<td>1</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>Chicken muscle</td>
<td>23</td>
<td>12</td>
<td>33</td>
<td>18</td>
<td>1</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Chicken egg yolk</td>
<td>29</td>
<td>9</td>
<td>43</td>
<td>11</td>
<td></td>
<td></td>
<td>8</td>
</tr>
<tr>
<td>Salmon fillet</td>
<td>11</td>
<td>4</td>
<td>25</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>45†</td>
</tr>
<tr>
<td>Cod liver</td>
<td>19</td>
<td>5</td>
<td>15</td>
<td>2</td>
<td></td>
<td></td>
<td>59†</td>
</tr>
<tr>
<td>Green leaves</td>
<td>13</td>
<td>1</td>
<td>7</td>
<td>16</td>
<td>56</td>
<td></td>
<td>7</td>
</tr>
<tr>
<td>Coconut oil</td>
<td>9</td>
<td>2</td>
<td>7</td>
<td>2</td>
<td></td>
<td></td>
<td>80‡</td>
</tr>
<tr>
<td>Palm oil</td>
<td>42</td>
<td>4</td>
<td>43</td>
<td>8</td>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Rapeseed oil</td>
<td>4</td>
<td>1</td>
<td>54</td>
<td>23</td>
<td>10</td>
<td></td>
<td>8</td>
</tr>
<tr>
<td>Soya oil</td>
<td>10</td>
<td>4</td>
<td>25</td>
<td>52</td>
<td>7</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Olive oil</td>
<td>12</td>
<td>2</td>
<td>72</td>
<td>11</td>
<td>1</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Butter</td>
<td>26</td>
<td>11</td>
<td>28</td>
<td>2</td>
<td>trace</td>
<td></td>
<td>33§</td>
</tr>
<tr>
<td>Monounsaturated margarine</td>
<td>12</td>
<td>6</td>
<td>58</td>
<td>21</td>
<td>1</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Polyunsaturated margarine</td>
<td>11</td>
<td>9</td>
<td>18</td>
<td>53</td>
<td>1</td>
<td></td>
<td>8</td>
</tr>
</tbody>
</table>

† High amounts of eicosapentaenoic (C20:5) and docosahexaenoic acids (C22:6)
‡ High amounts of short- and medium-chain saturated acids (C8:0, C10:0, C12:0, C14:0)
§ Short and medium-chain saturated acids (C4:0-C14:0).
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[6]. Two points that contribute to this are the short time nised to preserve a large part of the nutrient value of food – mainly deep-fat frying. The latter method is now recog-

ture is that about half of the total fat comes from cooking still, by far, the most important. A second interesting fea-
ture can be reduced by the presence of anti-oxidants which may be natural (such as tocopherols in olive oil) or synthetic (e.g. butylated hydroxytoluene). Lipid peroxida-
tion, if unchecked, will not only reduce the content of es-
sential fatty acids and vitamins but can give rise to prod-

ucts carrying serious health risks, such as in cancer or ar-
teriovascular disease. The peroxidation reactions apply to sterols as well as unsaturated fatty acids and there has been quite a deal of work on, for example, the harmful ef-

fects of oxidised cholesterol derivatives. Again tocoph-
erols and other vitamin E compounds have a potent protective effect here (see [5]).

As mentioned above the Mediterranean Diet has two main aspects with regard to lipids. First, olive oil is the major edible lipid used – currently representing about 2/3rds of the total. Thus, although other oils are increas-

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though the food is immersed in oil, the final lipid content of the food is not significantly different from other methods of cooking although there is some enrichment of lean foods and exchange of fat with fatty foods [7].

The above factors generally represent good aspects of the use of olive oil. However, deep-fat frying means that the cooking oil will be used repeatedly. The useful life of an oil depends on its type but olive oil is much more sta-

ble than polyunsaturated fatty acid (PUFA)-rich oils [8]. In part, this stability is a reflection of the anti-oxidants (e.g. tocopherols, oleuropein) which it contains [9]. To an ex-

tent the life of an oil also depends on the use to which it has been put because, as mentioned above, exchange of food lipid with the cooking oil takes place. Thus, if used for cooking meat, the olive oil will become enriched with satu-
rated fatty acids whereas cooking fish will reduce its re-

usability because the enrichment with PUFAs renders the oil less thermostable. On the other hand the exchange of meat fat with the cooking oil enriches the former’s olate content and lowers its saturation index – desirable as-

pects with regard to arteriovascular disease.

As cooking oils are re-used, degradation products including polymeric and oxidised triacylglycerols are produced. The first substances formed are cyclic monomers of triacylglyc-
erols, which later polymerise. Provided that the oils are not re-used excessively then the polymeric material is insuffi-

cient to change the normal properties of the oil, nor is it di-
gested and absorbed.

The principal degradative aspects of storage or cooking involve oxidation of fats, especially in the presence of trace metals. Reactive oxygen radicals attack double bonds of unsaturated fatty acids with the initial formation of a lipid peroxide. The susceptibility to oxidation is very much increased by polyunsaturation so that the mono-

enoic-enriched olive oil is less prone to this type of attack than, say, soya bean or maize oils. Moreover, peroxida-
tion can be reduced by the presence of anti-oxidants which may be natural (such as tocopherols in olive oil) or synthetic (e.g. butylated hydroxytoluene). Lipid peroxida-
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erols, which later polymerise. Provided that the oils are not re-used excessively then the polymeric material does not significantly reduce the functional properties of the oil, nor is it digested or absorbed [4]. However, in many cases large amounts of degradation can be detected – more than 25% – especially for oils used to fry fish [10].

Because of the possibility of peroxidation of PUFAs, in particular, other cooking oils are often much less stable than olive oil. Olive oil not only benefits from its high monounsaturated and low PUFA contents but also from its natural anti-oxidants. This is clearly shown in Tab. 3, where there are obvious differences between sunflower (up to 74% linoleate) and olive oil. Thus, not only were the total degradative products higher in sunflower, but poly-

merisation and oxidation of triacylglycerols were en-

hanced also. In comparison, olive oil showed more hy-

drolysis to non-esterified fatty acids and diacylglycerols.

1.4 Digestion and absorption

A good general description of fat digestion and absorption in the human is given in [4]. Typically, 90-95% of dietary

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**Tab. 2.** Comparison of consumption trends in fat consumption in Spain with the composition of Spanish olive oil.

<table>
<thead>
<tr>
<th>Year</th>
<th>Consumption [% total FA]</th>
<th>Olive oil (average value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total saturates</td>
<td>13.6</td>
<td>30.0</td>
</tr>
<tr>
<td>Monounsaturates</td>
<td>68.7</td>
<td>55.7</td>
</tr>
<tr>
<td>Total PUFAs</td>
<td>17.7</td>
<td>14.3</td>
</tr>
</tbody>
</table>
Fat is in the form of triacylglycerols with small contributions from phosphoglycerides, glycolipids and sterols. The triacylglycerols must be partially hydrolysed before they can be absorbed. About 25% of the hydrolysis is catalysed by gastric lipase while enzymes secreted by the pancreas degrade the remaining fat. In general, hydrolysis goes as far as 2-monoacylglycerol which is readily absorbed. Efficient digestion and absorption does, however, depend not only on adequate lipase activity but also on bile salts secreted from the liver which solubilise the fatty material.

Phosphoglycerides are similarly partially catabolised to monoacyl-derivatives (by the action of pancreatic phospholipase A2). A major source of phosphoglycerides for digestion are brush-border cells which are continually lost from the intestinal epithelial layer. Steryl esters are hydrolysed to free sterols. The absorption of cholesterol thus released can be reduced by the presence of plant sterols and this forms a basis for some so-called “cholesterol-lowering” formulae which have been developed recently. Once fatty acids, sterols and other partial hydrolysis products have been absorbed, the majority are packaged for export in the various serum lipoproteins in enterocytes. For a general description of the intracellular phase of fat absorption, see [4].

1.5 Transport of lipid in the body

Lipoproteins are the major form of lipid transported in the bloodstream. They consist of a core of triacylglycerol (TAG) and/or cholesteryl esters with an outer surface of phospholipid and free cholesterol as well as a protein component, conferring solubility, specificity and regulation of metabolism. Chylomicrons (CM) and very low-density lipoproteins (VLDL) carry TAG, which can be used as fuel by a number of tissues through the action of lipoprotein lipase. CM function to transport lipids of dietary origin, secreted by the intestine, whereas VLDL transport lipid of endogenous origin, secreted by the liver. Hydrolysis of TAG in VLDL converts the particle to a low-density lipoprotein (LDL), so that LDL is a breakdown product of VLDL. The role of LDL is to transport cholesterol to tissues where it may be required for membrane structure or conversion into metabolites such as steroid hormones. LDL are therefore the major carriers of cholesterol in man. High-density lipoproteins (HDL) are also cholesterol carriers, but their role is to bring about the removal of cholesterol from tissues and to transport it to the liver for excretion – a process termed reverse cholesterol transport. Plasma levels of LDL are positively associated with coronary heart disease, while levels of HDL are inversely associated [10]. Importantly, blood cholesterol levels are not simply determined by dietary cholesterol, but also by dietary fat intake, with saturated fats having a greater effect than unsaturated fats, according to the Keys equation [10]. Thus, different classes of dietary fat may affect risk of heart disease indirectly through effects on blood lipid levels; this will be explored in more detail in section 3.1.

Tab 3. Comparison of the degradation products in sunflower or olive cooking oils, discarded after repeated use. Data taken from reference [7], means ± S.D. shown.

<table>
<thead>
<tr>
<th>Total degradation products [%]</th>
<th>Olive oil</th>
<th>Sunflower oil</th>
</tr>
</thead>
<tbody>
<tr>
<td>[% of degradative products]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triacylglycerol dimers</td>
<td>20.1 ± 8.4</td>
<td>31.7 ± 4.8</td>
</tr>
<tr>
<td>Triacylglycerol polymers</td>
<td>3.9 ± 1.9</td>
<td>8.8 ± 8.3</td>
</tr>
<tr>
<td>Oxidised triacylglycerols</td>
<td>29.8 ± 6.6</td>
<td>36.8 ± 8.9</td>
</tr>
<tr>
<td>Diacylglycerols</td>
<td>33.5 ± 11.8</td>
<td>16.8 ± 4.0</td>
</tr>
<tr>
<td>Fatty acids plus unsaponifiable</td>
<td>11.0 ± 5.8</td>
<td>5.9 ± 1.8</td>
</tr>
</tbody>
</table>

Olive oil Sunflower oil

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Tab 4. Roles of dietary lipids and implications for health.

<table>
<thead>
<tr>
<th>Quantitative aspects</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calories</td>
<td>Obesity</td>
</tr>
<tr>
<td>Digestibility</td>
<td>Diabetes, heart disease, sprue</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Qualitative aspects</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamins</td>
<td>Vitamin-deficiency</td>
</tr>
<tr>
<td>Cholesterol, sterols</td>
<td>Arterio-vascular disease</td>
</tr>
<tr>
<td>Fatty acid quality (sats., monoenes, PUFAs)</td>
<td>EFA deficiency, cancer</td>
</tr>
<tr>
<td>trans-fatty acids</td>
<td>Arterio-vascular disease, inflammation</td>
</tr>
<tr>
<td>Conjugated fatty acids</td>
<td>Unknown/controversial</td>
</tr>
<tr>
<td>Others</td>
<td>Not established (? Beneficial)</td>
</tr>
<tr>
<td></td>
<td>Specific effects for unusual components e.g. cyclopropene acids can cause ‘pink-white disease’</td>
</tr>
</tbody>
</table>
2 Nutritional aspects of lipids

There are both quantitative and qualitative aspects of dietary lipids. Both of these are pertinent to human health and disease. A summary of the overall implications for health is shown in Tab. 4.

2.1 Palatability

Fats contribute to palatability in two ways. First, by responses to their texture in the mouth (‘mouth feel’) and second by olfactory responses. The latter are a combination of taste in the mouth and aroma or odour in the nose, which together are normally referred to as flavour. Fat is itself not only a source of taste and aroma but will affect the perception of these from other sources because it affects their distribution between different (water, lipid, vapour) phases. Many flavour components are produced by lipolysis or oxidation, particularly of unsaturated fatty acids. For more details of these aspects see [4].

The palatability of food is also affected by the total amount of fat in the diet. To some extent the amount of fat that can be tolerated in food is a matter of habit - for example, Eskimos can tolerate amounts of fat (up to 80% total energy) which would nauseate most Europeans. Moreover, tolerance to high fat diets is greatest in adult life and is much less in the young and elderly. Present dietary advice is to reduce total calories from fat to 20-35% of total [12], depending on the country, of which not more than 10% energy should be from saturates, 3-10% from polyunsaturated acids and >10% from monounsaturates.

2.2 Essential fatty acids

There are two classes of EFAs for humans. From plants, the usual sources of these are α-linolenate (an n-3 PUFA) and linoleate (an n-6 PUFA), respectively. EFA are needed both as membrane components and as precursors of biologically active signalling molecules, especially the eicosanoids. Some of the most obvious signs of EFA deficiency involve epithelial cells and the skin. Both can become permeable to water and dermatosis is obvious.

Because the C18, linoleic and α-linolenic acids have to be further metabolised to produce the immediate precursors of eicosanoids (which are C20 or C22 acids), essential fatty acid deficiency can be diagnosed metabolically. Thus, in the absence of adequate supplies of n-3 and n-6 PUFAs, the desaturases and elongases normally involved in EFA metabolism, convert oleic acid into an unusual product, all- cis-5,8,11-eicosatrienoic acid (C20:3 n-9) (Fig. 1). This is often referred to as the “Mead acid” after James Mead who was the first to realise its significance. Since that time the ratio of Mead acid to arachidonate in serum is often used as a measure of EFA deficiency. In health the ratio of C20:3n-9 to C20:4n-6 is 0.1 or less. A ratio of 0.4 has usually been taken as indicating EFA deficiency although some authors have recently said that a ratio of 0.2 might be more prudent to use [4]. The advantage of using the serum ratio of C20:3n-9/C20:4n-6 is that it is sensitive and it can also be detected before overt EFA deficiency signs are apparent [4].

The recognition that lipids were essential for good health was made in 1929 [13] when symptoms produced by a fat-free diet were cured with fats containing n-6 PUFA. However, it was not until the 80s that it was realised that n-3 PUFA were also needed. Since that time it has been realised that not all the requirements for PUFA can be explained because they are precursors for eicosanoids (see below), although that is clearly a major function. Because of various roles for EFA that may be unconnected with eicosanoid biosynthesis, advice on the desirable amounts of such fatty acids in the diet has been subject to considerable debate and is still not resolved. It is generally thought that very small quantities are required purely to prevent EFA deficiency. However, what are the desirable levels of such acids in the diet? In the past, 1-3% of total energy as PUFA has been thought advisable, with the

Fig. 1. Principal metabolic pathways for desaturation and elongation of 'parent acids' to long-chain PUFAs of the n-9, n-6 and n-3 families. (Taken from reference [4] with permission of the authors and Blackwells).

A minor family n-7 (whose 'parent' acid is palmitoleic acid, 9c-C16:1) has been omitted for simplicity. As far as we know it has little nutritional significance. The figure aims to illustrate the sequence of alternate desaturations and elongations of the parent acids in each family and the competition between families for the Δ5- and Δ6-desaturases. For example, it should be readily apparent how the Mead acid accumulates in preference to arachidonic acid when there is a dietary deficiency of C18:2n-6 and an excess of C18:1n-9. An important continuation of the n-3 pathway via further elongation to C22 and further metabolism to form docosahexaenoic acid (DHA, C22:6n-3) has also been omitted.
higher figure applying, for example, in pregnancy where there are extra requirements [4]. However, as pointed out above, latest advice in different countries varies from 3-10% of total energy as PUFA [12]. Finally, it has been recognised recently that the ratio of n-3/n-6 PUFA is important for optimal health and that this may be too high in current Western diets.

2.3 Major roles of dietary fatty acids

Fatty acids fulfil three major roles in the body, which can be classified as structural, storage and metabolic functions. Triacylglycerols provide a major source of metabolic energy particularly in affluent countries. At present 35-45% of dietary energy in industrialised countries comes from triacylglycerols. Most common food fats are well digested and there is little difference although there are some particular differences [4]. The major components of olive oil (palmitate, olate, linoleate) are all well absorbed. Most of the energy production from fats comes by β-oxidation in the peroxisomes and mitochondria. Although, in healthy individuals most fats can be readily utilised, those with particular digestive problems may use tailor-made products such as medium-chain triacylglycerols, which can be directly taken up into the hepatic portal circulation.

Fatty acids are components of phospholipids in the lipid bilayer of cell membranes and as such play an important structural role in maintaining cell integrity. Furthermore, the degree of unsaturation of cell membranes regulates their fluidity and can influence the behaviour of membrane proteins. During times of tissue development and growth there may be special requirements for dietary fats. Such situations would be represented by foetal or child growth [14] and brain development [15, 16]. In the latter case, in particular, there is increasing evidence that the supply of arachidonic acid (AA) and docosahexaenoic acid (DHA) is critical. Brain development continues after birth and, because of the high amounts of very long chain PUFAs in brain tissue there is increasing evidence that such acids are desirable in the diet – hence the addition of n-3 PUFA to some infant formulae.

Arachidonic acid is the major precursor for a group of lipid-derived mediators collectively termed eicosanoids (illustrated in Fig. 2). It is generally agreed that a fatty acid precursor has to be released from membrane lipids as a first step. Clearly, the role of phospholipase \( A_2 \) is very important here. Once released, the fatty acid can be oxidised via a cyclooxygenase, a lipoxygenase or a cytochrome P-450 system to produce, ultimately, various biologically active products. The products of cyclooxygenase activity (viz. prostaglandins, thromboxanes, prosta-

**Fig. 2.** The arachidonic acid cascade to produce different types of eicosanoids and other signalling molecules.
functions is beyond the scope of this review but the reader should consult [4] and references therein for more details. The effects of oleic acid on eicosanoid metabolism are less clear. The metabolism of n-9 fatty acids does not give rise to eicosanoid precursors, but whether they have any effects on the synthesis of eicosanoids from other precursors is not known.

3 Olive oil in health and disease

3.1 Obesity

The adipose tissues of the body act as protective layers and can supply a ready source of metabolic energy during times of fasting or starvation. The tissue also has other more specialised functions such as the production and secretion of steroid hormones. However, with affluence there is often a tendency to consume more food than is needed and the excess energy is stored in adipose tissues where their normal function of accumulating triacylglycerol can be seen as a handicap. Increases in adipose tissue beyond normal (modest) requirement are associated statistically with reduced life expectancy, increased susceptibility to diabetes, cardiovascular diseases, some types of cancer and many other aspects of poor health [1].

The most commonly used measure of obesity is the body mass index (BMI). It is calculated by dividing body weight (in kg) by the square of height (in m). BMI values for good health are thought to be 20-25 while 25-30 is considered overweight and >30 obese. The % of individuals in the last two categories for both sexes in a country such as the U.S.A. is noticeable and this impacts on the nation’s health budget to a significant extent [19].

Although avoidance of obesity is simple in scientific terms, in practice social activity and psychological factors make it more difficult. Satiation is important and, of the major nutrients, protein has the greatest satiating effect and fat the least [20]. Moreover, obese individuals seem to have a greater preference for fatty rather than lean foods [21]. These factors can lead to the consumption of increased amounts of energy-rich edible fats. Moreover, fat stores increase more if energy is supplied as dietary fat rather than carbohydrate [1]. Hence, in laboratory experiments lean men made large fat gains when the diet provided 60% energy as fat, little change at 40% and lost stored fat when dietary fat was 20% of energy [22]. Such studies have contributed to dietary advice [12] for fat to represent about 30% of total calories.

Although obesity is generally associated with poor health, the actual distribution of fat is also important. A proportional increase in upper body fat is associated with a much higher incidence of several diseases including coronary heart disease and the risk of developing diabetes [4]. This is related to both the differences in metabolic activity in adipocytes isolated from different depots as well as with disturbances to normal dietary fat and serum lipoprotein metabolism.

Very little is known about the influence of the Mediterranean Diet on obesity. It is uncertain whether a diet containing >35% of energy as fat, predominantly as olive oil, promotes obesity in a sedentary population any more than a diet with an equivalent amount of energy, but a lower fat content [23]. It is clear, however, that some features of the Mediterranean Diet are gradually being lost or altered [24]. Not only are the contributions of food groups being altered [24], but populations are participating in significantly less physical activity than in the 1960s [2] and the importance of this additional lifestyle factor should not
be overlooked. While the impact of olive oil consumption on obesity is not well understood, it is possible that migration from Mediterranean regions may increase the prevalence of obesity, heart disease and cancer; a study comparing the dietary and health status of elderly migrant Greeks living in Melbourne (Australia) with their rural Greek controls demonstrated lower intakes of cereals and olive oil in the migrant Greeks, as well as a higher prevalence of obesity and abdominal fatness [29].

3.2 Cardiovascular disease

Atherosclerosis is a predominant cause of morbidity in middle-aged and elderly individuals in western societies and manifests itself in the form of lesions consisting of lipids, cells and extracellular matrix on the inner surface of the larger arteries. The “response to injury” hypothesis describes injury to the arterial endothelium as the first stage in the process, this being initiated by a number of potential factors, including hypercholesterolaemia, mechanical stress, high blood pressure, smoking etc. As a result of the injury, endothelial cells produce chemotactic factors and express adhesion molecules, which together encourage the transgression of monocytes from the circulation into the subendothelial areas of the intima, where they differentiate into macrophages. Modified LDL is taken up by macrophages, endothelial cells and smooth muscle cells within the arterial intima, creating a fatty streak. The build-up of lipid, cells and matrix over time produces an atherosclerotic plaque, which contains a lipid core and is separated from the circulation by a fibrous cap. It is thought that the plaque environment is highly pro-inflammatory and thrombogenic, with macrophages secreting cytokines, tissue factor and matrix-degrading enzymes. Some of these factors result in proliferation of smooth muscle cells, causing thickening of the vessel walls and loss of elasticity. Some factors may destabilize the fibrous cap, allowing the exposure of the thrombogenic contents of the lesion to the powerful coagulation system in the circulation. Platelet aggregation and thrombosis results, which can occlude the artery and lead to a potentially fatal event, a myocardial infarction in the case of a coronary thrombosis or stroke in the case of a thrombosis in the carotid arteries.

There are a number of pre-disposing factors for atherosclerosis, some of which are non-modifiable (e.g. genetic, age, sex) and others, which are modifiable (e.g. smoking, hypertension, diabetes, obesity, plasma lipids, plasma fibrinogen). Modifiable risk factors can be influenced by drugs, diet or both. The influence of diet, and in particular, dietary fat, has attracted considerable attention. There is a simplistic public (mis)conception that dietary cholesterol and saturated fats are ‘bad’ while polyunsaturated lipids are ‘good’. The perceived link between cholesterol and coronary heart disease led to considerable expenditure of money on huge epidemiological trials to show that lowering dietary saturated fat and cholesterol would lead to a lowering of blood cholesterol and, hence, to a lowering of cardiovascular disease. A superb review by Gurr [27] summarises the mis-guided nature of much of this work. Put simply, cardiovascular disease is much more closely linked to high LDL-cholesterol and low HDL-cholesterol than to total serum cholesterol [4]. Moreover, the method of controlling serum cholesterol levels through the sterol regulatory element binding protein (SREBP) system means that, under normal circumstances, dietary cholesterol plays a small role in influencing serum cholesterol levels. Nevertheless, dieticians still advocate low cholesterol diets and plant sterols (which reduce cholesterol absorption) are being used in spreads. Olive oil contains small amounts of such sterols (about 2g/kg), as well as cholesterol (around 5% total sterols) but it seems unlikely that these are sufficient to affect cholesterol uptake from the intestine.

There are a number of mechanisms by which dietary fat composition can potentially influence atherosclerosis. First, since serum lipids and lipoproteins provide the source of the lipid material in plaques, they provide a direct link between diet and atherosclerosis. Moreover, the intake of different classes of fat affects plasma cholesterol levels, with saturated fats raising blood cholesterol levels. Second, the eicosanoids derived from EFAs play a significant role in the clotting process and alteration of the type of dietary fat could therefore influence the likelihood or extent of thrombosis. Third, atherosclerosis has a strong inflammatory component and it is possible that dietary fatty acids may exert their influence through effects on the inflammatory response, either as eicosanoid precursors, or through alternative pathways.

The Seven Countries Study, conducted by Ancel Keys, was a landmark study, which showed clearly that the type of fat, rather than the level of fat, was related to risk of coronary heart disease (CHD). It demonstrated that Mediterranean countries with relatively high intakes of total fats (~35% energy) had lower rates of CHD and this was strongly correlated with a low intake of saturated fatty acids [11]. Not all Mediterranean countries have low rates of CHD; a notable exception is Malta, where there is a strong influence of British dietary habits and the incidence of CHD is equivalent to that in the United Kingdom [28]. More recently, the Lyon Diet Heart Study, a secondary prevention trial investigating the effects of a Cretan-style Mediterranean diet on recurrence after a first myocardial infarction, confirmed the protective effect of the diet on infarction [29]. The protective effects were ascribed to higher intakes of oleic acid and α-linolenic acid.
and lower intakes of saturated fatty acids and linoleic acid [29].

It is thought that differences in saturated fat intake explain two-thirds of the differences in median plasma cholesterol concentration between countries in the Seven Countries Study [30]. Thus the consensus view is that it is desirable to decrease the intake of saturated fats to below 10% of energy intake [31], although it should be noted that not all of the saturated fatty acids have the same effects [32]. However, the question of what should replace saturated fats has been disputed. Low-fat, high-carbohydrate diets do not appear to be very effective in lowering plasma lipids and have been reported to decrease HDL-cholesterol levels, which is undesirable [33, 34]. High intakes of carbohydrate also result in increased postprandial insulin output and hyperglycaemia [35]. A second alternative is to replace saturated fats with $n$-6 PUFA, a concept which has been widely advocated during the last few decades. This strategy lowers LDL-cholesterol levels, which lowers risk of CHD [32]. Intakes of linoleic acid up to 12% of dietary energy do not affect HDL-cholesterol [36]. However, higher levels of $n$-6 PUFA lower HDL-cholesterol, which is undesirable [37]. Furthermore, $n$-6 PUFA-rich oils are susceptible to oxidation, which may have negative consequences, including the increased oxidation of LDL and its uptake into lesions. Some studies have also suggested that high intakes of linoleic acid increase the incidence of gallstones [38]. Several studies have shown that MUFA are as effective at lowering total cholesterol and LDL-cholesterol as $n$-6 PUFA when they replace saturated fats. Katan et al [32] have predicted changes in LDL- and HDL-cholesterol as a result of replacement of all of the fat in an average Dutch diet by a particular fat or oil. These calculations are illustrated in Fig. 4, which shows MUFA and $n$-6 PUFA-rich oils to decrease both LDL- and HDL-cholesterol. However, the effects of MUFA on HDL-cholesterol are disputed, since some studies demonstrate that MUFA-rich diets reduce LDL-cholesterol without affecting the cardioprotective HDL-cholesterol fraction [39, 40]. This is also supported by two meta-analyses, which showed that replacement of saturated fat with MUFA decreases total and LDL-cholesterol, but has no effect on HDL-cholesterol [36, 41]. Furthermore, since MUFA-containing oils are more stable and less susceptible to oxidation than those containing $n$-6 PUFA, they have emerged as the fat of choice in terms of replacing saturated fats. It has also been suggested that a MUFA-rich diet promotes the rapid absorption of dietary triacylglycerol, resulting in larger postprandial CM, which may have lower atherogenicity due to their efficient hydrolysis and removal from the circulation [39]; this remains to be proven.

### 3.3 Inflammation

As described above, the inflammatory response is an inherent part of the development and progression of atherosclerosis and a number of studies have suggested that the effects of olive oil on inflammation and immune function may also play a role in the protection against coronary heart disease. There is substantial evidence from animal studies that MUFA-rich oils influence immune function; effects observed include suppression of lymphocyte proliferation, natural killer cell activity, expression of adhesion molecules and in vivo graft versus host responses (see [43] for review). Very few studies have been carried out in humans, but available data suggest that in contrast to animal studies, consumption of a MUFA-rich diet by humans does not bring about a general suppression of immune cell functions, yet it does decrease the ex-
pression of adhesion molecules on peripheral blood mononuclear cells (PBMC) and may, therefore, have specific anti-inflammatory effects [44]. The effects of MUFA on inflammation in humans may be clinically important since a small number of studies have suggested that there may be beneficial effects of olive oil consumption on inflammatory diseases, such as rheumatoid arthritis [45, 46].

Several studies have examined the effects of dietary olive oil or in vitro addition of oleic acid on cellular processes directly related to atherogenesis or thrombosis. An olive oil-rich diet consumed for five weeks was demonstrated to increase the resistance of LDL to oxidation and to decrease LDL-induced adhesion of monocytes to endothelial cells [47, 48]. Dietary studies in humans have also shown that when exposed to oxidative stress, LDL enriched in oleic acid promotes less monocyte chemotaxis compared with LDL enriched with linoleic acid [48]. Animal studies suggest that an olive oil-rich diet may decrease the expression of scavenger receptors on macrophages, reducing the extent of foam cell formation [49]. Recent research suggests that the anti-inflammatory effects of olive oil may extend to modulation of endothelial function. Perez-Jimenez et al. [50] demonstrated that a MUFA-rich diet decreased plasma levels of plasminogen activator inhibitor type 1 (PAI-1; the main inhibitor of fibrinolysis), von Willebrand factor, E-selectin and thrombomodulin. Furthermore in vitro studies using human umbilical vein endothelial cells have demonstrated suppression of adhesion molecule expression by oleic acid [51, 52]. Effects of olive oil on aspects of the coagulation cascade have also been explored; Roche et al. [39] reported a reduction in factor VII activation as a result of isoenergetic substitution of MUFA for SFA.

It is unclear whether the effects of olive oil on immune function are due to its fatty acid composition (i.e. its high oleic acid content) or to non-lipid components of olive oil or both. There is increasing interest in the effects of plant-derived phenolic compounds on immune function and inflammation, including many of the compounds which give olive oil its characteristic flavour, aroma and colour. There is evidence that at least some of the effects of olive oil on immune function in animal studies are due to oleic acid rather than trace elements or antioxidants, since an animal study has demonstrated similar effects of olive oil and a high-oleic sunflower oil on a range of immune responses [53]. However, there is also some evidence that non-lipid components of olive oil have effects on LDL oxidation and immune function. Since olive oil-derived phenolics are essentially hydrophilic, they are abundant in olive oil waste waters (concentration about ten times higher than in the oil phase), which are generated during olive oil production and discarded. Visioli et al., have demonstrated that olive mill waste water extracts are able to inhibit human LDL oxidation and to scavenge superoxide anions and hypochlorous acid at concentrations of 20 ppm [54]. In addition, two of the three extracts used inhibited the production of leukotrienes by human neutrophils [54]. In fact, a number of phenolic compounds are antioxidants and possess lipooxygenase and cyclooxygenase inhibitory activity [55], which could explain their reported pain relief and antipyretic effects, such as in the treatment of inflamed joints, treatment of insect bites and stings and in oral surgery [56]. However, some of the effects of these components are suggested to be due to antioxidant-independent mechanisms, such as direct effects on gene and protein expression [57, 58]. Most of the studies investigating mechanisms of the effects of phenolic compounds on immune function have used quercetin as the test compound; some have extended their studies to other fruit and vegetable-derived flavonoids, but very few have tested the effects of olive oil-derived phenolic compounds; there is clearly great scope for more work in this area.

### 3.4 Cancer

There is a large body of evidence for a role of dietary lipids in different cancers. However, for many of the epidemiological studies the results are unconvincing or conflicting (see [4] and references therein). A fairly strong link was, however, found between obesity (particular central fat deposition) and the risk of both endometrial and breast cancers in post-menopausal women. It has therefore been suggested that one way in which dietary fat intake may affect breast cancer risk in post-menopausal women is by its influence on body fat mass, since adipose tissue is the primary source of circulating oestrogen in this group [58]. A review by Guthrie and Carroll [5] distinguishes indirect effects of dietary fat (such as above) from direct effects.

For many years, animal studies have consistently shown that n-6 PUFA enhance tumour growth and that n-3 PUFA suppress tumour growth [59]. This tumour-enhancing effect of linoleic acid has been partly attributed to PGE2 production. Numerous studies have demonstrated that the levels of prostaglandins are greater in various cancers, including breast cancer, than in normal tissues (see [60]). Epidemiological studies have shown that the use of aspirin or other nonsteroidal anti-inflammatory drugs (inhibitors of prostaglandin synthesis) can reduce the risk of breast cancer (see [60]) and tend to decrease tumour growth in animal models (although the effects are varied and complicated and not all studies agree [59]). Given the wide range of known functions of PGE2, it is likely that it will play a multifunctional and complex role in carcinogenesis, perhaps controlling growth, metastasis and host immune responses, not necessarily in combination or
through the same mechanism. Thus, while there is potential for modulation of some aspects of carcinogenesis by dietary fatty acids, the evidence for an effect is still weak.

There has been significant interest in the effect of consumption of olive oil on breast cancer incidence. Some studies report an inverse association, particularly in postmenopausal women. However, the World Cancer Research Fund Report [61], which reviewed all of the evidence for effects of MUFA on cancer, concluded that an association was unlikely; certainly the evidence is not as strong as for a positive association between total fat intake or saturated fat intake and cancer incidence. Nevertheless, a study documenting patterns of fat consumption and trends in mortality from breast, colorectal and ovarian cancer in a number of northern and southern European countries suggests that a decrease in the consumption of key components of the Mediterranean Diet has led to increased incidence of and mortality from ovarian and colorectal cancers and, to a lesser extent, breast cancer [24].

Of course, the key components of the Mediterranean Diet include an abundance of fruits and vegetables. Case-control and cohort studies present convincing evidence that diets rich in fruits and vegetables protect against several common cancers [62, 63]. These foods are rich in antioxidants, such as the natural compounds tocopherols or lycopene (the red carotenoid pigment of tomatoes), which have been linked to protection against certain cancers. Although it can be reasoned, that such compounds reduce lipid peroxidation and hence free radical production to initiate cancer, evidence is not unequivocal. Thus, in one study of β-carotene supplementation there was an increased mortality from lung cancer (in patients already at high risk) [4]. Nevertheless, if anti-oxidants are useful, then the significant tocopherol and phenolic content of olive oil [3] may be pertinent.

4 Concluding remarks

In recent years there have been other aspects to olive oil use which may well benefit the consumer. Olive oil is unique amongst major oils in that it is extracted by pressing rather than by solvent extraction. This has beneficial consequences for its flavour because it allows partly water-soluble materials to be included in the oil. Moreover, in recent years low water extraction systems have been used during malaxation and centrifugation. Although originally designed to minimise waste water, the low water methods have the added benefit that anti-oxidant (tocopherols, phenols) contents are increased with consequent advantages to the stability and flavour of olive oil. Thus, the latest technology has resulted in some improvements to the quality of the most ancient of all edible oils.

The health-promoting effects of olive oil have been cited anecdotally for many years. However, as highlighted in this review, the scientific basis for these effects is still unclear. There is good evidence that olive oil is protective in cardiovascular diseases. Its mechanism of action may involve effects on blood lipids, but other mechanisms, including effects on immune function, endothelial function and the coagulation pathways remain possible and are being actively researched. The effects of olive oil consumption on the incidence of and mortality from cancer are not clear. Finally, many questions still remain about the potential health effects of the many non-lipid components of olive oil.

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