Metabolic Syndrome

Chapter 1

Dietary Lipids Linking Postprandial Metabolism and Metabolic Syndrome

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Abstract

The current pandemic of obesity, metabolic syndrome, and type 2 diabetes is intimately associated with an atherogenic dyslipidemic phenotype. The core components of the dyslipidemia of the metabolic syndrome, which most likely initiate atherosclerosis, are the “lipid triad” of high plasma triglycerides, low levels of high-density lipoproteins, and a preponderance of small, dense low-density lipoproteins at fasting. However, postprandial (non-fasting) TG (postprandial hyperlipidemia) are also recognized as an important component for atherosclerosis. Olive oil is the primary source of fat in the Mediterranean diet, which is associated with a significant improvement in health status, as measured by reduced mortality from several chronic diseases. Herein, the purpose of this book chapter was to provide an update on effects and mechanisms related to the olive oil on postprandial metabolism and its implications for the onset and progression of metabolic syndrome.

Keywords: Olive oil; Postprandial metabolism; Hyperlipidemia; Metabolic syndrome; Lipoproteins

1. Dietary Fatty Acids in Mediterranean Diet

Olive oil plays a pivotal role as the main source of fat in the Mediterranean diet. This diet that has traditionally been linked to longevity in Mediterranean populations and is associated
with a significant improvement in health status, as measured by reduced mortality from several chronic diseases [1]. Virgin olive oils are those obtained from the mesocarp of the drupe from the fruit of the olive tree (Olea europaea L.) [2]. Extra virgin olive oil is a virgin olive oil whose free acidity, expressed as oleic acid, is not more than 0.8 gram per 100 grams and organoleptic characteristics (flavour and colour) are excellent (for olive oil classification and definitions see Ref. [3]). The composition of virgin olive oil includes minor compounds (unsaponifiable fraction) that could range from one to 3% of the oil [4]. The constituents of minor compounds are present in low concentrations but they are responsible for the unique and delicate flavour of virgin olive oil (aldehydes, alcohols, esters, hydrocarbons, ketones, furans, and others). This fraction contains important bioactive compounds.

Fatty acids (FAs) are carboxylic acids and often contain a long, unbranched aliphatic chain. FAs are categorized as saturated (SFAs), MUFAs, and polyunsaturated (PUFAs) based on their structural and chemical properties. SFAs do not contain any double bonds or other functional groups along the chain, which is fully saturated with hydrogen atoms. The principal dietary SFAs are palmitic (16:0) and stearic (18:0) acids, which are composed of 16 and 18 carbon atoms, respectively. MUFAs contain one pair of carbon atoms linked by a cis double bond. Oleic acid (18:1n−9), which contains 18 carbon atoms with a double bond at the 9th carbon from the methyl end of the FA molecule, is the major dietary MUFA and represents 55 to 83% of the total FAs in virgin olive oil (Table 1). Carbon chains containing 2 or more cis double bonds, with the first double bond located between either the 3rd and 4th or the 6th and 7th carbon atoms from the methyl end of the FA molecule, belong to the n−3 or n−6, respectively, PUFA families. These families cannot be synthesized by the human body (double bonds can be introduced into all positions of the FA chain with the exception of the n−3 and n−6 positions) and therefore must be obtained from the diet as α-linolenic acid (18:3n−3) and linoleic acid (18:2n−6) or their long-chain PUFA derivatives. Of these FAs, eicosapentaenoic acid (EPA, 20:5n−3), docosahexaenoic acid (DHA, 22:6n−3), dihomo-γ-linolenic acid (20:3n−6), and arachidonic acid (AA, 20:4n−6) are the most metabolically significant [5]. The concentrations of SFAs (palmitic + stearic acids) and PUFAs (α-linolenic + linoleic acids) in virgin olive oil range from 8 to 26% and from 3 to 22% of the total FAs, respectively.

Oleic acid is the primary component of virgin olive oil (≈83% oleic acid in position sn−2 of the triglycerides, TGs) and is also found in peanut oil (≈59% oleic acid) and canola oil (≈37% oleic acid). Oleic acid is a key component of TGs and membrane lipids [6]. Importantly, oleic acid is the most common FA in nature, as well as in our diet (generally, oleic acid supplies an amount of calories equivalent or greater than the amount provided by SFAs and PUFAs combined). Tight restrictions on SFA consumption (<10% of total daily calories; less than 7% for high-risk individuals) and PUFA consumption (<5%) have been recommended. By contrast, oleic acid may provide up to 20–25% of total daily calories.
The unsaponifiable fraction of virgin olive oil contains highly bioactive compounds (>200 constituents) (Table 2). Despite their wide variety and nutritional significance, they commonly account up to 3% of the total oil composition (reaching individual concentrations as smaller as ppm) [7].

Among the several minor compounds of virgin olive oil, the most abundant fraction is hydrocarbons (squalene and, in smaller amounts, the carotenoids β-carotene and lutein). Other minor compounds of virgin olive oil include phytosterols, such as β-sitosterol, Δ5-avenasterol, and campesterol; triterpenic compounds in the form of dialcohols (erythrodiol and uvaol) or acids (oleanolic and maslinic acids); and phenolic compounds, representing the polar fraction [5].

2. Digestion of Triglycerides of Dietary Lipids and Absorption of Fatty Acids

In general, the first event in the transformation of insoluble oil into soluble and absorbable lipids is the formation of an initial emulsion (chyme) by mastication in the mouth where the dispersion of triglycerides (TGs) happens. The surface area of TGs is then increased, which benefits their emulsion (formation of lipid droplets) in the stomach. During the initial gastric process, partially emulsified TGs are attached by lingual and gastric lipases [8]. Gastric lipase activity does not contribute to the hydrolysis of phospholipids (PLs) and cholesteryl esters (CEs), and is functional in the pH range of 3 to 6. In the stomach, this enzyme hydrolysates only 10 to 30% of ingested TGs because of an inhibition process induced by the long-chain free FAs (FFAs) generated, which are mostly protonated at gastric pH. It explains the limited lipolysis of TGs under gastric conditions regarding the complete TGs hydrolysis by pancreatic lipase in the duodenum [9,10]. Absorption of lipid moleculestakes place along the epithelial cells of the small intestine, mainly in the proximal jejunum but also in parts that are more distal. Short-chain (2-4 carbon atoms) and medium-chain (6-12 carbon atoms) FAs are more rapidly absorbed than FAs of more than 14 carbon atoms, because they do not need micellar solubilisation, just bound to albumin and are transported directly to the liver by the portal vein [11].

3. Assembly of Intestinal Lipoproteins Containing Triglycerides from Dietary Lipid Ingestion

In the enterocyte, FFAs from absorption and the pool of endogenous metabolismare used for re-synthesis of TGs. This process is initiated with the activation of FFAs to the corresponding acyl-CoA by acyltransferases. These enzymes form a complex called “triglyceride synthetase” [12]. It contributes to 80% of the intestinal TG re-synthesis in the fed state. The composition of these novel TGs closely resembles the composition of TGs from diet [13]. These TGs are coated with cholesterol, PLs, and one molecule of apolipoprotein (apo) B48 at the rough and smooth endoplasmic reticulum in a microsomal TG transfer protein (MTP)-dependent step [14], and
further processed in the Golgi apparatus before being released as chylomicrons (CMs) by the enterocyte through exocytosis. It occurs through the basolateral membrane of enterocytes and CMs enter the lymphatic capillaries of intestinal microvilli that drain into lymphatic channels, reaching the systemic circulation through the thoracic duct [15]. The body can also secrete very low-density lipoproteins (VLDLs). While CMs are of intestinal origin and formed after the ingestion of fatty meals, VLDLs are the major lipoproteins secreted by the liver during fasting [16]. Both CMs and VLDLs are considered TG-rich lipoproteins (TRLs).

4. Postprandial Metabolism

Postprandial hyperlipemia is a normal and transient physiological phenomenon that occurs in response to the ingestion of a fatty meal. Dietary lipids are absorbed as described above and intestinally secreted TRLs have the function to stabilize the absorbed dietary lipids for transport in the aqueous plasma environment and to provide cells with exogenous FAs by receptor (e.g., apoB48 receptor, LDL receptor, and LDL receptor-related protein) or non-receptor-dependent mechanisms for energy and numerous metabolic pathways [17]. In healthy people, the levels of plasma TGs usually peak 3-4 h after a fat meal and tend to return to baseline within 6-8 h. However, postprandial hyperlipemia can become pathological when magnitude and duration of TRL response is exacerbated, resulting in the accumulation of postprandial TRLs and their remnants in the circulation. In that cases, the postprandial hyperlipemic peak may be two to three-fold higher than normal and prolonged, even up to 10-12 h after the dietary fat ingestion [18].

5. Postprandial Metabolism and Metabolic Syndrome

Metabolic syndrome (MetS) is a major and escalating public health and clinical challenge worldwide in the wake of urbanization, surplus energy intake, increasing obesity, and sedentary life habits. It is estimated that around 20-25% of the world’s adult population has MetS. In Spain, a national survey reported that the prevalence of MetS reached up to 30% in 2010 [19]. MetS confers a 5-fold increase in the risk of type-2 diabetes (T2D) and 2-fold the risk of cardiovascular diseases (CVD) over the next 5 to 10 years [20]. Further, patients with MetS are at 2- to 4-fold increased risk of stroke, a 3- to 4-fold increased risk of myocardial infarction (MI), and 2-fold the risk of dying from such events compared with those without MetS [21] regardless of a previous history of cardiovascular problems [22]. MetS is considered as a first order risk factor for atherothrombotic complications and its presence or absence should therefore be considered an indicator of long-term risk.

MetS is defined by a constellation of an interconnected physiological, biochemical, clinical, and metabolic factors that directly increase the risk of atherosclerotic CVD, T2D, and all causes of mortality [23,24]. This collection of unhealthy body measurements and abnormal laboratory test outcomes includes atherogenic dyslipidemia, hypertension, glucose intolerance,
and pro-inflammatory and pro-thrombotic states [25,26]. There have been several definitions of MetS, but the most commonly used criteria for definition at present are from the World Health Organization (WHO) [27], the European Group for the study of Insulin Resistance (EGIR) [28], the National Cholesterol Education Programme Adult Treatment Panel III (NCEP ATP III) [29], the American Association of Clinical Endocrinologists (AACE) [30], and the International Diabetes Federation (IDF) (Tables 3 and 4).

The core components of the atherogenic dyslipidemia in MetS are the “lipid triad” of high plasma TGs, low levels of HDL-C, and a preponderance of small, dense LDL-C at fasting [32,33]. Several studies have described abnormalities during the postprandial state in patients with CVD [34], showing that non-fasting TGs is an independent predictor of CVD in multivariate analysis [35], even after adjustment for fasting TGs or HDL-C in normolipidemic men. Elevated non-fasting TGs are often found in insulin-resistant subjects. Some reports have indicated that postprandial hyperinsulinemia and/or decreased insulin sensitivity are also involved in altered acute metabolism of dietary fats [36]. We have previously shown that the nature of the dietary fats in the meal influences on postprandial TG concentrations and control of insulin secretion and sensitivity in subjects with normal [37] and high [38] fasting triglyceride concentrations. Our studies provided evidence that subjects had decreased postprandial β-cell function and became less insulin resistant postprandially as the proportion of MUFAs compared with SFAs in dietary fats increased.

One challenge aspect of MetS is to understand the cellular mechanisms that link the metabolic abnormalities with the pathophysiological effects that generate this disease. One important link has been derived from the finding that pro-inflammatory cytokines are overexpressed during fat abdominal accumulation, which later will lead to several obesity-related disorders [39]. Adipose tissue is a heterogeneous mix of adipocytes, stromal pre-adipocytes, immune cells, and endothelium, which can respond rapidly and dynamically to alterations under nutrient excess through adipocyte hypertrophy and hyperplasia [40]. With obesity and progressive adipocyte enlargement, the blood supplied to adipocytes may be reduced with consequent hypoxia [41]. This condition of inadequate oxygen supply has been proposed to be an inciting aetiology of adipocyte necrosis and macrophage infiltration into adipose tissue, leading to an overproduction of pro-inflammatory factors (e.g., adipokines) and to a local inflammation that propagate an overall systemic inflammation associated with the development of obesity-related comorbidities [42]. Tumour necrosis factor-alpha (TNF-α), adiponectin, visfatin/NAMPT (nicotinamide phosphoribosyltransferase), and interleukin-6 (IL-6) are among the most important adipokines involved in the pathogenesis of MetS and produced by adipocytes and by infiltrated macrophages into adipose tissue [43].
6. Conclusions

MetS is a major and escalating public health and clinical challenge worldwide in the wake of urbanization. The complexity of the molecular pathophysiology of MetS requires rational therapeutic and dietary strategies. Olive oil is a natural fruit product that contains a unique composition of oleic acid and minor constituents. Within this context, the consumption of olive oil has shown a broad range of promising activities in the postprandial disturbances. Nonetheless, further efforts are needed to mechanistically define the biochemical and biological postprandial activities of olive oil on atherosclerosis and MetS.

7. Tables

Table 1: Chemical structure and range of major fatty acids in virgin olive oil.

<table>
<thead>
<tr>
<th>Fatty acid</th>
<th>Regulation* (%)</th>
</tr>
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<tbody>
<tr>
<td>16:0, palmitic acid</td>
<td>7.5-20.0</td>
</tr>
<tr>
<td>16:1n-7, palmitoleic acid</td>
<td>0.3-3.5</td>
</tr>
<tr>
<td>18:0, stearic acid</td>
<td>0.5-3.0</td>
</tr>
<tr>
<td>18:1n-9, oleic acid</td>
<td>55.0-83.0</td>
</tr>
<tr>
<td>18:2n-6, linoleic acid</td>
<td>3.5-21.0</td>
</tr>
<tr>
<td>18:3n-3, α-linolenic acid</td>
<td>≤ 1.0</td>
</tr>
</tbody>
</table>

*International Olive oil council [5].

Table 2: Minor compounds in virgin olive oil [5].

<table>
<thead>
<tr>
<th>Minor compounds</th>
<th>Concentration (mg/kg oil)</th>
</tr>
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<tbody>
<tr>
<td>Squalene</td>
<td>800-8000</td>
</tr>
<tr>
<td>β-carotene and lutein</td>
<td>4-10</td>
</tr>
<tr>
<td>Sterols</td>
<td>1000-3000</td>
</tr>
<tr>
<td>Triterpenic compounds</td>
<td>200-300</td>
</tr>
<tr>
<td>Phenols</td>
<td>200-1500</td>
</tr>
<tr>
<td>Tocopherols and tocotrienols</td>
<td>250-350</td>
</tr>
</tbody>
</table>
Table 3: Criteria proposed for the clinical diagnosis of MetS [31]

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Insulin resistance</td>
<td>IGT, IFG, T2D, or lowered insulin sensitivity plus any 2 of below clinical measures</td>
<td>Plasma insulin &gt;75th percentile</td>
<td>None, but any 3 of below clinical measures</td>
</tr>
<tr>
<td>Body weight</td>
<td>Men: waist-to-hip ratio &gt;0.90; women: waist-to-hip ratio &gt;0.85 and/or BMI &gt;30 kg/m²</td>
<td>WC ≥94 cm in men or ≥80 cm in women</td>
<td>WC ≥102 cm in men or ≥88 cm in women</td>
</tr>
<tr>
<td>Lipids (at fasting)</td>
<td>TGs ≥150 mg/dL and/or HDL-C &lt;35 mg/dL in men or &lt;39 mg/dL in women</td>
<td>TGs ≥150 mg/dL and/or HDL-C &lt;39 mg/dL in men or women</td>
<td>TGs ≥150 mg/dL and/or HDL-C &lt;40 mg/dL in men or &lt;50 mg/dL in women</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>≥140/90 mm Hg</td>
<td>≥140/90 mm Hg or on Rx against hypertension</td>
<td>&gt;130/85 mm Hg</td>
</tr>
<tr>
<td>Glucose (at fasting)</td>
<td>IGT, IFG or T2D</td>
<td>IGT or IFG (but not diabetes)</td>
<td>&gt;110 mg/dL (includes diabetes)</td>
</tr>
</tbody>
</table>

Table 4: Criteria proposed for the clinical diagnosis of MetS [31].

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Insulin resistance</td>
<td>IGT or IFG plus any of below clinical measures</td>
<td>None</td>
</tr>
<tr>
<td>Body weight</td>
<td>BMI ≥25 kg/m²</td>
<td>Increased WC (population specific) plus any 2 of below clinical measures</td>
</tr>
<tr>
<td>Lipids (at fasting)</td>
<td>TGs ≥150 mg/dL and HDL-C &lt;40 mg/dL in men or &lt;50 mg/dL in women</td>
<td>TGs ≥150 mg/dL or on Rx against TGs. HDL-C &lt;40 mg/dL in men or &lt;50 mg/dL in women or on Rx to increase HDL-C</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>≥130/85 mm Hg</td>
<td>≥130 mm Hg systolic or ≥85 mm Hg diastolic or on Rx against hypertension</td>
</tr>
<tr>
<td>Glucose (at fasting)</td>
<td>IGT or IFG (but not diabetes)</td>
<td>≥100 mg/dL (includes diabetes)</td>
</tr>
</tbody>
</table>

IFG: impaired fasting glucose; IGT: impaired glucose tolerance; Rx: receiving treatment; WC: waist circumference.

8. References


Squalene targets pro- and anti-inflammatory mediators and pathways to modulate over-activation of neutrophils, monocytes and macrophages, J. Funct. Foods, 2015, 14, 779-790.


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