

**Olive oil and postprandial hyperlipidemia: Implications for atherosclerosis and metabolic syndrome**

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**ABSTRACT**

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. 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. Herein, the purpose of this review was to provide an update on effects and mechanisms related to the olive oil on postprandial hyperlipidemia and its implications for the onset and progression of atherosclerosis and metabolic syndrome.

**Keywords:** Olive oil, postprandial hyperlipidemia, atherosclerosis, metabolic syndrome, lipoproteins, cardiovascular diseases

## OLIVE OIL

### Generalities

Virgin olive oil plays a pivotal role as the main source of fat in the Mediterranean diet, declared by the UNESCO as an Intangible Cultural Heritage since 2013. 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.<sup>1</sup>

According to EC Regulations (EU Regulation 1348/2013; EU Regulation 29/2012; EEC Regulation 1513/2001), virgin olive oils are those obtained from the mesocarp of the drupe from the fruit of the olive tree (*Olea europaea* L.), obtained exclusively from fresh and healthy olives by physical procedures under low thermal conditions (<27°C). Spain is by far the largest producer of virgin olive oil in the world, accounting for approximately 50% (≈1,600,000 tons) of total global production in 2015.<sup>2</sup>

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.<sup>3</sup>). The levels of fatty acids (FAs) in virgin olive oils vary during the different maturation stage of the olives, the variety, and the growing conditions. It is generally accepted that cooler areas will give oil with higher monounsaturated FAs (MUFAs) content than warmer climates.<sup>4</sup>

The composition of virgin olive oil includes minor compounds (unsaponifiable fraction) that could range from one to 3% of the oil.<sup>5</sup> 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.

### **Brief description of olive oil composition**

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 9<sup>th</sup> 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 3<sup>rd</sup> and 4<sup>th</sup> or the 6<sup>th</sup> and 7<sup>th</sup> 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  $\alpha$ -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- $\gamma$ -linolenic acid (20:3n-6), and arachidonic acid (AA, 20:4n-6) are the most metabolically significant.<sup>6</sup> The concentrations of SFAs (palmitic + stearic acids) and PUFAs ( $\alpha$ -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 ( $\approx 83\%$  oleic acid in position *sn*-2 of the triglycerides, TGs) and is also found in peanut oil ( $\approx 59\%$  oleic acid) and canola oil ( $\approx 37\%$  oleic acid). Oleic acid is a key component of TGs and membrane lipids.<sup>7</sup> 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 small as ppm).<sup>8</sup> This fraction is fundamental in contributing to specific characteristics of virgin olive oil, such as its oxidative stability and its special flavour (aroma and taste) as well as its colour.<sup>9</sup>

Among the several minor compounds of virgin olive oil (**Figures 1–3**), the most abundant fraction is hydrocarbons (squalene and, in smaller amounts, the carotenoids  $\beta$ -carotene and lutein). Other minor compounds of virgin olive oil include phytosterols, such as  $\beta$ -sitosterol,  $\Delta 5$ -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. The main classes of phenolic compounds in virgin olive oil are secoiridoids, as ester derivatives of elenolic acid in either its aglyconic form or glycosylated with hydroxytyrosol (oleuropein) or tyrosol (ligustroside); simple phenols, in the form of alcohols (tyrosol and hydroxytyrosol) or acids (*p*-coumaric, *o*-coumaric, caffeic, ferulic, sinapic, gallic,

gentisic, syringic, vanillic, protocatechuic, and *p*-hydroxybenzoic acids); hydroxyisochromans formed by the reaction between hydroxytyrosol and benzaldehyde or vanillin; flavonoids (luteolin, apigenin, and quercetin); and the lignans (+)-pinoresinol, 1-(+)-acetoxypinoresinol, and 1-(+)-hydroxypinoresinol. The lipophilic phenols include tocopherols (α-, β-, γ-, and δ-tocopherols) and tocotrienols (α-, β-, γ-, and δ-tocotrienols), with α-tocopherol as the predominant constituent in virgin olive oil. It is important to note that only virgin olive oil contains minor compounds, since mostly of them disappear during refining processes.<sup>6,9</sup>

### **Digestion of triglycerides of olive oil and absorption of oleic acid and other 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 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.<sup>10</sup>

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 hydrolyses 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.<sup>11,12</sup>

During gastric lipolysis, FFAs have higher affinity for the surface than the core of the lipid droplets.<sup>13</sup> There is a considerable fusion between lipid droplets, probably due to the presence of FFAs, monoglycerides (MGs), and diglycerides (DGs) that are known to be fusogenic. This change in the lipid composition of the droplet surface during lipolysis could modify the interfacial tension or the surface pressure and could then interfere with gastric lipase binding and activity.<sup>14</sup> The accumulation of FFAs at the droplet surface leads to an inhibition of lipolysis by gastric lipase. The mechanism by which this happens is attributed to the formation of clusters at the surface of the lipid droplets. In the intestine, the smaller size of lipid droplets increases proportionally the lipid surface exposed to the pancreatic lipase.<sup>15</sup> The FAs released from the initial gastric lipolysis and the amino acids and peptides formed by gastric proteolytic activity stimulate specific receptors in intestinal epithelial cells to secrete cholecystokinin. It stimulates gallbladder contraction delivering bile salts to the duodenum. The fat droplets covered with bile salts are not accessible to pancreatic lipase, but the co-lipase enzyme allows the pancreatic lipase molecule to bind to the lipid aqueous interface and facilitates the stabilization of emulsified TGs. Pancreatic lipase cleaves the *sn*-1 and *sn*-3 positions of TGs obtaining *sn*-2 MGs and FFAs.<sup>16</sup> In olive oil, up to 83% of total *sn*-2 positions in TGs are occupied by oleic acid, which means that olive oil acts as a supplier of oleic acid-rich hydrocarbon skeletons and free oleic acid for energy or for cellular synthesis of TGs and PLs.<sup>17</sup>

Absorption of lipid molecules, such as *sn*-2 MGs and oleic acid, takes place along the epithelial cells of the small intestine, mainly in the proximal jejunum but also in parts that are more distal. The epithelial cells of the small intestine show an apical membrane with a brush border made up of many microvilli, which have a

width of about 100 nm and being much smaller (5-20 nm) the spaces between them. Lipid metabolites generated throughout the digestion of olive oil are more polar than the parent TGs, but they still have a limited solubility in the aqueous environment of the intestinal lumen. Micelles and sub-micelles are the main vehicles for approximating *sn*-2 MGs and FFAs successfully to the membrane of the microvilli. There, the acidic microclimate (pH 5.3-6) promotes both micellar dissociation and FA protonation, facilitating the passive diffusion of FFAs across the cellular membrane.<sup>18</sup> Enterocytes may also take up FFAs via energy dependent and carrier-mediated processes. It is known the existence of two isotypes (I and L) of FA binding proteins (FABPs), which differ in their binding specificity. I-FABP binds strongly to FFAs, whereas L-FABP preferentially binds to *sn*-2 MGs.<sup>19</sup> These carriers play an important role at low FFA concentrations (probably to ensure sufficient uptake of lipid nutrients), whereas passive diffusion predominates at high FFA concentrations. Other proteins, including GP330 (megalin), CD36, SR-BI, and caveolin can bind lipids and related metabolites.<sup>20</sup> Differences in the rate of absorption of FFAs have been described as a function of chain length and of number and place of double bonds.<sup>21</sup> 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.<sup>22</sup>

#### ***Assembly of intestinal lipoproteins containing triglycerides from olive oil ingestion***

In the enterocyte, FFAs (mainly oleic acid) from absorption and the pool of endogenous metabolism, together with *sn*-2 MGs, are used for re-synthesis of TGs. This process is initiated with the activation of FFAs to the corresponding acyl-CoA. In this form, FFAs are sequentially transferred to *sn*-2 MGs by MG and DG



acyltransferases. These enzymes form a complex called “triglyceride synthetase”,<sup>23</sup> and the pathway favours the stereospecific reacylation at the *sn*-1 position. It contributes to 80% of the intestinal TG re-synthesis in the fed state. Acyl-CoA can also be transferred to  $\alpha$ -glycerophosphate (derived from glucose metabolism) by the phosphatidic acid pathway, which accounts for the remaining 20%.<sup>21</sup> The composition of these novel TGs closely resembles the composition of TGs from olive oil.<sup>24</sup> 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,<sup>25</sup> 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.<sup>26</sup> 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.<sup>21</sup> Both CMs and VLDLs are considered TG-rich lipoproteins (TRLs).

## POSTPRANDIAL HYPERLIPIDEMIA

### Generalities

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.<sup>27</sup> 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 (**Figure 4**). 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.<sup>28</sup> 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.<sup>29</sup>

### **Postprandial hyperlipemia and atherosclerosis**

Zilversmit first described postprandial hyperlipemia as an atherogenic phenomenon in 1979.<sup>30</sup> Later, it received more attention after the discovery of postprandial TRLs as cholesterol-independent atherogenic particles<sup>31</sup> and postprandial abnormalities in the TG metabolism as a hallmark of patients with established coronary heart disease (CHD).<sup>32</sup> The identification of postprandial TRLs (by means of apoB48) in human atheroma has provided further evidence for their direct role in atherogenesis.<sup>33</sup> The greater the magnitude and duration of the postprandial TRL response, the greater the exposure of the arterial wall to postprandial TRLs (and their remnants) and the greater the likelihood that TGs will replace CEs in LDL-C and HDL-C particles. Postprandial TRLs can penetrate the arterial wall and can reach the subendothelial space (**Figure 5**), causing endothelial lipid (notably TG) deposits, attraction of monocytes, production of inflammatory markers, and oxidative stress.<sup>34</sup>  
<sup>36</sup> The role of TGs in atherosclerosis-mediated inflammation not only depends on their direct vascular effects, but it is also related to profound changes in the functionality of HDL-C that include protection against vessel inflammation or disorders of immune response.<sup>37</sup>

Prospective epidemiology on non-fasting levels of plasma TGs in response to normal food intake include three large-scale studies: the Copenhagen City

Heart Study,<sup>38</sup> Women's Health Study,<sup>39</sup> and the Norwegian Counties Study;<sup>40</sup> all of which have demonstrated that: (i) non-fasting levels of plasma TGs are increased among populations with established cardiovascular disease (CVD) or with multiple risk factors predisposing to CVD; and (ii) long-term follow-up of subjects in prospective, population-based studies links non-fasting (and, less robustly, fasting) TGs to the incidence of CVD events or deaths.<sup>41</sup> Many patients with CVD remain at high risk for CVD events even when the LDL-C goal has been achieved with lipid-lowering therapy.<sup>42</sup> These lines of evidence indicate that non-fasting levels of plasma TGs may be predictive and independent of traditional LDL-C-related risk of CVD.

### **Postprandial hyperlipemia 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 (**Figure 6**).<sup>43</sup> MetS confers a 5-fold increase in the risk of type-2 diabetes (T2D) and 2-fold the risk of CVD over the next 5 to 10 years.<sup>44</sup> 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<sup>45</sup> regardless of a previous history of cardiovascular problems.<sup>46</sup> 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.<sup>47,48</sup> This collection of

unhealthy body measurements and abnormal laboratory test outcomes includes atherogenic dyslipidemia, hypertension, glucose intolerance, and pro-inflammatory and pro-thrombotic states.<sup>49,50</sup> There have been several definitions of MetS, but the most commonly used criteria for definition at present are from the World Health Organization (WHO),<sup>51</sup> the European Group for the study of Insulin Resistance (EGIR),<sup>52</sup> the National Cholesterol Education Programme Adult Treatment Panel III (NCEP ATP III),<sup>53</sup> the American Association of Clinical Endocrinologists (AACE),<sup>54</sup> 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.<sup>56,57</sup> Several studies have described abnormalities during the postprandial state in patients with CHD,<sup>58</sup> showing that non-fasting TGs is an independent predictor of CHD in multivariate analysis,<sup>59</sup> 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.<sup>60</sup> The decreased insulin sensitivity commonly associated with obesity<sup>61</sup> and the fat abdominal accumulation<sup>62</sup> may well play an important part in the development of MetS.

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.<sup>63</sup> 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.<sup>64</sup> With obesity and progressive adipocyte enlargement, the blood supplied to adipocytes may be reduced with consequent hypoxia.<sup>65</sup> 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.<sup>66</sup> Tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ), 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.<sup>67</sup>

TNF- $\alpha$  is a pro-inflammatory cytokine that exerts numerous effects in adipose tissue including on lipid metabolism and insulin signalling. An increase in TNF- $\alpha$  promotes the secretion of other pro-inflammatory cytokines, such as IL-6, and reduces the production of anti-inflammatory cytokines, such as adiponectin.<sup>68</sup> There is evidence suggesting that TNF- $\alpha$  may induce apoptosis in adipocytes<sup>69</sup> and may promote peripheral insulin resistance by the inhibition of the insulin receptor substrate 1 signalling pathway.<sup>70</sup> Adiponectin exerts an anti-inflammatory activity and modulates insulin sensitivity by stimulating glucose utilization and FA oxidation.<sup>71</sup> Adiponectin is almost exclusively secreted by adipose tissue. Its levels decrease in obesity and are inversely correlated with visceral adipose tissue accumulation.<sup>72</sup>

Visfatin/NAMPT is a protein with several functions. Although the first discovery of this molecule as a pre-B-cell colony-enhancing factor suggested primarily a cytokine function, its rediscovery as the key enzyme in nicotinamide

(NAM) adenine dinucleotide (NAD<sup>+</sup>) generation has considerably widened its potential biological activities.<sup>73</sup> Although originally produced in adipose tissue by adipocytes and infiltrating macrophages, it seems to be secreted by other cells and tissues such as skeletal muscle, liver, immune cells, cardiomyocytes, and brain.<sup>74</sup> Visfatin/NAMPT has a broad spectrum of effects and is mirrored by its potential involvement in a wide range of disorders, including MetS, myocardial failure, atherosclerosis, inflammatory diseases, malignancies, neurodegenerative disorders, and aging.<sup>75</sup>

IL-6 is a multifaceted, pleiotropic cytokine that is a central player in the regulation of inflammation, haematopoiesis, immune responses, and host defence mechanisms.<sup>76</sup> Because one-third of circulating IL-6 in healthy individuals is estimated to originate from adipose tissue, IL-6 is considered an adipokine. Moreover, IL-6 has been found to be crucial in immunoregulation. It can itself enhance leukocyte differentiation and proliferation, immunoglobulin secretion, acute phase protein production, and macrophage/monocyte activation. IL-6 is considered as an early key factor that triggers acute phase reactants and metabolic abnormalities tightly associated to inflammatory responses.<sup>77</sup>

### ***Pharmacological approaches affecting postprandial hyperlipemia***

The large majority of drugs affecting lipid metabolism also affects postprandial hyperlipemia; however, well-designed and robust clinical studies in this specific field are limited due the difficulties of setting up a postprandial study in a large cohort of patients.

Improved understanding of the physiology and genetic regulation of postprandial TG metabolism could lead to the identification of new targets for therapy.<sup>78</sup> However, data from randomized clinical trials on the benefits of lowering

TGs are much less robust than for the benefits of lowering LDL-C with statins as inhibitors of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase.<sup>79,80</sup> This could be due to the lack of high-grade evidence for benefits of TG-lowering drugs, which is reflected by the lack of specific target goals for both fasting and non-fasting levels of plasma TGs. Appropriate dietary changes limiting fat content, caloric restriction resulting in weight loss, restriction of alcohol intake, and increased exercise may be fundamental for management of high fasting<sup>28,81,82</sup> and non-fasting<sup>83-85</sup> levels of plasma TGs. Current guidelines do not stipulate the atherogenic lipid profile in the postprandial state as a target for therapy nor do they give any target values for the parameters of postprandial hyperlipemia. Statin therapy is recommended as the first pharmacological step to reduce elevated levels of plasma TGs in individuals with high or very high CVD risk based on global risk assessment, particularly in subjects with MetS and T2D.<sup>86</sup> Available data have pointed that statins also reduce non-fasting levels of plasma TGs.<sup>87</sup> Interestingly, ezetimibe has been reported to reduce apoB48 secretion in human intestine, suggesting a direct effect of this drug on assembly of postprandial TRLs in enterocytes.<sup>88</sup> Studies on fibrates have given consistent results reporting significant lowering of non-fasting levels of plasma TGs in response to a standardized fat challenge.<sup>28,88</sup> Furthermore, fenofibrate also reduced levels of plasma apoB48 and biomarkers for postprandial TRL remnants.<sup>89</sup>

New pharmacological and non-pharmacological approaches, such as dual peroxisome proliferator-activated receptor (PPAR) $\alpha$ /PPAR $\delta$  agonists, dietary oils rich in DGs, inhibitors of DG-O-acyltransferase-1, and microsomal TG transfer protein, antisense oligonucleotides for apoB100, apoB48, and apoCIII, and incretin-based treatments could be employed alone or in combination with conventional therapies to optimize treatment for management of dyslipidemia due to high fasting

and non-fasting levels of plasma TGs.<sup>28</sup> However, the clinical efficacy, mechanisms of action, safety, and tolerability of these newer agents requires further testing in clinical trials.

### **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.

### **Conflicts of interest**

The authors state no conflict of interest.

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**ABBREVIATIONS**

**AA:** arachidonic acid

**Apo:** apolipoprotein

**CE:** cholesteryl ester

**CHD:** coronary heart disease

**CM:** chylomicron

**CVD:** cardiovascular disease

**DG:** diacylglycerol

**DHA,** docosahexaenoic acid

**EPA:** eicosapentaenoic acid

**FA:** fatty acid

**FABP:** fatty acid binding protein

**FFA:** free fatty acid

**HDL:** high-density lipoprotein

**IL:** interleukin

**LDL:** low-density lipoprotein

**MCP:** monocyte chemotactic protein

**MetS:** metabolic syndrome

**MG:** monoacylglycerol

**MI:** myocardial infarction

**MTP:** microsomal triglyceride transfer protein

**MUFA:** monounsaturated fatty acid

**NAD:** nicotinamide adenine dinucleotide

**NAM:** nicotinamide

**NAMPT:** nicotinamide phosphoribosyltransferase

**PL:** phospholipid

**PPAR:** peroxisome proliferator-activated receptor

**PUFA:** polyunsaturated fatty acid

**SFA:** saturated fatty acid

**T2D:** type-2 diabetes

**TG:** triglyceride

**TNF:** tumour necrosis factor

**TRL:** triglyceride-rich lipoprotein

**VLDL:** very low-density lipoprotein

## References

1. S. Lopez, B. Bermudez, S. Montserrat-de la Paz, S. Jaramillo, R. Abia and F.J. Muriana. Virgin olive oil and Hypertension, *Curr. Vasc. Pharmacol.*, 2016, **14**, 323-329.
2. J.M. Ochando-Pulido and A. Martinez-Ferez. On the recent use of membrane technology for olive mil wastewater purification, *Membranes*, 2015, **5**, 513-531.
3. B. Bermudez, S. Lopez, A. Ortega, L.M Varela, Y.M. Pacheco, R. Abia and F.J. Muriana. Oleic acid in olive oil: from a metabolic framework toward a clinical perspective, *Curr. Pharm. Des.*, 2011, **17**, 831-843.
4. A.B. Mansour, B. Gargouri, G. Flamini and M. Bouaziz. Effect of agricultural sites on differentiation between Chemlali and Neb Jmel olive oils, *J. Oleo Sci.*, 2015, **64**, 381-392.
5. A. Cardeno, M. Sanchez-Hidalgo, M. Aparicio-Soto and C. Alarcon-de-la-Lastra. Unsaponifiable fraction from extra virgin olive oil inhibits inflammatory response in LPS-activated murine macrophages, *Food Chem.*, 2014, **147**, 117-123.
6. S. Lopez, B. Bermudez, S. Montserrat-de la Paz, S. Jaramillo, L.M. Varela, A. Ortega-Gomez, R. Abia and F.J. Muriana. Membrane composition and dynamics: A target of bioactive virgin olive oil constituents, *BBA-Biomembranes*, 2014, **1838**, 1638-1656.
7. L. Hodson and B.A. Fielding. Stearoyl-CoA desaturase: rogue or innocent bystander? *Prog. Lipid. Res.*, 2013, **52**, 15-42.
8. C.A. De la Lastra. An up-date of olive oil and bioactive constituents in health: molecular mechanisms and clinical implications, *Curr. Pharm. Des.*, 2011, **17**, 752-753.

9. E. Frankel, A. Bakhouché, J. Lozano-Sánchez, A. Segura-Carretero and A. Fernández-Gutiérrez. Literatura review on production process to obtain extra virgin olive oil enriched in bioactive compounds. Potential use of byproducts as alternative sources of polyphenols, *J. Agric. Food Chem.*, 2013, **61**, 5179-5188.
10. P.J. Tomasik, A. Wedrychowicz, I. Rogatko, A. Zajac, K. Fyderek and K. Sztelfko. Gastric lipase secretion in children with gastritis, *Nutrients*, 2013, **5**, 2924-2932.
11. K. Johnson, L. Ross, R. Miller, X. Xiao and M.E. Lowe. Pancreatic lipase-related protein 2 digests fats in human milk and formula in concert with gastric lipase and carboxyl ester lipase, *Pediatr. Res.*, 2013, **74**, 127-132.
12. Y. Pafumi, D. Lairon, P.L. de la Porte, C. Juhel, J. Storch, M. Hamosh and M. Armand. Mechanisms of inhibition of triacylglycerol hydrolysis by human gastric lipase, *J. Biol. Chem.*, 2002, **277**, 28070-28079.
13. D.A. Gross and D.L. Silver. Cytosolic lipid droplets: from mechanisms of fat storage to disease, *Crit. Rev. Biochem. Mol. Biol.*, 2014, **49**, 304-326.
14. Y. Gargouri, G. Pieroni, F. Ferrato and R. Verger. Human gastric lipase. A kinetic study with dicaprin monolayers, *Eur. J. Biochem.*, 1987, **169**, 125-129.
15. J. Iqbal and M.M. Hussain. Intestinal lipid absorption, *Am. J. Physiol. Endocrinol. Metab.*, 2009, **296**, E1183-E1194.
16. S.G. Young and R. Zechner. Biochemistry and pathophysiology of intravascular and intracellular lipolysis, *Genes Dev.*, 2013, **27**, 459-484.
17. R. Abia, J.S. Perona, Y.M. Pacheco, E. Montero, F.J.G. Muriana and V. Ruiz-Gutiérrez. Postprandial triacylglycerols from dietary virgin olive oil are selectively cleared in humans, *J. Nutr.*, 1999, **129**, 2184-2192.

18. K. Murota and J. Storch. Uptake of micellar long-chain fatty acid and sn-2-monoacylglycerol into human intestinal Caco-2 cells exhibits characteristics of protein-mediated transport, *J. Nutr.*, 2005, **135**, 1626-1630.
19. W.S. Lagakos, A.M. Gajda, L. Agellon, B. Binas, V. Choi, B. Mandap, T. Russnak, Y.X. Zhou and J. Storch. Different functions of intestinal and liver-type fatty acid-binding proteins in intestine and in whole body energy homeostasis, *Am. J. Physiol. Gastrointest. Liver Physiol.*, 2011, **300**, G803-G814.
20. C. Rohrl and H. Stangl. HDL endocytosis and resecretion. *Biochim. Biophys. Acta.*, 2013, **1831**: 1626-1633.
21. H. Mu and C.E. Hoy. The digestion of dietary triacylglycerols, *Prog. Lipid. Res.*, 2004, **43**, 105-133.
22. C.H. Kim, J. Park and M. Kim. Gut microbiota-derived short chain fatty acids, T cells, and inflammation, *Immune Netw.*, 2014, **14**, 277-288.
23. F. Wilfling, H. Wang, J.T. Haas, N. Krahmer, T.J. Gould, A. Uchida, J.X. Cheng, M. Graham, R. Chistiano, F. Fröhlich, *et al.* Triacylglycerol synthesis enzymes mediate lipid droplet growth by relocalizing from ER to lipid droplets, *Dev. Cell.*, 2013, **24**, 384-399.
24. A. Bysted, G. Holmer, P. Lund, B. Sandstrom and T. Tholstrup. Effect of dietary fatty acids on the postprandial fatty acid composition of triacylglycerol-rich lipoproteins in healthy male subjects, *Eur. J. Clin. Nutr.*, 2005, **59**, 24-34.
25. A. Giammanco, A.B. Cefalu, D. Noto and M.R. Averna. The pathophysiology of intestinal lipoprotein production, *Front. Physiol.*, 2015, **6**, 61.
26. B. Bermudez, Y.M. Pacheco, S. Lopez, R. Abia and F.G.M. Muriana. Digestion and absorption of olive oil, *Grasas y Aceites*, 2004, **55**, 1-10.

27. L.M. Varela, A. Ortega-Gomez, S. Lopez, R. Abia, F.J. Muriana and B. Bermudez. The effects of dietary fatty acids on the postprandial triglyceride-rich lipoprotein/apoB48 receptor axis in human monocyte/macrophage cells, *J. Nutr. Biochem.*, 2013, **24**, 2031-2039.
28. S. Montserrat-de la Paz, B. Bermudez, M.C. Naranjo, S. Lopez, R. Abia and F.J.G. Muriana. Pharmacological effects of niacin on acute hyperlipemia, *Curr. Med. Chem.*, 2016, **25**, 2826-2835.
29. J.S. Cohn. Postprandial lipemia and remnant lipoproteins, *Clin. Lab. Med.*, 2006, **26**, 773-786.
30. D.B. Zilversmit. Atherogenesis: a postprandial phenomenon, *Circulation*, 1979, **60**, 473-485.
31. A.D. Sniderman. Postprandial hypertriglyceridemia(s): time to enlarge our pathophysiologic perspective, *Eur. J. Clin. Invest.*, 2000, **30**, 935-937.
32. J.R. Patsch, G. Miesenbock, T. Hopferwieser, V. Mühlberger, E. Knapp, J.K. Dunn, A.M. Jr. Gotto and W. Patsch. Relation of triglyceride metabolism and coronary artery disease. Studies in the postprandial state, *Arterioscler. Thromb.*, 1992, **12**, 1336-1345.
33. S.D. Proctor, D.F. Vine and J.C. Mamo. Arterial retention of apolipoprotein B(48)- and B(100)-containing lipoproteins in atherogenesis, *Curr. Opin. Lipidol.*, 2002, **13**, 461-470.
34. A. Pirillo, G.D. Norata and A.L. Catapano. Postprandial lipemia as a cardiometabolic risk factor, *Curr. Med. Res. Opin.*, 2014, **30**, 1489-1503.
35. M.C. Naranjo, I. Garcia, B. Bermudez, S. Lopez, M.P. Cardelo, R. Abia, F.J.G. Muriana and S. Montserrat-de la Paz. Acute effects of dietary fatty acids on

- osteoclastogenesis via RANKL/RANK/OPG system, *Mol. Nutr. Food Res.*, 2016, DOI 10.1002/mnfr.201600303
36. S. Montserrat-de la Paz, M.C. Naranjo, B. Bermudez, S. Lopez, W. Moreda, R. Abia and F.J.G. Muriana. Postprandial dietary fatty acids exert divergent inflammatory responses in retinal-pigmented epithelium cells. *Food Funct.*, 2016, **7**, 1345-1353.
37. S. Patel, R. Puranik, S. Nakhla, P. Lundman, R. Stocker, X.S. Wang, G. Lambert, K.A. Rye, P.J. Barter, S.J. Nicholls *et al.* Acute hypertriglyceridaemia in humans increases the triglyceride content and decreases the anti-inflammatory capacity of high density lipoproteins, *Atherosclerosis*, 2009, **204**, 424-428.
38. A.S. Lindman, M.B. Veierod, A. Tverdal, J.L. Pedersen and R. Selmer. Nonfasting triglycerides and risk of cardiovascular death in men and women from the Norwegian counties study, *Eur. J. Epidemiol.*, 2010, **25**, 789-798.
39. J. Boren, N. Matikainen, M. Adiels, and M.R. Taskinen. Postprandial hypertriglyceridemia as a coronary risk factor, *Clin. Chim. Acta.*, 2014, **431**, 131-142.
40. M. Miller, C.P. Cannon, S.A. Murphy, J. Qin, K.K. Ray and E. Braunwald. Impact of triglyceride levels beyond low-density lipoprotein cholesterol after acute coronary syndrome in the PROVE IT-TIMI 22 trial, *J. Am. Coll. Cardiol.*, 2008, **51**, 724-730.
41. B.G. Nordestgaard, M. Benn, P. Schnohr and A. Tybjaerg-Hansen. Nonfasting triglycerides and risk of myocardial infarction, ischemic heart disease, and death in men and women, *JAMA*, 2007, **298**, 299-308.

42. S. Bansal, J.E. Buring, N. Rifai, S. Mora, F.M. Sacks and P.M. Ridker. Fasting compared with nonfasting triglycerides and risk of cardiovascular events in women, *JAMA*, 2007, **298**, 309-316.
43. D. Fernandez-Berges, A. Cabrera de Leon, H. Sanz, R. Elosua, M.J. Guembe, M. Alzamora, T. Vega-Alonso, F.J. Félix-Redondo, H. Ortiz-Marrón, F. Rigo, *et al.* Metabolic syndrome in Spain: prevalence and coronary risk associated with harmonized definition and WHO proposal. DARIOS study, *Rev. Esp. Cardiol.*, 2012, **65**, 241-248.
44. K.G.M.M. Alberti, R.H. Eckel, S.M. Grundy, P.Z. Zimmet, J.I. Cleeman, K.A. Donato, J.C. Fruchart, W.P. James, C.M. Loria, S.C. Jr. Smith, *et al.* Harmonizing the metabolic syndrome: a joint interim statement of the international diabetes federation task force on epidemiology and prevention; National heart, lung, and blood institute; American heart association; World heart federation; International atherosclerosis society; And international association for the study of obesity, *Circulation*, 2009, **120**, 1640–1645.
45. K.G.M.M. Alberti, P. Zimmet and J. Shaw. The metabolic syndrome—a new worldwide definition, *Lancet*, 2005, **366**, 1059–1062.
46. J.K. Olijhoek, Y. Van Der Graaf, J.D. Banga, A. Algra, T.J. Rabelink and F.L. Visseren. The metabolic syndrome is associated with advanced vascular damage in patients with coronary heart disease, stroke, peripheral arterial disease or abdominal aortic aneurysm, *Eur. Heart J.*, 2004, **25**, 342-348.
47. S.M. Grundy, J.I. Cleeman, S.R. Daniels, K.A. Donato, R.H. Eckel, B.A. Franklin, D.J. Gordon, R.M. Krauss, P.J. Savage, S.C. Jr. Smith, *et al.* Diagnosis and management of the metabolic syndrome: an American Heart Association/National



Heart, Lung, and Blood Institute scientific statement, *Circulation*, 2005, **112**, 2735–2752.

48. P.W.F. Wilson, R.B. D'Agostino, H. Parise, L. Sullivan and J.B. Meigs. Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus, *Circulation*, 2005, **112**, 3066–3072.

49. S. Montserrat-de la Paz, M.C. Naranjo, S. Lopez, R. Abia, F.J.G. Muriana and B. Bermudez. Olive oil, compared to a saturated dietary fat, has a protective role on atherosclerosis in niacin-treated mice with metabolic syndrome, *J. Funct. Foods*, 2016, **26**, 557-564.

50. S. Montserrat-de la Paz, M.C. Naranjo, S. Lopez, R. Abia, F.J.G. Muriana and B. Bermudez. Olive oil, compared to a saturated dietary fat, has a protective role on atherosclerosis in niacin-treated mice with metabolic syndrome, *Food Funct.*, 2016, **7**, 2233-2238.

51. K.G.M.M. Alberti and P.Z. Zimmet. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation, *Diabetic Med.*, 1998, **15**, 539–553.

52. B. Balkau and M.A. Charles. Comment on the provisional report from the WHO consultation: European Group for the Study of Insulin Resistance (EGIR), *Diabetic Med.*, 1999, **16**, 442–443.

53. J.I. Cleman. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III), *J. Am. Med. Assoc.*, 2001, **285**, 2486–2497.

54. D. Einhorn, G.M. Reaven, R.H. Cobin, E. Ford, O.P. Ganda, Y. Handelsman, R. Hellman, P.S. Jellinger, D. Kendall, R.M. Krauss, *et al.* American College of Endocrinology position statement on the insulin resistance syndrome, *Endocrine Practice*, 2003, **9**, 237–252.
55. J. Kaur. A comprehensive review on metabolic syndrome, *Cardiol. Res. Pract.*, 2014, **2014**, 943162.
56. F. Emanuela, M. Grazia, de R. Marco, L. Maria Paola, F. Giorgio, B. Marco. Inflammation as a Link between Obesity and Metabolic Syndrome, *J. Nutr. Metab.*, 2012, **2012**, 476380.
57. K. Nakajima. Pharmacotherapy of mixed dyslipidemia in the metabolic syndrome, *Curr. Clin. Pharmacol.*, 2010, **5**, 133-139.
58. T. Nakamura, J.E. Obata, H. Takano, K. Kawabata, K. Sano, T. Kobayashi, D. Fujioka, Y. Saito, T. Yano and K. Kugiyama. High serum levels of remnant lipoproteins predict ischemic stroke in patients with metabolic syndrome and mild carotid atherosclerosis, *Atherosclerosis*, 2009, **202**, 234-240.
59. B.G. Nordestgaard, A. Langsted and J.J. Freiberg. Nonfasting hyperlipidemia and cardiovascular disease, *Curr. Drug Targets*, 2009, **10**, 328-335.
60. B. Enkhmaa, Z. Ozturk, E. Anuurad and L. Berglund. Postprandial lipoproteins and cardiovascular disease risk in diabetes mellitus, *Curr. Diab. Rep.*, 2010, **10**, 61-69.
61. G.M. Reaven. Insulin resistance: the link between obesity and cardiovascular disease, *Med. Clin. North Am.*, 2011, **95**, 875-892.
62. L. Yang, Y.P. Samarasinghe, P. Kane, S.A. Amiel and S.J. Aylwin. Visceral adiposity is closely correlated with neck circumference and represents a significant

- indicator of insulin resistance in WHO grade III obesity, *Clin. Endocrinol.*, 2010, **73**, 197-200.
63. G.S. Hotamisligil, N.S. Shargill and B.M. Spiegelman. Adipose expression of tumor necrosis factor- $\alpha$ : direct role in obesity-linked insulin resistance, *Science*, 1993, **259**, 87–91.
64. N. Halberg, I. Wernstedt-Asterholm and P.E. Scherer PE. The adipocyte as an endocrine cell Endocrinology and Metabolism, *Clinics of North America*, 2008, **37**, 753–768.
65. S. Cinti, G. Mitchell, G. Barbatelli, I. Murano, E. Ceresi, E. Faloia, S. Wang, M. Fortier, A.S. Greenberg and M.S. Obin. Adipocyte death defines macrophage localization and function in adipose tissue of obese mice and humans, *J. Lipid Res.*, 2005, **46**, 2347–2355.
66. P. Trayhurn and I.S. Wood. Adipokines: inflammation and the pleiotropic role of white adipose tissue, *Br. J. Nutr.*, 2004, **92**, 347–355.
67. K. Karastergiou and V. Mohamed-Ali. The autocrine and paracrine roles of adipokines, *Mol. Cell Endocrinol.*, 2010, **318**, 69–78.
68. B. Wang and P. Trayhurn. Acute and prolonged effects of TNF- $\alpha$  on the expression and secretion of inflammation-related adipokines by human adipocytes differentiated in culture, *Pflugers Arch.*, 2006, **452**, 418–427.
69. J.B. Prins, C.U. Niesler, C.M. Winterford, N.A. Bright, K. Siddle, S. O’Rahilly, N.I. Walker and D.P. Cameron. Tumor necrosis factor- $\alpha$  induces apoptosis of human adipose cells, *Diabetes*, 1997, **46**, 1939–1944.

70. G.S. Hotamisligil, P. Peraldi, A. Budavari, R. Ellis, M.F. White and B.M. Spiegelman. IRS-1-mediated inhibition of insulin receptor tyrosine kinase activity in TNF- $\alpha$ -and obesity-induced insulin resistance, *Science*, 1996, **271**, 665–668.
71. S. Bertoli, I.G. Neri, C. Trentani, C. Ferraris, R. De Amicis, A. Battezzati, P. Veggiotti, V. De Giorgis and A. Tagliabue. Short-term effects of ketogenic diet on anthropometric parameters, body fat distribution, and inflammatory cytokine production in GLUT1 deficiency syndrome, *Nutrition*, 2015, **31**, 981-987.
72. L. Pietrzyk, A. Torres, R. Maciejewski and K. Torres. Obesity and Obese-related Chronic Low-grade Inflammation in Promotion of Colorectal Cancer Development, *Asian Pac. J. Cancer Prev.*, 2015, **16**, 4161-4168.
73. A. Garten, S. Schuster, M. Penke, T. Gorski, T. de Giorgis and W. Kiess. Physiological and Pathological roles of NAMPT and NAD metabolism, *Nat. Rev. Endocrinol.*, 2015, **11**, 535-546.
74. P. Wang and C.Y. Miao. NAMPT as a therapeutic target against stroke, *Trends Pharmacol. Sci.*, 2015, **36**, 891-905.
75. B. Halvorsen, M.Z. Espeland, G.O. Andersen, A. Yndestad, E.L. Sagen, A. Rashidi, E.C. Knudsen, M. Skjelland, K.R. Skagen, K. Krohg-Sorensen, *et al.* Increased expression of NAMPT in PBMC from patients with acute coronary syndrome and in inflammatory M1 macrophages, *Atherosclerosis*, 2015, **243**, 204-210.
76. M. Hoene and C. Weigert. The role of interleukin-6 in insulin resistance, body fat distribution and energy balance, *Obes. Rev.*, 2008, **9**, 20-29.
77. J. Scheller, C. Garbersb and S. Rose-John. Interleukin-6: From basic biology to selective blockade of pro-inflammatory activities, *Semin. Immunol.*, 2014, **26**, 2-12

78. A. Varbo, M. Benn, A. Tybjaerg-Hansen, A.B. Jorgensen, R. Frikke-Schmidt and B.G. Nordestgaard. Remnant cholesterol as a causal risk factor for ischemic heart disease, *J. Am. Coll. Cardiol.*, 2013, **61**, 427-436.
79. M. Miller, N.J. Stone, C. Ballantyne, V. Bittner, M.H. Criqui, H.N. Ginsberg, A.C. Golberg, W.J. Howard, M.S. Jacobson, P.M. Kris-Etherton, *et al.* Triglycerides and cardiovascular disease. *Circulation*, 2011, **123**: 2292-2333.
80. A.L. Catapano, Z. Reiner, G. De Backer, I. Graham, M.R. Taskinen, O. Wiklund, S. Agewall, E. Alegria, M. Chapman, P. Durrington, *et al.* ESC/EAS guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS), *Atherosclerosis*, 2011, **217**, 3-46.
81. L. Berglund, J.D. Brunzell, A.C. Goldberg, I.J. Goldberg, F. Sacks, M.H. Murad, A.F. Stalenhoef and Endocrine society. Evaluation and treatment of hypertriglyceridemia: an Endocrine Society clinical practice guideline, *J. Clin. Endocrinol. Metab.*, 2012, **97**, 2969-2989.
82. G.F. Watts, E.M. Ooi and D.C. Chan. Demystifying the management of hypertriglyceridaemia, *Nat. Rev. Cardiol.*, 2013, **10**, 648-661.
83. S. Lopez, B. Bermudez, A. Ortega, L.M. Varela, Y.M. Pacheco, J. Villar, R. Abia and F.J. Muriana. Effects of meals rich in either monounsaturated or saturated fat on lipid concentrations and on insulin secretion and action in subjects with high fasting triglyceride concentrations, *Am. J. Clin. Nutr.*, 2011, **93**, 494-499.
84. S. Lopez, B. Bermudez, Y.M. Pacheco, J. Villar, R. Abia and F.J. Muriana. Distinctive postprandial modulation of beta cell function and insulin sensitivity by

dietary fats: monounsaturated compared with saturated fatty acids, *Am. J. Clin. Nutr.*, 2008, **88**, 638-644.

85. Y.M. Pacheco, B. Bermudez, S. Lopez, R. Abia, J. Villar and F.J. Muriana. Ratio of oleic to palmitic acid is a dietary determinant of thrombogenic and fibrinolytic factors during the postprandial state in men, *Am. J. Clin. Nutr.*, 2006, **84**, 342-349.

86. Task Force Members, L. Ryden, P.J. Grant, S.D. Anker, C. Berne, F. Cosentino, N. Danchin, C. Deaton, J. Escaned, H.P. Hammes, *et al.* ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD), *Eur. Heart J.*, 2013, **34**, 3035-3087.

87. G.D. Kolovou, D.P. Mikhailidis, J. Kovar, D. Lairon, B.G. Nordestgaard, T.C. Ooi, P. Perez-Martinez, H. Bilianou, K. Anagnostopoulou and G. Panotopoulos. Assessment and clinical relevance of non-fasting and postprandial triglycerides: an expert panel statement, *Curr. Vasc. Pharmacol.*, 2011, **9**, 258-270.

88. A.J. Tremblay, B. Lamarche, J.C. Hogue and P. Couture. Effects of ezetimibe and simvastatin on apolipoprotein B metabolism in males with mixed hyperlipidemia, *J. Lipid Res.*, 2009, **50**, 1463-1471.

89. D.C. Chan, A.T. Wong, S. Yamashita and G.F. Watts. Apolipoprotein B-48 as a determinant of endothelial function in obese subjects with type 2 diabetes mellitus: effect of fenofibrate treatment, *Atherosclerosis*, 2012, **221**, 484-489.



### Figure Legends

**Figure 1.** Chemical structures of squalene, carotenoids, sterols, triterpenic dialcohols, and triterpenic acids in virgin olive oil.<sup>6</sup>

**Figure 2.** Chemical structures of secoiridoids, phenyl-alcohols, and phenyl-acids in virgin olive oil.<sup>6</sup>

**Figure 3.** Chemical structures of hydroxyisochromans, flavonoids, lignans, tocopherols, and tocotrienols in virgin olive oil.<sup>6</sup>

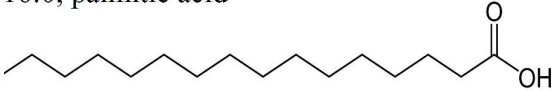
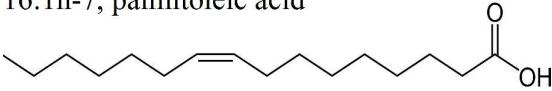
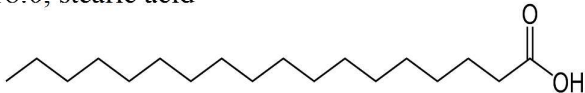
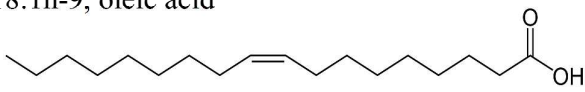
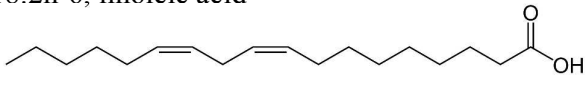
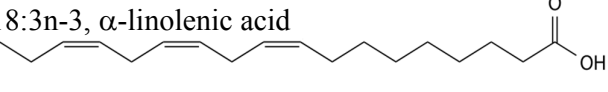
**Figure 4.** Serum TG levels after the ingestion of fatty meals. (A) Serum TG levels reach a peak at 3-4 h and slowly return to initial levels at 6-8 h after a fatty meal. (B) Most of the day is a non-fasting state (in other words a postprandial state) in people who eat at least three fatty meals a day.<sup>58</sup>

**Figure 5.** Concept of the initiation of atherosclerosis by TRLs: lipoproteins enter the subendothelial space via nonspecific transcytotic processes. This is often a non-pathologic process, because the lipoproteins leave (TRLs with greater difficulty than LDL-C) the subendothelial space again via the vasa vasorum. Lipoproteins can be easily taken up by macrophages. Circulating TRLs themselves also contribute to the presence of subendothelial macrophages. Monocytes can bind and take up TRLs, which stimulates monocytes to become activated. Subsequently, activated monocytes express adhesion molecules on the outer membrane and stimulate the expression of endothelial cellular adhesion molecules (CAMs), which allows monocytes to home the endothelium and migrate into the subendothelial space. Finally, the macrophages change into highly atherogenic foam cells when lipid uptake exceeds lipid efflux.

**Figure 6.** Prevalence of MetS in the Spanish population aged 18 years or older from 2008 to 2010.<sup>43</sup>



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

Fatty acid	Regulations <sup>a</sup> (%)
16:0, palmitic acid 	7.5-20.0
16:1n-7, palmitoleic acid 	0.3-3.5
18:0, stearic acid 	0.5-5.0
18:1n-9, oleic acid 	55.0-83.0
18:2n-6, linoleic acid 	3.5-21.0
18:3n-3, $\alpha$ -linolenic acid 	$\leq 1.0$
MUFA, monounsaturated fatty acids	55-87
SFA, saturated fatty acids	8-26
PUFA, polyunsaturated fatty acids	3-22

<sup>a</sup>International Olive oil council<sup>6</sup>

**Table 2.** Minor compounds in virgin olive oil.<sup>6</sup>

<b>Minor compounds</b>	<b>Concentration (mg/kg oil)</b>
Squalene	800-8000
$\beta$ -carotene and lutein	4-10
Sterols	1000-3000
Triterpenic compounds	200-300
Phenols	200-1500
Tocopherols and tocotrienols	250-350

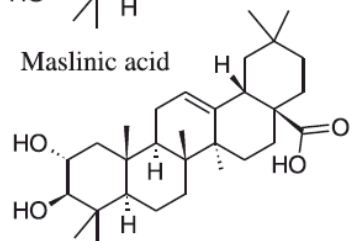
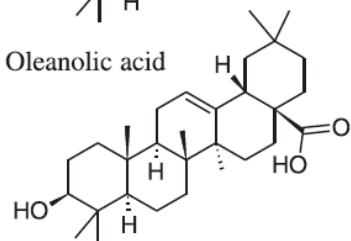
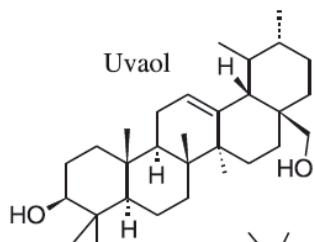
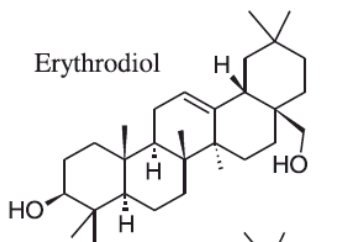
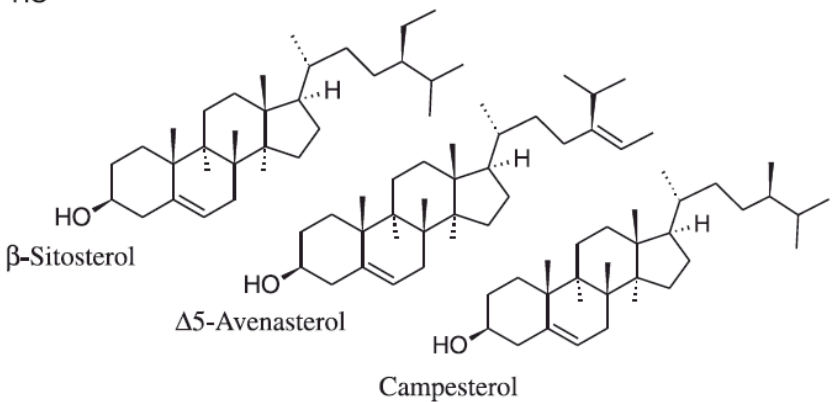
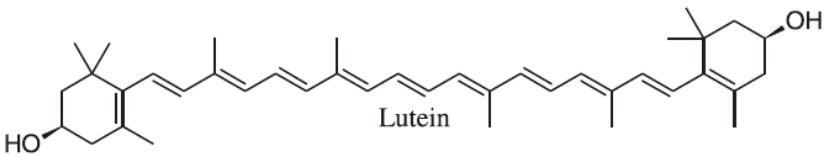
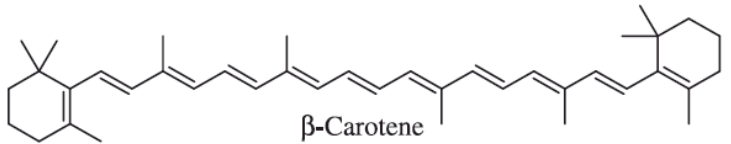
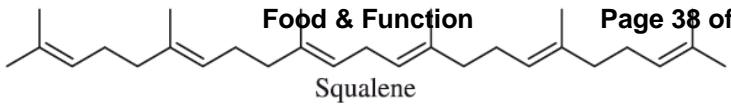
**Table 3.** Criteria proposed for the clinical diagnosis of MetS.<sup>55</sup>

Clinical measures	WHO (1998)	EGIR (1999)	ATP (2001)	III
<b>Insulin resistance</b>	IGT, IFG, T2D, or lowered insulin sensitivity plus any 2 of below clinical measures	Plasma insulin >75 <sup>th</sup> percentile	None, but any 3 of below clinical measures	
<b>Body weight</b>	Men: waist-to-hip ratio >0.90; women: waist-to-hip ratio >0.85 and/or BMI >30 kg/m <sup>2</sup>	WC ≥94 cm in men or ≥80 cm in women	WC ≥102 cm in men or ≥88 cm in women	
<b>Lipids (at fasting)</b>	TGs ≥150 mg/dL and/or HDL-C <35 mg/dL in men or <39 mg/dL in women	TGs ≥150 mg/dL and/or HDL-C <39 mg/dL in men or women	TGs ≥150 mg/dL HDL-C <40 mg/dL in men or <50 mg/dL in women	
<b>Blood pressure</b>	≥140/90 mm Hg	≥140/90 mm Hg or on Rx against hypertension	>130/85 mm Hg	
<b>Glucose (at fasting)</b>	IGT, IFG or T2D	IGT or IFG (but not diabetes)	>110 mg/dL (includes diabetes)	

**Table 4.** Criteria proposed for the clinical diagnosis of MetS.<sup>55</sup>

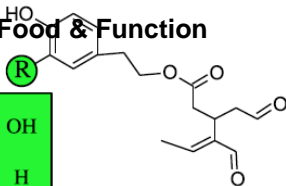
<b>Clinical measures</b>	<b>AACE (2003)</b>	<b>IDF (2005)</b>
<b>Insulin resistance</b>	IGT or IFG plus any of below clinical measures	None
<b>Body weight</b>	BMI $\geq 25$ kg/m <sup>2</sup>	Increased WC (population specific) plus any 2 of below clinical measures
<b>Lipids (at fasting)</b>	TGs $\geq 150$ mg/dL and HDL-C $< 40$ mg/dL in men or $< 50$ mg/dL in women	TGs $\geq 150$ mg/dL or on Rx against TGs. HDL-C $< 40$ mg/dL in men or $< 50$ mg/dL in women or on Rx to increase HDL-C
<b>Blood pressure</b>	$> 130/85$ mm Hg	$\geq 130$ mm Hg systolic or $\geq 85$ mm Hg diastolic or on RX against hypertension
<b>Glucose (at fasting)</b>	IGT or IFG (but not diabetes)	$\geq 100$ mg/dL (includes diabetes)

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



Dialdehyde forms of secoiridoids

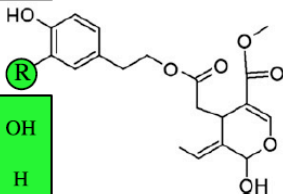
Decarboxymethyl elenolic acid  
linked to hydroxytyrosol  
Decarboxymethyl elenolic acid  
linked to tyrosol



OH  
H

Secoiridoid aglycones

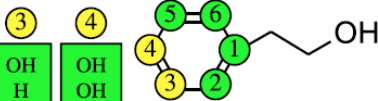
Elenolic acid  
linked to hydroxytyrosol  
Elenolic acid  
linked to tyrosol



OH  
H

Phenyl-alcohols

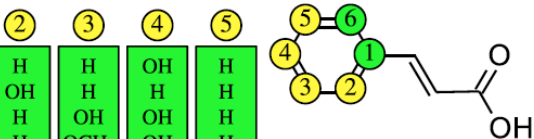
Hydroxytyrosol  
Tyrosol



3  
4  
OH H  
OH H

Cinnamic  
and derivative acids

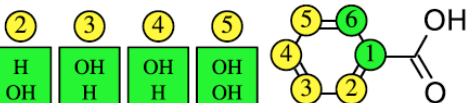
*p*-Coumaric acid  
*o*-Coumaric acid  
Caffeic acid  
Ferulic acid  
Sinapic acid



2 3 4 5  
H H OH H  
OH H H H  
H OH OH H  
H OCH<sub>3</sub> OH H  
H OCH<sub>3</sub> OH OCH<sub>3</sub>

Benzoic  
and derivative acids

Gallic acid  
Gentisic acid  
Syringic acid  
Vanillic acid  
Protocatechuic acid  
*p*-Hydroxybenzoic acid



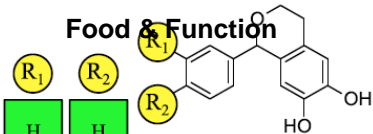
2 3 4 5  
H OH OH OH  
OH H H OH  
H OCH<sub>3</sub> OH OCH<sub>3</sub>  
H OCH<sub>3</sub> OH H  
H OH OH H  
H H OH H

Phenyl-acids

Phenyl-acids

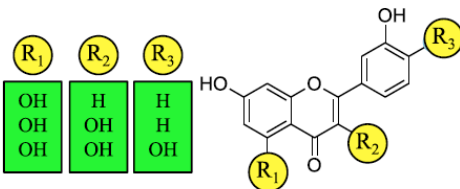
Hydroxyisochromans

Hydroxytyrosol linked to benzaldehyde	H	H
Hydroxytyrosol linked to vanillin	OCH <sub>3</sub>	OH



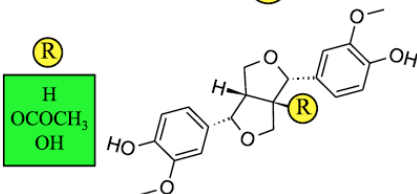
Flavonoids

Apigenin	OH	H	H
Luteolin	OH	H	H
Quercetin	OH	OH	OH



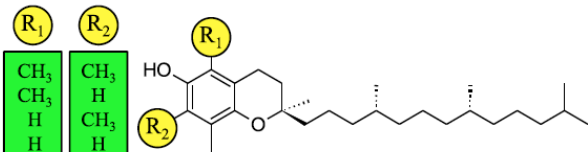
Lignans

(+)-Pinoresinol	H
1-(+)-Acetoxypinoresinol	OCOCH <sub>3</sub>
1-(+)-Hydroxypinoresinol	OH



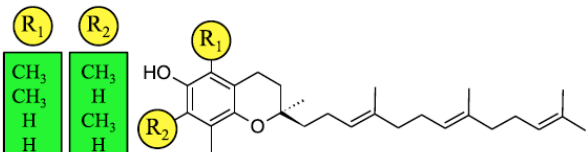
Tocopherols

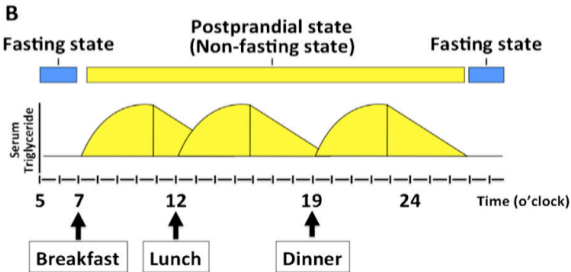
α-Tocopherol	CH <sub>3</sub>	CH <sub>3</sub>
β-Tocopherol	CH <sub>3</sub>	H
γ-Tocopherol	H	CH <sub>3</sub>
δ-Tocopherol	H	H



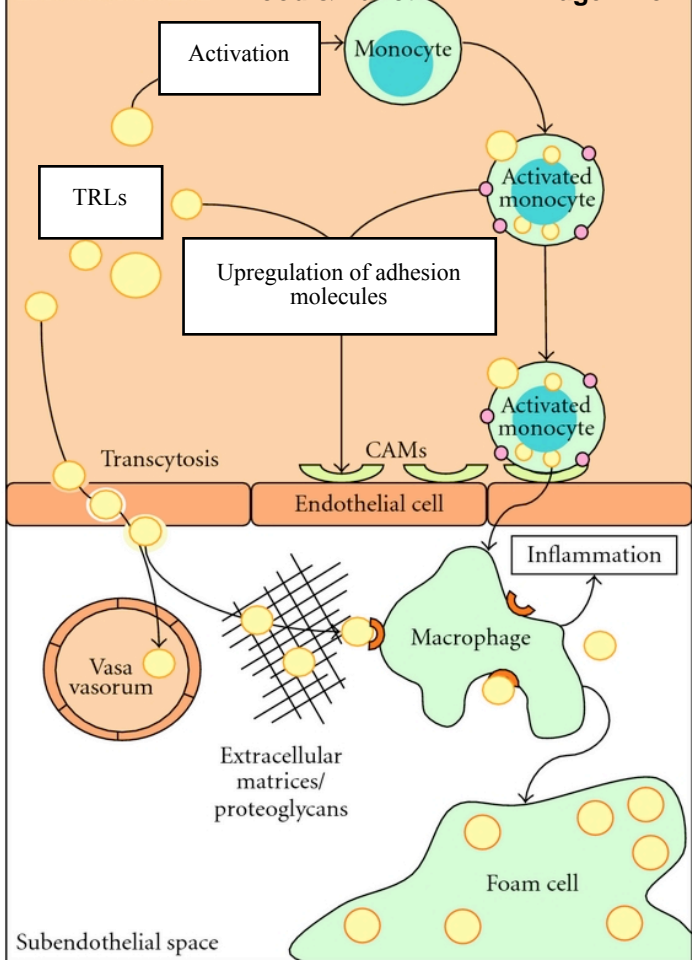
Tocotrienols

α-Tocotrienol	CH <sub>3</sub>	CH <sub>3</sub>
β-Tocotrienol	CH <sub>3</sub>	H
γ-Tocotrienol	H	CH <sub>3</sub>
δ-Tocotrienol	H	H

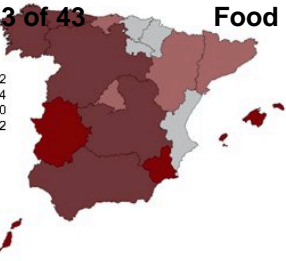
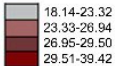








Prevalence  
men, %



# Food & Function

Prevalence  
women, %

