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Nutrigenomics and Atherosclerosis: The Postprandial and Long-Term Effects of Virgin Olive Oil Ingestion

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1. Introduction

Epidemiological studies over the past 50 years have revealed numerous risk factors for atherosclerosis. They can be grouped into factors with an important genetic component and environmental factors, particularly diet, which is one of the major, constant environmental factors to which our genes are expose through life. When a gene is activated, or expressed, functionally distinct proteins are produced which can initiate a host of cellular metabolic effects. Gene expression patterns produce a phenotype, which represents the physical characteristics of an organism (e.g., hair color), or the presence or absence of a disease. Nutrition scientists realize more and more that phenotypic treats (health status) are not necessarily produce by genes alone but also by the interaction of bioactive food components on the levels of DNA, RNA, protein and metabolites (Müller & Kersten, 2003). Nutritional genomics came into being at the beginning of the 1990s. There is some confusion about the delimitation of the concept, as often the terms of nutritional genomics, nutrigenetics, and nutrigenomics, are used as synonyms. Nutritional genomics refers to the joint study of nutrition and the genome including all the other omics derived from genomics: transcriptomics (mRNA), proteomics (proteins), and metabolomics (metabolites) (Fig. 1). The terms nutritional genomics would be equivalent to the wide-ranging term of gene-diet interaction. Within the wide framework of the concept of nutritional genomics, we can distinguish 2 subconcepts: nutrigenetics and nutrigenomics. Currently, there is a wide consensus on considering nutrigenetics as the discipline that studies the different phenotypic response to diet depending on the genotype of each individual. The term nutrigenomics is subject to a greater variability in its delimitation, but it seems that there is a certain consensus in considering nutrigenomics as the discipline which studies the molecular mechanisms explaining the different phenotypic responses to diet depending on the genotype, studying how the nutrients regulate gene expression, and how these changes are interrelated with proteomics and metabolomics (Corella & Ordovas, 2009). This interpretation of the nutrigenomics concept is the one that we shall use in this Chapter.
Atherosclerosis is a complex, multifactorial disease associated with accumulation of lipids in lesions along blood vessels, leading to the occlusion of blood flow, with oxidative and

inflammatory components playing major roles in its cause. Environmental factors with particular emphasis on nutrition as well as genetic factors appear to be responsible for these aberrant oxidative and inflammatory components and the lipid abnormalities associated with the disease. Diet may contribute to the atherosclerotic process by affecting lipoprotein concentration, their composition and degree of oxidation. Although certain key risk factors affecting atherosclerosis have been identified, the full molecular characterization will remain a challenge in the next century to come. As a complex biological process, the cellular and molecular details of the growth, progression and regression of the vascular lesions of atherosclerosis call for application of the newly developing omics techniques of analysis. Profiling gene expression using microarrays has proven useful in identifying new genes that may contribute to features of the atherosclerosis lesion (transcriptomics). One of the interesting challenges of modern biology is to define the diet that best fits the needs of the human species. Understanding the details of gene-nutrient interactions and of how changes in a gene or in the amount or form of a nutrient influence atherosclerosis is essential to developing insight into how to support optimal health from a nutritional perspective. There has been much interest regarding the components that contribute to the beneficial health effects of the Mediterranean diet. Recent findings suggest that bioactive components found in extra-virgin olive oil (EVOO) (oleic acid and polyphenol compounds) are endowed with several biologic activities that may contribute to the lower incidence of atherosclerosis in the Mediterranean area. This review summarizes more recent studies, including omics technologies that have lead to the development of new hypothesis concerning the cellular response to virgin olive oil (VOO) ingestion and to identify the major cellular pathways responsive to them.
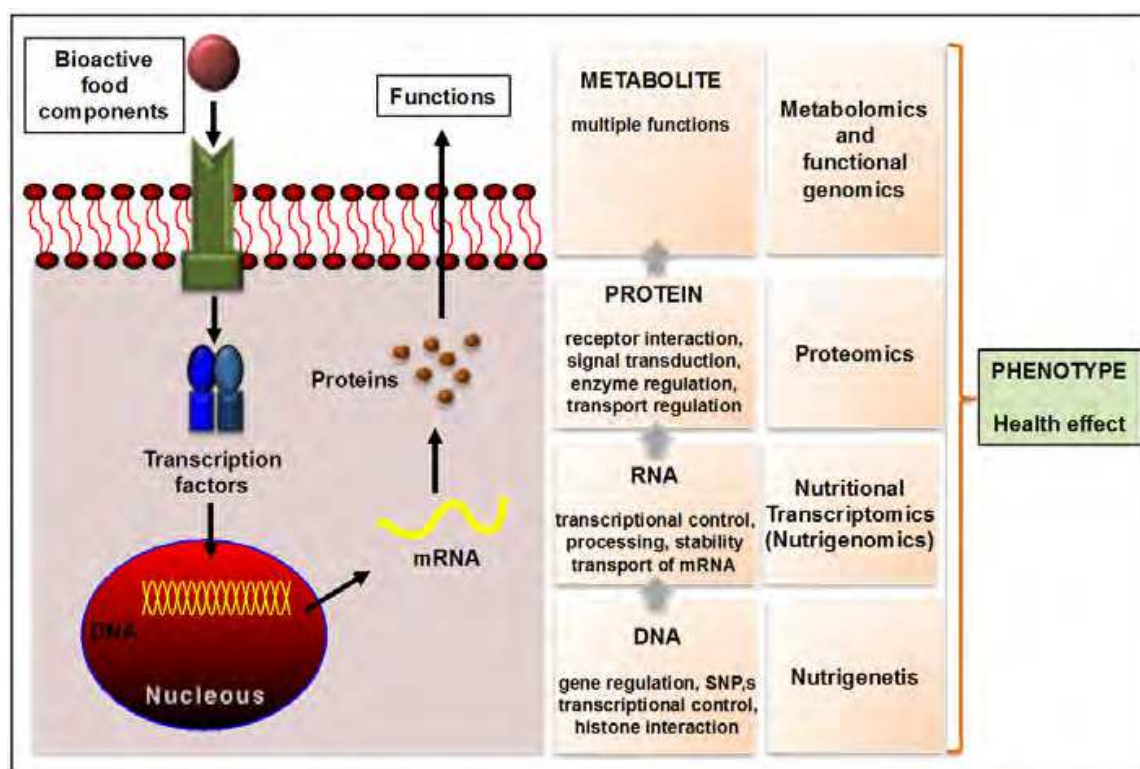

Fig. 1. Health effects of bioactive food components are related to specific interactions on a molecular level. (Adapted from Van Ommen, 2004; Müller & Kersten, 2003). SNP, single nucleotide polymorphism.

2. Olive oil and atherosclerosis

2.1 Olive oil classification according to International Olive Council

Olive oil is the main source of fat in the Mediterranean diet, and different categories of olive oils may be distinguished according to the International Olive Oil Council. Olive oil is obtained solely from the fruit of the olive tree (*Olea europaea*; family Oleaceae), and is not mixed with any other kind of oil. Olive oil extraction is the process of extracting the oil present in the olive drupes for food use. The oil is produced in the mesocarp cells, and is stored in a particular type of vacuole called a lipovacuole; every cell within an olive contains a tiny olive oil droplet. Olive oil extraction is defined as the process of separating the oil from the other fruit contents (vegetative extract liquid and solid material) and extracting the oil present in the drupes for food use. This separation is attained only by physical procedures under thermal conditions that do not alter the oil.

Several different types of oil can be oil extracted from the olive fruit and are classified as follows:

Virgin indicates that the oil was extracted by physical procedures only with no chemical treatment, and is in essence crude oil.

Refined indicates that the oil has been chemically treated to neutralise strong tastes (which are characterized as defects) and neutralise the acid content (free fatty acids). Refined oil is commonly regarded as a lower quality than virgin oil.

Pomace olive oil indicates oil that has been extracted from the pomace (ground flesh and pits left after pressing olives) using chemical solvents (typically hexane) and by heat.

Oil can be classified into different grades as follow:

Extra-virgin olive oil is the highest quality of olive oils and is produced by cold extraction of the olives; the oil has a free acidity of no more than 0.8 grams of oleic acid per 100 grams (0.8% acidity), and is often thought to have a superior taste. There can be no refined oil in extra-virgin olive oil.

Virgin olive oil has an acidity of less than 2%, and is often thought to have a good taste. There can be no refined oil in virgin olive oil.

Olive oil. Oils labelled as Olive oil are usually a blend of refined olive oil and one of the above two categories of virgin olive oil; typically, these blends contain less than or equal to 1.5% acidity. This grade of oil commonly lacks a strong flavour. Different blends are produced by adding more or less virgin oil to achieve different tastes.

Olive-pomace oil is a blend of refined pomace olive oil and possibly some virgin oil. This oil is safe to consume, but it may not be called olive oil.

Lampante oil is olive oil that is not used for consumption; lampante comes from olives that have strong physico-chemical and organoleptic defects and contain greater than 3,3% of acidity.

2.2 Olive oil composition

VOO is composed mainly of TGs (98-99 % of the total oil weight) and contains small quantities of free fatty acids (FFAs), and more than 230 chemical compounds such as aliphatic and triterpenic alcohols, sterols, hydrocarbons, volatile compounds and antioxidants. TGs are the major energy reserve for plants and animals. Chemically speaking, these are molecules derived from the natural esterification of three fatty acid molecules with a glycerol molecule. The glycerol molecule can simplistically be seen as an "E-shaped" molecule, with the fatty acids in turn resembling longish hydrocarbon chains, varying (in

the case of olive oil) from about 14 to 24 carbon atoms in length (Fig. 2). The fatty acid composition of olive oil varies widely depending on the cultivar, maturity of the fruit, altitude, climate, and several other factors. A fatty acid has the general formula: CH3(CH2)nCOOH where n is typically an even number between 12 and 22. If no double bonds are present the molecules are called saturated fatty acids (SFAs). If a chain contains double bonds, it is called an unsaturated fatty acid. A single double bond makes monounsaturated fatty acids (MUFAs). More than one double bond makes polyunsaturated fatty acids (PUFAs). The major fatty acids in olive oil triglycerides are: oleic acid (C18:1), a monounsaturated omega-9 fatty acid. It makes up 55 to 83% of olive oil. Linoleic acid (C18:2), a polyunsaturated omega-6 fatty acid that makes up about 3.5 to 21% of olive oil. Palmitic acid (C16:0), a SFA that makes up 7.5 to 20% of olive oil. Stearic acid (C18:0), a SFA that makes up 0.5 to 5% of olive oil (Fig. 2). Linolenic acid (C18:3) (specifically alpha-Linolenic acid), a polyunsaturated omega-3 fatty acid that makes up 0 to 1.5% of olive oil. In the triglycerides the main fatty acids are represented by monounsaturates (oleic acid), with a slight amount of saturates (palmitic and stearic acids) and an adequate presence of polyunsaturates (linoleic and α-linolenic acid) (Bermudez et al., 2011). Most prevalent in olive oil is the oleic-oleic-oleic (OOO) triglyceride, followed, in order of incidence, by palmitic-oleic-oleic (POO), oleic-oleic-linoleic (OOL), palmitic-oleic-linoleic (POL), and stearic-oleic-oleic (SOO).
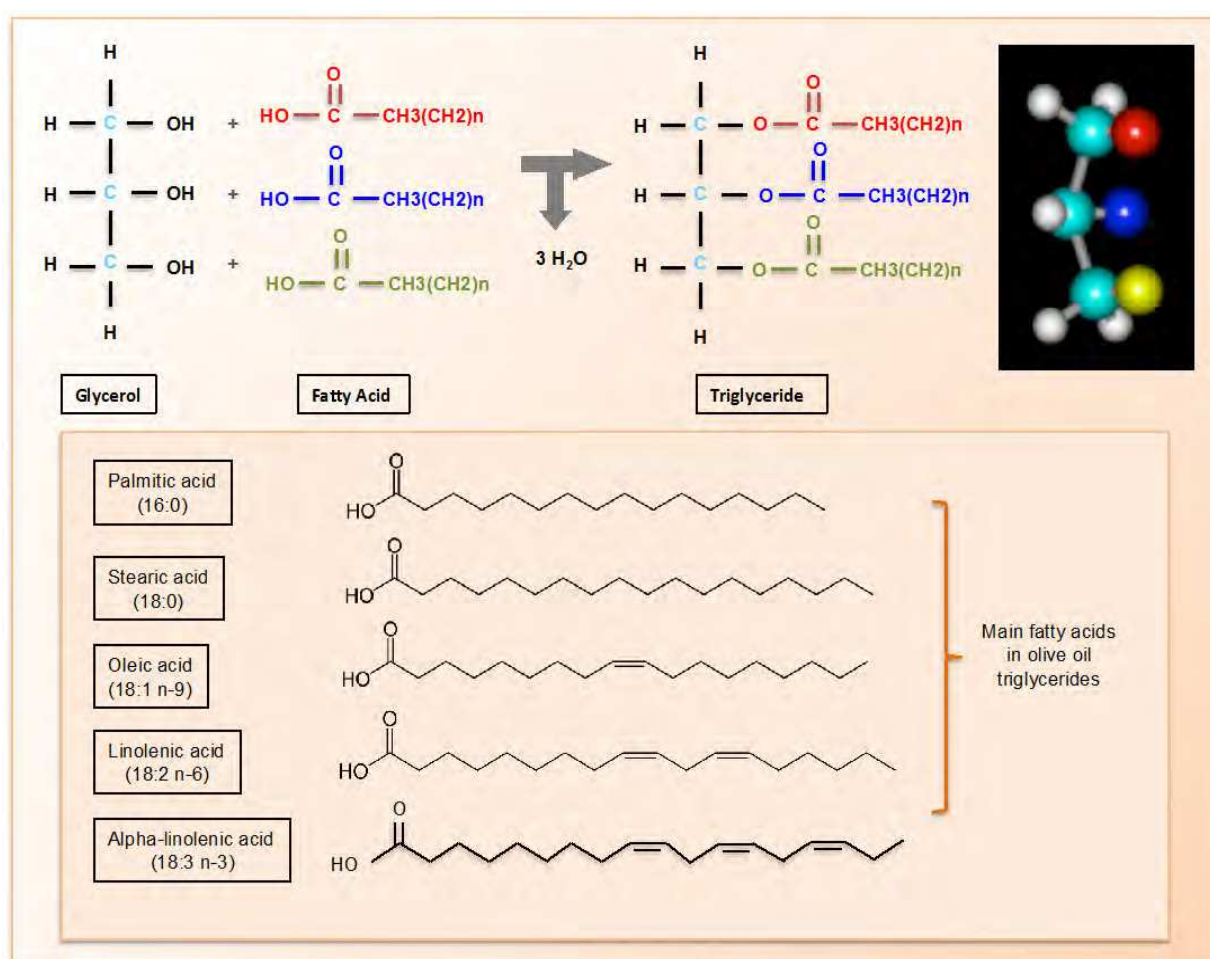

Fig. 2. Structure of triglycerides and main fatty acids in olive oil triglycerides.

The minor components of VOO are α-tocopherol, phenol compounds, carotenoids (β-carotene and lutein), squalene, pytosterols, and chlorophyll (in addition to a great number of aromatic substances). The factor that can influence the composition of VOO, especially in regard to its minor components, are the type of cultivar, the characteristics of the olive tree growing soil, climatic factors, fruit ripening stage, time of harvesting and degree of technology used in its production. The main antioxidants of VOO are phenols represented by lipophilic and hydrophilic phenols. Carotenes, on the contrary are contained in small concentrations. The lipophilic phenols, such as tocopherols and tocotrienols, can be found in other vegetable oils. In VOO more than 90% of total concentration of tocopherols is constituted by α-tocopherol. The VOO hydrophilic phenols constitute a group of secondary plant metabolites showing peculiar organoleptic and healthy properties. They are not generally present in other oils and fats (Servili et al., 2009). VOO contains four major classes of phenolic compounds: flavonoids, lignans, simple phenolics and secoiridois (Table 1). Although some cultivars contain flavonoids, the content in olive oil is low compared to other fruits and vegetables. Lignans are present at more significant

Phenolic alcohols (simple phenolics)	Phenolic acids and derivatives
(3,4-Dihydroxyphenil) ethanol (3,4 DHPEA) (HY)	Vanillic acid
(4-Hydroxyphenil) ethanol (p-HPEA) (TYR)	Syringic acid
(3,4-Dyhydroxyphenyl) ethanol-glucoside	p-Coumaric acid
Flavones	o-Coumaric acid
Apigenin	Gallic acid
Luteolin	Caffeic acid
Rutin	Protocatechuic acid
Lignans	p-Hydroxibenzoic acid
(+)-Acetoxypinoresinol	Ferulic acid
(+)-Pinoresinol	Cinnamic acid
(+)-Hydroxypinoresinol	4-(acetoxyithil)-1,2-Dihydroxybenzene
	Benzoic acid
	Hydroxy-isocromas
	Phenyl-6,7-dihydroxi-isochroman
Secoiridoids	
Dialdehydic form of decarboxymethyl elenolic acid linked to 3,4-DHPEA (3,4 DHPEA-EDA)	
Dialdehydic form of decarboxymethyl elenolic acid linked to p-HPEA (p-HPEA-EDA)	
Oleuropein aglycon (3,4 DHPEA-EA)	
Ligstroside aglycon	
Oleuropein	
p-HPEA-derivative	
Dialdehydic form of oleuropein aglycon	
Dialdehydic form of ligstroside aglycon	

Table 1. Phenolic composition of a Virgin Olive Oil.

amounts. The levels of secoiridoids and simple phenolics, many of which are exclusive to VOO, are the major phenolics found in olive oil. The simple phenolics present in VOO are predominantly hydroxytyrosol (HT) (3,4-dihydroxyphenylethanol) and tyrosol (TYR) (4-hydroxyphenylethanol) whilst the secoiridoids are derived from the glusosides of oleuropein and ligstroside forms, they contain in their chemical structure an HT (oleuropein derivatives) or TYR (ligstroside derivatives) moiety linked to elenolic acid (Corona et al., 2009). After ingestion, olive oil polyphenols can be partially modified in the acidic environment of the stomach, aglycone secoiridoids are subject to hydrolysis leading to approximate 5-fold increase in the amount of free HT and 3-fold increase in free TYR. If the ingested secoiridoid is glucosylated it appears not to be subject to gastric hydrolysis, meaning that phenolics such as glucosides of oleuropein enter the small intestine unmodified, along with high amount of free HT and TYR and remaining secoiridoid aglycones. The major site for the absorption of olive oil polyphenols is the small intestine, HT and TYR are dose-dependently absorbed and they are metabolized primarily to O-glucuronidated conjugates. HT also undergoes O-methylation by the action of catechol-O-methyl-transferase, and both homovanillic acid and homovanillyl alcohol have been detected in human and animal plasma and urine after the oral administration of either VOO or pure HT and TYR. Studies have also demonstrated that secoiridoids, which appear not to be absorbed in the small intestine, undergo bacterial catabolism in the large intestine with oleuropein undergoing rapid degradation by the colonic microflora producing HT as the major end product (Corona, et al., 2006). The intense interest in VOO polyphenols and their metabolites can be attributed to the association of such substances with several biological activities; these include antioxidant activity as well as other important healthy properties that will be discussed later. For this reason, olive polyphenols are recognized as potential nutraceutical targets for food and pharmaceutical industries.

2.3 Atherosclerosis and virgin olive oil

Atherosclerosis underlies the leading cause of death in industrialised societies (Lloyd-Jones et al., 2010). The key-initiating step of early stages of atherosclerosis is the subendothelial accumulation of apolipoprotein B-containing lipoproteins. These lipoproteins are produced by the liver and the intestinal cells and consist of a core of neutral lipids, mainly cholesteryl esters and triglycerides (TGs), surrounded by a monolayer of phospholipids and proteins. Hepatic apoB-lipoproteins are secreted as very-low density lipoproteins (VLDL), and they are converted to atherogenic low-density lipoproteins (LDL) during the circulation; in contrast, the intestinal apoB-lipoproteins are secreted as chylomicrons. The VLDL and chylomicrons can be converted into atherogenic remnant lipoproteins by lipolysis. The VLDL, chylomicrons and their remnants, which are known as triglyceride-rich lipoproteins (TRLs), appear in the blood after a high-fat meal (postprandial state) and are considered to be highly atherogenic (Havel, 1994; Zilversmith, 1979). In fact, chylomicronemia causes atherosclerosis in mice (Weinstein et al., 2010) and decreasing the TRLs level reduces the progression of coronary artery disease to the same degree as decreasing the LDL-cholesterol level (Hodis et al., 1999). TRLs comprise a large variety of nascent and metabolically modified lipoprotein particles that vary in size and density, as well as lipid and apolipoprotein composition. Studies have indicated that the size and the specific structural arrangement of lipids and apolipoproteins are associated with atherogenicity. Morover,

studies have consistently shown that there is an inverse relationship between the lipoprotein particle size and the ability to enter the arterial wall. Small TRLs and their remnants can enter the arterial wall and are independently associated with the presence, severity, and progression of atherosclerosis (Hodis, 1999). Short-term intake of the Mediterranean diet and the acute intake of an olive oil meal could favour the lower cardiovascular risk in Mediterranean countries by secreting a reduced number and higher-size TRLs particles compared with other fat sources (Perez-Martinez et al., 2011). Recent studies suggest that lipoproteins may also contribute to atherogenesis by affecting the mechanisms of the control of gene expression. Many lipoproteins-gene interactions have only been investigated under fasting conditions, Lopez et al., 2009 nicely reviews the emerging importance of gene-nutrient interactions at the postprandial state, which impacts ultimately on atherosclerosis risk.

A large body of knowledge exists from epidemiological, clinical, experimental animal models and in vitro studies that have indicated that olive oil can be regarded as functional food for its anti-atherogenic properties. Diets enriched with olive oil prevent the development and progression of atherosclerosis (Aguilera et al., 2002; Kanrantonis et al., 2006) and may also play an important role in atherosclerosis regression (Mangiapane et al., 1999; Tsalina et al., 2007, 2010). These and recent reports have suggested that the beneficial effects of olive oil on atherosclerosis may be influenced by the high oleic acid content and the minor fraction of the oil; potential benefitial microconstituents include tocopherols, phenolic compounds, phytosterols, triterpenoids and unusual glycolipids that exert an antagonistic effect on PAF (1-O-hexadecyl-2-acetyl-sn-glycero-3-phosphocholine). There are several mechanisms by which olive oil affects the development of atherosclerosis. Theses mechanisms have been nicely reviewed by Carluccio et al., 2007, and include the following: 1) regulation of cholesterol levels as olive oil decreases LDL-cholesterol and increases HDL-cholesterol; 2) decreased susceptibility of human LDL to oxidation, because of the lower susceptibility of its MUFAs content and to the ability of its polyphenol fraction to scavenge free radicals and reduce oxidative stress; 3) both, oleic acid and olive oil antioxidant polyphenols inhibit endothelial activation and monocyte recruitment during early atherogenesis; 4) decreased macrophage production of inflammatory cytokines, eicosanoid inflammatory mediators derived from arachidonic acids and increased nitric oxide (NO) production, which improves vascular stability; 5) decreased macrophages matrix-metalloproteinases (MMPs) production, which improves plaque stability; 6) oleic acid and olive oil polyphenols are associated with a reduced risk of hypertension; 7) oleic acid and olive oil polyphenols also affect blood coagulation and fibrinolytic factors, thereby reducing the risk of acute thrombotic cardiovascular events; and 8) a decreased rate of oxidation of DNA (Machowetz et al., 2007); human atherosclerosis is associated with DNA damage in both circulating cells and cells that comprise the vessel wall.

EVOO is therefore becoming more important due to its beneficial effects on human health. EVOO has proven effective in controlling atherosclerotic lesions, mainly within the framework of a Mediterranean-type diet (low cholesterol). An animal model that reproduces the processes taking place in the development of human atherosclerosis has been crucial to obtaining these conclusions, and this has been provided by the apoE-deficient mouse. Using this model, it has been proved that EVOO possesses beneficial antiatherogenic effects, and its enrichment with polyphenols (Rosenblat et al., 2008) and with long chain n-3 PUFAs (Eilertsen et al., 2011) further improves these effects, leading to the attenuation of

atherosclerosis development. Feeding these mice with various olive oils rich in different minor components or with these components in isolation has made it possible to assess the contribution of those molecules to the beneficial effect of this food, these effects have been review by Guillen et al., 2009 and include the following: 1) increase of small, dense HDL enriched with apo A-IV tightly bound to paraoxonase; these apolipoprotein A-IV-enriched particles were very effective in inactivating the peroxides present in the low-density lipoproteins (LDL) which are thought to initiate atherosclerosis; 2) minor components decrease plasma triglycerides and LDL-colesterol and very low density lipoprotein cholesterol (VLDL-colesterol), as well as 3) parameters of oxidative stress, such as isoprostane (8-iso-prostaglandin F2a); 4) EVOO acts against oxidative stress, which occurs primarily through a direct antioxidant effect as well as through an indirect mechanism that involves greater expression and activity of certain enzymes with antioxidant activities such as catalase and glutathione peroxidase-1 (Oliveras-Lopez et al., 2008). Among the antioxidants from EVOO, phenolic compounds have received the most attention. Oleuropein derivatives, especially HT, have been shown to have protective effects against markers associated with the atherogenic process (González-Santiago et al., 2006; Zrelli et al., 2011), some studies (Acin et al., 2006), however, have shown opposite results with HT administration in the atherosclerotic process. Given the anti-atherogenic properties of EVOO evident in animal models fed a Western diet, clinical trials are needed to establish whether these oils are a safe and effective means of treating atherosclerosis.

3. Nutrigenomics of olive oil

3.1 Gene-diet interactions after acute ingestion of olive oil

In addition to the mechanisms described above, olive oil components can exert an anti-atherogenic affect by acting at the genomic level. Nearly all evidence for the impact of olive oil on gene expression is derived from research using animal or human cells in culture. Carefully designed human clinical studies to establish a cause-and-effect relationship between olive oil affecting gene expression and the atherosclerotic process are scare and will be review here. Recent in vivo studies have shown that sustained consumption of VOO influence peripheral blood mononuclear cells (PBMNCs) gene expression (nutritional transcriptomics) (Table 2). PBMNCs are often used to asses changes in gene expression in vivo because the leucocytes recruitment from the circulation to the vessel wall for subsequent migration into the sub-endothelial layer is a critical step in atherosclerotic plaque formation; additionally, PBMNCs can be easily obtained from volunteers through simple blood draws. Previous studies have shown that in healthy individuals, a 3-week consumption of VOO as a principal fat source in a diet low in natural antioxidants (Khymenets et al., 2009) up-regulated the expression of genes associated with DNA repair proteins such as, the excision repair cross complementation group (ERCC-5) and the X-ray repair complementing defective repair Chinese hamster cells 5 (XRCC-5). VOO consumption also up-regulated aldehyde dehydrogenase 1 family, member A1 (ALDH1A1) and LIAS (lipoic acid synthetase) gene expression. ALDH1A1 is a gene encoding protein which protect cells from the oxidative stress induced by lipid peroxidation; the LIAS protein plays an important role in α-(+)-lipolitic acid (LA) synthesis. LA is an important antioxidant that has been shown to inhibit atherosclerosis in mouse models of human atherosclerosis due to its anti-inflammatory, antihyperglyceridemic and weight-reducing effects. Morover, apoptosis-related genes such as, BIRC-1 (baculoviral IAP repeat-containing protein 1) and TNSF-10 (tumor necrosis factor (ligand) superfamily, member 10),

were also upregulated. BIRC-1 inhibits apoptosis while TNSF-10 promotes macrophages and lymphocytes apoptosis. VOO ingestion also modified OGT gene expression (O-linked N-acetylglucosamine (GlcNAc) transferase). Nuclear and cytoplasmic protein glycosylation is a widespread and reversible posttranslational modification in eukaryotic cells; intracellular glycosylation via the addition of N-acetylglucosamine to serine and threonine is catalysed by OGT. Thus, OGT plays a significant role in modulating protein stability, protein-proteins interactions, transactivation processes, and the enzyme activity of target proteins; moreover OGT plays a critical role in regulating cell function and survival in the cardiovascular system. VOO consumption also profoundly impacted the expression of the USP-48 (ubiquitin specific peptidase-48) gene. USP-48 is a member of the ubiquitin proteasome system that removes damaged, oxidized and /or misfolded proteins; it also plays a role in inflammation, proliferation and apoptosis. PPARBP (peroxisome proliferator-activated receptor-binding protein), which is an essential transcriptional mediator of adipogenesis, lipid metabolism, insulin sensitivity and glucose homeostasis via peroxisome proliferator-activated receptor-γ (PPAR-γ) regulation, and ADAM-17 (a disintegrin and metalloproteinase domain 17), a membrane –anchored metalloprotease, were also upregulated. ADAM-17 is a candidate gene of atherosclerosis susceptibility in mice models of atherosclerosis (Holdt et al., 2008), it mediates the release of several cell-signaling and cell adhesion molecules such as vascular endothelial (VE)-cadherin, vascular cell adhesion molecule-1   (VCAM-1), intercellular adhesion molecule-1 (ICAM-1) or L-selectin affecting endothelial permeability and leukocyte transmigration. According with this study, Reiss et al. 2011, have recently show that unsaturated FFA increase ADAM-mediated substrate cleavage, with corresponding functional consequences on cell proliferation, cell migration, and endothelial permeability, events of high significance in atherogenesis.

LLorent-Cortes et al. 2010, have also concluded that a Mediterranean-type diet in a high-risk cardiovascular population impacts the expression of genes involved in inflammation, vascular foam cell formation and vascular remodelling in human monocytes. Inflammation plays a role in the onset and development of atherosclerosis. In this study, VOO ingestion prevented an increase in cyclo-oxygenase-2 (COX-2) expression and decreased monocyte chemotactic protein-1 (MCP-1) gene expression compared with a traditional Mediterranean diet (TMD) with nuts or a low fat diet. COX-2 is a pro-inflammatory enzyme that increases prostanoid levels (thromboxane A2; TXA2 and prostaglandine E2; PGE2); bioactive molecules present in VOO such as 1-hydroxityrosol and phenyl-6,7-dihydroxi-isochroman which is an ortho-diphenol present in EVOO, down-regulate COX-2 synthesis by preventing nuclear factor-kappaB (NF-kB) activation in macrophages and monocytes (Maiuri et al., 2005; Trefiletti et al., 2011). MCP-1 is a potent regulator of leucocyte trafficking, and animal studies have shown that a VOO diet can reduce neutrophil accumulation and decreases the MCP-1 blood levels (Leite et al., 2005); again, these data support the hypothesis that VOO is anti-inflammatory. Morover, the dietary intervention with VOO specifically prevented low density lipoprotein receptor-related protein-1 (LRP-1) overexpression in the high cardiovascular risk population. LRP-1 plays a major role in macrophage-foam cell formation and migration; additionally, LRP-1 is also a key receptor for the prothrombotic transformation of the vascular wall. Morover, VOO dietary intervention prevented an increase in the expression of genes involved in intracellular lipid accumulation in macrophages and monocytes (e.g., CD36 antigen; CD36) and in the process of thrombosis (e.g., tissue factor pathway inhibitory, FFPI) compared to a TMD enriched with nuts (high in PUFAs).

Reference	Subjects	Study design	Intervention	Gene Expression	Function
Khyments et al., 2009	Healthy men (6) and women (4)		Virgin olive oil in a diet low in antioxidants (1 wk washout, 3 wk 25ml VOO)	XRCC5, ERCC5 ALDH1A1, LIAS OGT, BIRC1, TNFSF-10 PPARBP, USP48, ADAM17.	DNA repair Oxidative stress Protein stability Apoptosis PPAR-γ regulation Tissue remodelling Endothelial permeability
Llorente-Cortes et al., 2010	Asymptomatic high cardiovascular-risk subjects (type 2 diabetes, hypertension, hypercholesterolemia, low HDL-cholesterol) (23 men, 26 women)	Randomized, controlled	Virgin olive oil or nuts in the context of a traditional Mediterranean diet (3 mo).	COX-2, MCP-1, TFPI, LRP1, CD36.	Inflammation Thrombosis Lipid accumulation
Konstantinidou et al., 2010	Healthy men and women (90)	Randomized, parallel, controlled	Virgin olive oil or washed virgin olive oil (without polyphenols) in the context of a traditional Mediterranean diet.	IFNγ, ARHGAP15, IL7R ADRB2 POLK	Inflammation Oxidative stress DNA repair

Table 2. Changes in gene expression of atherosclerotic-related genes after acute ingestion of virgin olive oil in human studies.

The last two nutritional interventions, suggest that the benefits associated with a TMD and VOO consumption can reduce cardiovascular risk via nutrigenomic effects; however, these studies could not distinguish between the effects elicited by minor components of VOO and those promoted by the fat content of the oil. A recent study by Konstantinidou et al, 2010 indicated that olive oil polyphenols play a significant role in the down-regulation of pro-atherogenic genes in human PBMNCs after 3 months of a dietary intervention with a TMD+VOO and TMD+WOO (washed virgin olive oil which has the same characteristics as VOO except for a lower polyphenol content). The dietary intervention decreased the expression of genes related to inflammation (e.g., interferon-γ, IFN-γ; Rho GTPase activating protein-15, ARHGAP-15; and Interleukin 7 receptor, IL7R) oxidative stress (e.g., adrenergic β-2 receptor surface, ADRB2) and DNA damage (e.g., polymerase DNA directed k, POLK). Changes in the expression of all of these genes, except POLK, were particularly observed when VOO, rich in polyphenols, was present in the TMD. The decrease in gene expression associated with inflammatory that was observed in this study agrees with previous studies that have reported a decrease in systemic inflammatory markers and oxidative stress due to the ingestion of polyphenols from olive oil and olive leaf extract (Poudyal et al., 2010; Puel et al., 2008). IFN-γ is considered to be a key inflammatory mediator and the release of this cytokine is regulated by polyphenols from red wine and dietary tea polyphenols (Deng et al., 2010; Magrone et al., 2008). ARHGAP-15 encodes for a Rho GTPase-activating protein that regulates the activity of GTPases. To date, little is known about the physiological role of ARHGAP-15, however, recent studies by Costa et al., 2011 have shown that this protein is associated with the selective regulation of multiple neutrophil functions. The protein encoded by the IL7R gene is a receptor for IL-7, which is associated with inflammation; interestingly, olive oil consumption has been shown to reduce the IL-7 serum concentration in patients with the metabolic syndrome (Esposito et al., 2004). POLK is a DNA repair gene that copies undamaged DNA templates. Previous studies have indicated that down-regulation of POLK is not associated with polyphenol content of VOO. Thus, the protective effect of VOO associated with DNA repair is related to the fat content (MUFA) and other minor oil components. ADRB2 has previously been associated with body composition (Bea et al., 2010), overexpression of the receptor that enhances reactive oxygen species (ROS) signalling (Di Lisa et al., 2011), and ADRB2 inhibition, which reduces macrophage cytokine production. Down-regulation of the ADRB2 gene, particularly in the TDM+VOO intervention group, along with an improvement in the oxidative status of the volunteers, may indicate that olive oil polyphenols protect against oxidative stress. Collectively, these studies support the hypothesis that olive oil polyphenol consumption in the context of a TMD may protect against cardiovascular disease by modulating the expression of atherosclerosis-related genes.

3.2 Influence of olive oil on gene-diet interaction at the postprandial state

Humans that reside in industrialised societies spend most of the daytime in a non-fasting state that is influence by meal consumption patterns and the amounts of food ingested. Postprandial lipaemia is characterised by an increase in TGs, specifically in the form of TRLs. Over 25 years ago, Zilversmit, 1979 proposed that atherogenesis was a postprandial phenomenon because high concentrations of lipoproteins and their remnants following food ingestion could deposit on the arterial wall and accumulate in atheromatous plaques. In postprandial studies, subjects usually receive a fat-loading test meal with a variable

composition according to the nutrient to be tested. In these studies, both, the amount and the type of fat ingested influence postprandial lipaemia. Although, controversial results have been obtained for comparing an olive oil fat meal with other dietary fats, some studies have shown that VOO intake decreases the postprandial TGs concentration and results in a faster TRLs clearance from the blood in normolipidemic subjetcs (Abia et al., 2001). The amount of fat ingested influences the results as small doses of olive oil (25 ml) did not promote postprandial lipaemia, whereas larger doses (40 and 50 ml) of any type of olive oil promoted lipaemia (Fitó et al., 2002; Covas et al., 2006). Olive oil is considered to be an optimal fat for the modulation of extrinsic cardiovascular risk factors in the postprandial state. The influence of olive oil on postprandial insulin release and action, endothelial function, blood pressure, inflammatory processes and hemostasis has been recently review by Bearmudez et al., 2011.

3.2.1 Postprandial effect of olive oil in PBMNCs

Early in vivo postprandial human studies have shown that VOO activates PBMCs immediately after ingestion and may induce changes in gene expression (Bellido et al., 2004). Postprandial studies have shown that high-fat meals can induce β cell dysfunction and insulin resistance in healthy individuals, as well as in subjects with type 2 diabetes or the metabolic syndrome. However, postprandial olive oil (MUFAs) can buffer β cell hyperactivity and insulin intolerance compared to butter (SFAs) in subjects with high fasting triglyceride concentrations (Lopez et al., 2011). Moreover, changes in expression of insulin sensitivity related genes occur in human PBMNCs after an oral fat load of VOO (Konstantinidou et al., 2009) (Table 3). In this study, the expression of genes such as OGT, arachidonate 5-lipoxygenase-activating protein (ALOX5AP), LIAS, PPARBP, ADBR2 and ADAM-17 were up-regulated at 6 h after VOO ingestion. LIAS and PPARBP regulate insulin sensitivity by activating and co-activating PPARγ, respectively. PPARγ is a nuclear hormone receptor that plays a crucial role in adipogenesis and insulin sensitisation. The authors hypothesised that the up-regulation of both of these genes may be one feed back mechanism that counteracts the postprandial oxidative stress that plays a role in the development of insulin resistance. The ADRB2 gene encodes for a major lipolytic receptor in human fat cells that modulates insulin secretion and protects against oxidative stress. Because insulin signaling activates the OGT gene, the authors attributed the increase in OGT expression with the several feedback mechanisms that serve to attenuate sustained insulin signalling. CD36 is an integral membrane glycoprotein expressed on the surface of cells active in fatty acid metabolism (adipocytes, muscle cells, platelets, monocytes, heart and intestine cells). This protein plays diverse functions, including uptake of long-chain fatty acids and oxidized low-density lipoproteins. CD36 deficiency underlies insulin resistance, defective fatty acid metabolism and hypertriglyceridemia in spontaneously hypertensive rats (SHRs), furthermore, lipid-induced insulin resistant has been associated with atherogenesis through mechanisms mediated by the expression of scavenger receptor CD36 (Kashyap et al., 2009). CD36 gene expression was modulated during the postprandial period after VOO ingestion (Konstantinidou et al., 2009), however the authors did not find a relationship between in CD36 gene expression and insulin levels in the subjects. Rather, they found an association with a postprandial increase in plasma fatty acids and the satiety response after VOO ingestion. ADAM-17 is considered to be an attractive target for controlling insulin resistance. It also regulates tumor necrosis factor (TNF-α), major negative regulator of the

Reference	Subjects	Study design	Intervention	Gene Expression	Function
Jimenez-Gomez et al., 2009	Healthy men (20)	Randomized, crossover Postprandial	Three diet intervention period of 4 wks [SFA (butter), MUFA (VOO) and PUFA (walnut)] followed by fat-load rich in either SFA, MUFA, or PUFA (60% fat)	TNF-α, IL-6	Inflammation
Konstantinidou et al., 2009	Healthy men (11)	Postprandial	Virgin olive oil (1 wk washout, followed by 50mL fat-load).	LIAS, PPARBP, ADRB2, ADAM17 OGT, ALOX5AP CD36	Insulin-sensitivity Scavenger receptor, satiety
Konstantinidou et al., 2009	Healthy men (6)	Postprandial	Virgin olive oil (1 wk washout, followed by 50mL fat-load).	IL-10, IFN-Y DCLRE1C, POLK OGT, ADAM17 USP48, ABCA7	Inflammation DNA repair Oxidative stress Tissue remodelling Apolipoprotein-dependent formation of HDL
Camargo et al., 2010	20 patiens (9 men, 11 women) suffering metabolic syndrome	Double-blinded, randomized, crossover postprandial	Virgin olive oil-based breakfast with high and low content of phenolic compounds. (1 wk washout period, followed by 40 mL fat-load)	CCL3, CXCL1, CXCL2, CXCL3, CXCR4 PTGS2 ILB1, IL6 SGK1, NFKBIA DUSP1, DUSP2, TRIB1	Leucocyte infiltration Prostaglandin biosynthesis Inflammation NF-kB activation Migration Proliferation, chemotaxis.

Table 3. Changes in gene expression of atherosclerotic-related genes after the ingestion of virgin olive oil in human studies during the postprandial period.

insulin receptor pathway, at posttranscriptional level. PPARBP may also increase insulin sensitivity by down-regulating the expression of TNF-α. The consumption of an olive oil-enriched breakfast decreases postprandial expression of TNF-α mRNA compared with a breakfast rich in butter and walnuts (Jimenez-Gomez et al., 2009). Correspondingly, acute consumption of EVOO decreased the circulating levels of soluble TNF-α in young healthy individuals (Papageorgiou et al., 2011). TNF-α activates a cytokine production cascade and thereby has a crucial role in the inflammatory process that is associated with atherogenesis; thus, dietary modification of TNF-α may prevent atherosclerosis.

In human interventional studies, an acute intake of olive oil increased the HDL cholesterol level, decreased inflammation, decreased lipid oxidation and decreased DNA oxidative damage. Studies by Konstantinidow et al. 2009, showed that there was a postprandial increase in the expression of PBMNCs genes related to DNA-repair (DNA-cross-link repair 1C, DCLRE1C and POLK) and inflammation (interleukin-10, IL-10; IFN-γ) 6h after ingestion of 50 mL of VOO. IL-10 is an anti-inflammatory cytokine that inhibits the production of interleukin-6 (IL-6), which is considered to be the most important inflammatory mediator. Il-6 release from rat adipocytes is regulated by the dietary fatty acid composition, and lower values of IL-6 are released with an olive oil diet (Garcia-Escobar et al., 2010); however, the postprandial change in plasma IL-6 concentrations does not seem to be altered by VOO ingestion (Teng et al., 2011; Manning et al., 2008). Postprandial VOO down-regulated IFN-γ gene expression. IFN-γ is a key pro-atherogenic cytokine that induces expression of adhesion molecules in endothelium and recruit leucocytes (Zhang et al., 2011), induces the expression of genes that have been implicated in atherosclerosis, promotes uptake of modified LDL (N. Li et al., 2010), and regulates macrophage foam cell formation and plaque stability, which are essential steps that mediate the pathogenesis of atherosclerosis. ATP-binding cassette, subfamily A, member 7 (ABCA7) is a protein that mediates the biogenesis of HDL with cellular lipids and helical apolipoproteins. In agreement with this, an increase in ABCA7 gene expression was observed in the postprandial studies after VOO ingestion.

The authors also observed up-regulation of several oxidative stress related genes and genes that may regulate NF-kB activation such as USP48 and a-kinase anchor protein-13 (AKAP-13). NF-kB regulates numerous processes in the cardiovascular system, including inflammation, cell survival, differentiation, proliferation and apoptosis. In vascular cells, NF-kB activation is mediated by diverse extracellular signals including Ang II, oxLDL, TRLs, advanced glycation end-products, and inflammatory cytokines. NF-kB activation by circulating cytokines has been linked to atherosclerosis and thrombosis and a number of NF-kB-regulated pro-inflammatory proteins are relevant for the initiation and progression of atherosclerosis. The induction of NF-κB signalling, results in transcriptional regulation of pro-inflammatory genes, including cytokines, chemokines, adhesion molecules, antioxidants, transcription factors, growth factors, and apoptosis and angiogenesis regulators (van der Heiden et al., 2010). The data showed so far, suggest that olive oil ingestion may protective during the postprandial by altering gene expression changes. However, the authors could not distinguish whether the protective effect was caused by the minor components of olive oil or to the fat content.

To adress this problem, Camargo et al., 2010 performed postprandial studies with two VOO based breakfast, with a high and low phenolic compounds content, administered to patients suffering form metabolic syndrome. The phenol fraction of VOO repressed the expression of several PBMNCs genes that are involved in inflammation processes mediated by cytokine-cytokine receptor interactions, arachidonic acid metabolism, mitogen-activated protein

kinases (MAPKs) and transcription factor NF-kB/AP-1, such as the SGK1 (serum/glucocorticoid-regulated kinase-1) and the NFKBIA (nuclear factor of kappa light chain gene enhancer in B cells inhibitor, alpha) genes. SGK1 encodes a serum/glucocorticoid-regulated kinase that enhances nuclear NF-kB activity by phosphorylating the inhibitory kinase IKKα. The NFKBIA gene, encodes the IkBα protein,which is a member of an inhibitory IkB protein family that sequesters NF-kB into the cytoplasm. As NF-kB binds to the IKBα promoter to activate its transcription, a decrease in NFKBIA expression should be associated with a decrease in NF-kB activation. The hypothesis that olive oil polyphenols decreases NF-kB activation is supported by in vivo studies, which showed that VOO ingestion reduces inflammatory response of PMBSCs mediated by transcription factor NF-kB when compared to, butter and walnut-enriched diets during the postprandial state (Bellido et al., 2004). The study also showed the VOO consumption decreased the expression of PTGS2 (prostagladin-endoperoxide synthase-2), interleukin 1- β (IL-1β) and IL-6. The PTGS2 gene encodes for COX-2, which is an inducible isozyme that mediates prostaglandin biosynthesis from the substrate arachidonic acid. Pro-inflammatory cytokines, prostaglandins and NO, which are produced by monocytes and activated macrophages, play critical roles in inflammatory diseases such as atherosclerosis. VOO and hydrolysed olive vegetation water (Bitler et al., 2005) exhibit anti-inflammatory activities in the human monocytic leukemia cell line (THP-1). Previous studies have shown that, HT down-regulates iNOS and COX-2 gene expression in THP-1 cells (Zhang et al., 2009) and in murine macrophages by preventing NF-kB, STAT-1alpha (signal transducer and activator of transcription-1) and IRF-1 (interferon regulatory factor-1) activation (Maiuri et al., 2005). In vitro studies by Graham et al., 2011 have recently shown that TRLs, isolated from healthy volunteers after ingestion of VOO and pomace olive oil, enriched in minor components, produces a decrease in IL-6 and IL-1B secretion along with a down-regulation of COX-2 mRNA in macrophages. IL-6 is a pro-inflammatory cytokines that may contribute to the development of atherosclerosis by promoting insulin resistance, dyslipidaemia and endothelial dysfunction (Wilson, 2008). IL-6 synthesis is stimulated by IL-1β, which is another pro-inflammatory cytokine that regulates endothelial cell proliferation and the expression of adhesion molecules on the arterial wall (Andreotti et al., 2002). Studies, with a high-fat diet induced insulin-resistant animal model, showed that the ingestion of green tea polyphenols decreased IL-1β and IL-6β mRNA expression in cardiac muscle (Qin et al., 2010).

Circulating monocytes are components of innate immunity, and many pro-inflammatory cytokines and adhesion molecules facilitate monocyte adhesion and migration to the vascular endothelial wall. Monocyte migration is a key event in the pathogenesis of atherosclerosis. Therefore, modulating PMBCs activity and creating a less deleterious inflammatory profile may decrease leucocytes recruitment from the circulation to the vessel wall, important process in the initiation of atherosclerosis. According to this, Camargo et al., 2010 observed a decreased expression of chemokine, cc motif, ligand-3 (CCL3), chemokine, cxc motif, ligan-1 (CXCL1), chemokine, cxc motif, ligan-2 (CXCL2), chemokine, cxc motif, ligan-3 (CXCL3) and chemokine, cxc motif, receptor-4 (CXCR4) after acute-intake of phenol-rich olive oil. The CCL3 gene, which encodes for macrophage inflammatory protein-1 (MIP-1) has been implicated in inducing leucocyte-endothelial cell interactions and leucocyte recruitment in vivo (Gregory et al., 2006). CXCL1, CXCL2 and CXCL3, regulate leucocytes cell trafficking. CXCR4 have been shown to mediate bone mesenchymal

stem cells migration through the endothelium in response to ox-LDL (M. Li et al., 2010). Dual-specificity phosphatase-1 (DUSP-1), dual-specificity phosphatase-2 (DUSP-2) and tribbes homology-1 (TRIB-1), gene expression were decreased by phenol-rich olive oil. DUSP-1 is actively involved in atherosclerosis and a chronic deficiency of DUSP-1 in ApoE(-/-) mice leads to decreased atherosclerosis via mechanisms involving impaired macrophage migration and defective extracellular signal-regulated kinase signalling (Shen et al., 2010). TRBIR1 is also involved in MAPK signalling and is up-regulated in vascular smooth muscle cells (SMCs) of human atherosclerotic plaques; TRBIR1 expression levels are key for modulating the extent of vascular SMCs proliferation and chemotaxis (Sung et al., 2007). Extracellular matrix degradation occurs in several pathological conditions such as atherosclerosis. Among the circulating cells, activated monocytes may directly contribute to atherosclerosis by expressing MMPs. In particular, monocytes express matrix metalloproteinase-9 (MMP-9), which is a member of the MMPs family that acts on the extracellular matrix, facilitates the migration of recruited monocytes to the sub-endothelial layer and acts on precursors of inflammatory cytokines, thereby amplifying the inflammatory response. In vitro studies showed that oleuropein aglycone, which a typical olive oil polyphenol, prevented an increase in MMP-9 expression and secretion in THP-1 cells (Dell´Agli et al., 2010); these data provide further evidence regarding the mechanisms by which olive oil reduces inflammation during atherosclerosis.

3.2.2 Postprandial effect of olive oil on the endothelium

Low-grade inflammation is often associated with endothelial dysfunction, which is associated with the development of atherosclerosis. Moreover, remnant like-lipoproteins have been associated with endothelial dysfunction and coronary artery disease in subjects with metabolic syndrome (Nakamura et al., 2005). A large number of genes are regulated after endothelial cells are exposed to TRLs with the net effect reflecting receptor and non-receptor mediated pathways that are activated or inhibited depending on the fatty acid type, lipid and apolipoprotein composition of TRLs and the presence or absence of lipoprotein lipase (Williams et al., 2004). TRLs have been shown to induce pro- and anti-inflammatory responses in the endothelium, and TRL composition plays a key role in determining these responses. TRLs that were isolated after a meal enriched in SFAs induced E-selectin, VCAM-1 and lectin-like oxidised-LDL receptor-1 (LOX-1) gene expression to a higher extent compared to TRLs that were isolated after a meal enriched in MUFAs and PUFAs (Williams et al., 2004); similarly, chylomicrons separated after ingestion of safflower oil, which is rich in polyunsaturated linoleic acid, induced a higher expression level of adhesion molecules compared with chylomicrons that were separated after ingestion of olive oil, rich in monounsaturated oleic acid (Jagla & Schrezenmeir, 2001). The effects of lipoproteins on vasoactive substances may also play a role in endothelial dysfunction. The endothelium-derived relaxing factor NO has gained wide attention because the current data suggests that it may protect against hypertension and atherosclerosis. In general, high-fat meals have often been associated with a loss of postprandial vascular reactivity compared to low fat meals. However several studies have shown that differences in food composition and the fatty acid content of meals may contribute to the observed effects on vascular reactivity via postprandial lipoproteins modifications. Thus, meals that contain MUFAs and eicosapentaenoic/docosahexaenoic acids (EPA/DHA) can attenuate the endothelial function impairment likely by reducing the most atherogenic postprandial lipoprotein

subclass containing apolipoproteins B and C (Hilpert et al., 2007). Olive oil polyphenols can also inhibit endothelial adhesion molecule expression through NF-kB inhibition (Carluccio et al., 2003). In endothelial cell models, oleic acid (Carluccio et al., 1999) and phenolic extracts from EVOO, strongly reduced the gene expression of the vascular wall cell adhesion molecules (ICAM-1, VCAM-1), being HT, oleuropein and oleuropein aglycone the main polyphenols responsible for these effects (Dell´Agli et al., 2006; Carluccio et al., 2003)

3.2.3 Postprandial effect of olive oil in smooth muscle cells

SMCs are essential for proper vasculature function. SMCs contract and relax to alter the luminal diameter, which enables the blood vessels to maintain an appropriate blood pressure. However, vascular SMCs can also proliferate and migrate and synthesise large amounts of extracellular matrix (ECM) components. Thus, SMCs plays an important role in atherogenesis. TRLs induce the SMCs proliferation and migration via MAPKs activation, G protein–coupled receptor (GPCR)–dependent or independent protein kinase C (PKC) activation, epidermal growth factor receptor (EGF) transactivation and heparing-binding EGF-like growth factor shedding. TRLs can exert their effects on SMCs by acting at the genomic level (Lopez et al., 1999). TRL up-regulates the expression of genes involved in proliferation (e.g., cycin D1, CCND1; cyclin E, CCNE1; proliferating cell nuclear antigen, PCNA), inflammation (e.g., interleukin-8, IL-8; IL-1B; COX-2; suppressor of cytokine signaling 5, SOCS-5), signal transduction (e.g., mitogen-activated protein kinase 1, MAP3K-1; mitogen-activated protein kinase phosphatase-3, MKP-3; dual-specificity tyrosine phosphorylation-regulated kinase 1A, DYRK1A), oxidative stress (e.g., stress-activated protein kinase-3, SAPK-3 and stress-activated protein kinase-2A, SAPK-2A) and cytoskeleton function and motility (e.g., vimentin, VIM; keratin 19, KRT-19; fibrillin, FBN; tubulin beta, TUBB) (Bermudez et al., 2008). Furthermore, increasing evidence has shown that the pathophysiological contribution of TRLs to atherosclerosis development of plaque stability depends on the fatty acid composition of TRLs. The same study showed that TRLs obtained after the ingestion of olive oil produced a less deleterious pro-atherogenic profile compared to TRLs obtained after ingestion of butter (SFAs) or a mix of vegetable and fish oils (PUFAs). Since the olive oil contained no minor components, the effects were mainly attributed to oleic acid. However, oleic acid is not the sole component of olive oil that confers health benefits. In that sense, oleanolic acid, which is a natural triterpenoid that is present in pommace olive oil, induces prostaglandine I2 (PGI2) production through a mechanism that involves COX-2 mRNA upregulation via MAPKs signalling pathways (Martinez-Gonzalez et al., 2008).

4. Conclusions

Nutrigenomic analyses directly asseses the influence of bioactive food compounds on gene expression. An increasing amount of data indicate that the fatty acids and polyphenols present in EVOO modulate the expression of key atherosclerotic-related genes, in vascular (macrophages, endothelial and smooth muscle cells) and peripheral blood mononuclear cells, towards a less-atherogenic gene profile. These compounds exert an effect after acute ingestion of the oil and during the postprandial state, and may provide protection during several stages of atherosclerosis. These data presented here, suggest that the traditional Mediterranean diet (rich in VOO) is optimal for both healthy and high-risk cardiovascular

populations for the prevention of atherosclerosis plaque progression. The current literature suggests that EVOO, with its adequate PUFAs content, being poor in SFAs, high in MUFAs, and rich in antioxidants, is the best dietary fat for the prevention of atherosclerotic disease and ischemic cardiopathy. The ultimate goal in the prevention and treatment of coronary atherosclerosis is to reduce the risk of new heart attacks and reduce the mortality associated with cardiovascular failure. Thus, identification of an optimal diet may aid in the prevention of disease development and decrease the risk of associated cardiovascular events.

5. Abbreviations

ABCA-7 = ATP-binding cassette, subfamily A, member-7
ADAM-17 = A disintegrin and metalloproteinase domain-17
ADRB2 = Adrenergic β-2 receptor surface
ARHGAP-15 = Rho GTPase activating protein-15
BIRC-1 = Baculoviral IAP repeat-containing protein-1
CCL3 = Chemokine, cc motif, ligand-3
CD36 = CD36 antigen
COX-2 = Cyclo-oxygenase-2
CXCL1 = Chemokine, cxc motif, ligan-1
CXCL2 = Chemokine, cxc motif, ligan-2
CXCL3 = Chemokine, cxc motif, ligan-3
CXCR4 = Chemokine, cxc motif, receptor-4
DUSP-1 = Dual-specificity phosphatase-1
DUSP-2 = Dual-specificity phosphatase-2
EVOO = Extra-virgin olive oil
FFA = Free fatty acids
HDL = High density lipoprotein
HT = Hydroxytyrosol
IFN-γ = Interferon-γ
ICAM-1 = Intercellular adhesion molecule-1
IL-1β = Interleukin 1-β
IL-6 = Interleukin-6
IL7R = Interleukin 7 receptor
IL-10 = Interleukin 10
LA = α-(+)-Lipolitic acid
LDL = Low-density lipoproteins
LIAS = Lipoic acid synthetase
LRP-1 = Lipoprotein receptor-related protein-1
MCP-1 = Monocyte chemotactic protein-1
MMPs = Matrix-metalloproteinases
MMP-9 = Matrix metalloproteinase-9
MUFAs = Monounsaturated fatty acids
NF-κB = Nuclear factor-kappaB
NFKBIA = Nuclear factor of kappa light chain gene enhancer in B cells inhibitor, alpha
NO = Nitric oxide
OGT = O-linked N-acetylglucosamine (GlcNAc) transferase

PBMNCs = Peripheral blood mononuclear cells
POLK = Polymerase DNA directed k
PPARBP = Peroxisome proliferator-activated receptor-binding protein
PPAR-γ = Peroxisome proliferator-activated receptor-γ
PTGS2 = Prostagladine-endoperoxide synthase-2
PUFAs = Polyunsaturated fatty acids
SFAs = Saturated fatty acids
SGK-1 = Serum/glucocorticoid-regulated kinase-1
SMCs = Smooth muscle cells
TGs = Triglycerides
TMD = Traditional Mediterranean diet
TNF-α = Tumor necrosis factor
TNSF-10 = Tumor necrosis factor (ligand) superfamily, member 10
TRIB-1 = Tribbes homology-1
TRLs = Triglyceride-rich lipoproteins
TYR = Tyrosol
USP-48 = Ubiquitin specific peptidase- 48
VCAM-1=Vascular cell adhesion molecule-1
VLDL = Very-low density lipoproteins
VOO = Virgin olive oil

6. Acknowledgements

7. References

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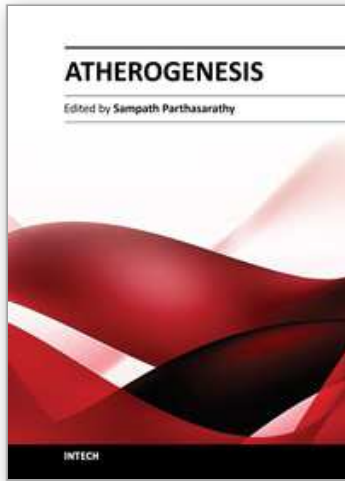
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