Mediterranean Diet Rich in Olive Oil and Obesity, Metabolic Syndrome and Diabetes Mellitus

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Abstract: After decades of epidemiological, clinical and experimental research, it has become clear that consumption of Mediterranean dietary patterns rich in olive oil has a profound influence on health outcomes, including obesity, metabolic syndrome (MetS) and diabetes mellitus. Traditionally, many beneficial properties associated with this oil have been ascribed to its high oleic acid content. Olive oil, however, is a functional food that, besides having high-monounsaturated (MUFA) content, contains other minor components with biological properties. In this line, phenolic compounds have shown antioxidant and antiinflammatory properties, prevent lipoperoxidation, induce favorable changes of lipid profile, improve endothelial function, and disclose antithrombotic properties. Research into the pharmacological properties of the minor components of olive oil is very active and could lead to the formulation of functional food and nutraceuticals. Although more data are mandatory the Mediterranean diet rich in olive oil does not contribute to obesity and appears to be a useful tool in the lifestyle management of the MetS. Moreover there is good scientific support for MUFA diets, especially those based on olive oil, as an alternative approach to low-fat diets for the medical nutritional therapy in diabetes. The objective of this review is to present evidence illustrating the relationship between Mediterranean diet, olive oil and metabolic diseases, including obesity, MetS and diabetes mellitus and to discuss potential mechanisms by which this food can help in disease prevention and treatment.

Keywords: Mediterranean diet, olive oil, metabolic syndrome, diabetes mellitus, obesity, functional food, phenolic compounds, inflammation, oxidative stress.

INTRODUCTION

Metabolic diseases, including obesity, diabetes mellitus, and the metabolic syndrome (MetS), have an outstanding impact on public health due to its increasing prevalence and poor prognosis. Morbidity and mortality from these chronic diseases in the general population have a multifactorial origin, resulting from the interaction between genetic background and environmental factors. Among the latter, diet is probably the most relevant factor. The basis of what constitutes optimal nutrition has been the subject of decades of research spanning the whole range of study designs, from ecological studies to in vitro modulation of gene expression. However, epidemiological studies have been at the forefront of scientific progress to establish the link between nutrition and health. Based on this approach, there is now sufficient evidence supporting the notion that the monounsaturated fatty acids (MUFA) as a nutrient, olive oil as a food, and the Mediterranean diet (MedDiet) as a food pattern are associated with a decreased risk of cardiovascular disease, obesity, MetS, and diabetes mellitus.

In the last decade, research in nutritional epidemiology has moved from the single food approach to the dietary pattern, which better reflects the complexity of interactive effects of multiple nutrients on health status [1-3]. In relation to the MedDiet, a recent meta-analysis of prospective studies based on 1.5 million subjects and 40,000 fatal and non-fatal events showed that a greater adherence to this dietary pattern was significantly associated with a reduction of overall mortality, cardiovascular mortality, cancer incidence and cancer mortality, and incidence of Alzheimer’s disease and Parkinson’s disease [4]. Recently, a cross-sectional assessment of baseline data from a cohort of high-risk participants in the PREMIDMED study, a large-scale feeding trial of primary cardiovascular prevention [5], showed that adherence to the MedDiet was inversely associated with the clustering of diabetes mellitus, obesity, hypertension and hypercholesterolemia. The follow-up of large cohorts of healthy populations living in Mediterranean countries, such as the Greek EPIC [2, 6-8] and ATTICA [9, 10] study cohorts and the Spanish EPIC [11] and SUN [12] study cohorts, are providing new information suggesting that increasing adherence to the MedDiet relates to a reduced prevalence of risk phenotypes.

The principal goals of medical nutrition therapy for subjects with obesity, MetS, and/or diabetes are to attain and maintain an optimal metabolic control, including blood glucose, lipid profiles, and blood pressure; to prevent and treat obesity and cardiovascular complications; and to improve general health and well-being through food choices that take personal and cultural preferences into consideration. In this regard, pioneering nutritional strategies, such as nutraceuticals, have been developed aimed at reducing the main metabolic risk factors and promoting cardiovascular health. Moreover, a growing body of clinical evidence has demonstrated positive cardiovascular effects associated with olive oil, antioxidants, and polyphenols intake. Traditionally, many beneficial properties associated with olive oil have been ascribed to its high oleic acid content. Olive oil, however, can be considered a functional food that, besides having high-MUFA content, contains other minor components with biological properties [13]. In this context, phenolic compounds have shown antioxidant and antiinflammatory properties, prevent lipoperoxidation, induce favorable changes of lipid profile, improve endothelial function, and disclose antithrombotic properties [14-19].

We review the state of the art illustrating the relationship between MedDiet rich in olive oil and metabolic diseases, including obesity, MetS and diabetes mellitus and to discuss potential mechanisms by which this food can help in disease prevention and treatment.

MEDITERRANEAN DIET, OLIVE OIL AND OBESITY

A continuous upward trend in high-energy food consumption and sedentary lifestyles have led to a worldwide epidemic of obesity and associated metabolic alterations, intimately related to vis-
cereal fat accumulation. Traditionally, nutritional advice for the treatment of obesity and associated disorders has emphasized avoiding animal fat and, preferably, all kinds of dietary fat, and replacing them with carbohydrate (CHO). The central arguments against the consumption of animal fats in particular, and of fatty foods in general, have been a high content in cholesterol-rising saturated fatty acids (SFA) and excess energy, thought to promote obesity. In fact, lowering the content of SFA in the diet remains a primary goal of nutrition therapy for health. Scientific evidence has accumulated in the last two decades about the beneficial role of diets with a relatively high MUFA content on a number of cardiovascular risk outcomes, including diabetes [20]. The debate on what is the best nutrient to replace energy sources from SFA in the diet, CHO or MUFA, has indirectly been solved by the Women’s Health Initiative study [21] showing the lack of protective effect of a high-CHO diet against cardiovascular disease. Recent results from a 20-year follow-up of the prospective Nurses’ Health Study [22] suggest that a low-CHO diet (high-fat and/or high-protein) does not promote coronary heart disease and might actually reduce its incidence when the diet is high in unsaturated fat and vegetable proteins.

The results of observational studies in Mediterranean countries, where people complying with the MedDiet consume significant amounts of olive oil, have shown that increasing adherence to such high-fat, high-MUFA dietary pattern is associated with decreasing obesity rates [23-25]. On the other hand, another prospective study from a Mediterranean country has shown that increasing olive oil use is not associated with weight gain [26]. Moreover, recent data from the Pizarra population-based cohort study (n=613) have demonstrated a significantly decrease in the incidence of obesity in those who consumed olive oil than in those who consumed sunflower oil after 6 years of follow up [27]. Restricted energy diets that were relatively high in fat because they incorporated olive oil were effective alternatives to the traditional low-fat diet for initial weight loss and maintenance in feeding studies in obese persons, while showing better palatability and compliance [28, 29]. Another randomized trial with ad libitum MedDiets enriched with olive oil or mixed nuts, the PREDIMED study, showed no 3-month weight gain with these high-fat diets [30]. A satiating effect of olive oil intake with ensuing food compensation might explain its lack of a fattening effect. In this regard, experimental evidence has been provided showing that mobilization of intestinally-derived oleoylethanolamide, a lipid messenger of satiety, is enabled by uptake of dietary oleic acid [31]. These positive effects attributed to the MedDiet have also been observed in other European region. Thus, in a recent study including a sample size of almost 500,000 individuals from 10 Mediterranean, Central, and Northern European countries, the adherence to a MedDiet, modified to apply across Europe, was associated with lower waist circumference in men and women after controlling for BMI, total energy intake, and other potential confounders. Interestingly, the inverse association between Mediterranean Diet Score (MDS) and waist circumference generally was stronger in men and women from Northern European regions who were overweight or obese [32]. Recently Romaguera et al. [33] conducted a prospective cohort study (EPIC-PANACEA) in 373,803 individuals from 10 European countries. They observed that individuals with a high adherence to the MedDiet showed a 5-y weight change of -0.16 kg (95% CI: -0.24, -0.07 kg) and were 10% (95% CI: 4%, 18%) less likely to develop overweight or obesity than were individuals with a low adherence to the MedDiet pattern. In this context it is important to highlight that a variant of the traditional MDS with potentially wide applicability in non-Mediterranean countries was used in the EPIC-PANACEA study. This variant differs from the original score, because it includes both

**Fig. (1).** Health effects of the Mediterranean Diet (MedDiet) rich in olive and the potential mechanisms by which this food can help in disease prevention and treatment.
MUFA and PUFA in its definition (instead of MUFA only). In the same line participants from the SUN cohort with the lowest adherence (3 points) to the MDS exhibited the highest average yearly weight gain, whereas participants with the highest (6 points) adherence exhibited the lowest weight gain. This inverse association was extended to other a priori–defined MDSs. The group with the highest adherence to the MDS also showed the lowest risk of relevant weight gain (5 kg) during the first 4 y of follow-up [34]. In conclusion, the MedDiet rich in olive oil does not contribute to obesity and may help curb it.

**MEDITERRANEAN DIET, OLIVE OIL AND METABOLIC SYNDROME**

The MetS comprises a cluster of cardiovascular risk factors (visceral obesity, low HDL-cholesterol and elevated blood pressure, fastiging glucose, and triglycerides) and thereby carries an elevated risk of cardiovascular disease. Its underlying feature is impaired glucose disposal or insulin resistance [35]. The factors that regulate body fat distribution, insulin resistance, and associated metabolic disturbances are not fully understood. Nevertheless, increasing scientific evidence suggests that dietary habits may be an important environmental factor regulating glucose and fat metabolism [36]. Epidemiological studies indicate that Western-style dietary patterns promote the MetS, while diets rich in fruits, vegetables, grains, fish and low-fat dairy products have a protective role [37-39]. Recently, 2 studies in Southern European populations showed that a greater adherence to the MedDiet was associated with reduced prevalent [40] and incident [41] MetS.

To date, four feeding trials have assessed the effect of dietary patterns on the MetS status [42-45]. These studies used a behavioral program to implement a relatively low-fat MedDiet [43], intensive lifestyle intervention with inclusion of a vegetable-rich diet restricted in animal fat [44], the DASH diet [42], and two MedDiets supplemented with virgin olive oil or nuts [45] in comparison with standard advices. Three studies [42-44] used energy-restricted diets that led to some degree of weight loss, while one study [45] used ad libitum diets. In all these studies, a decreased prevalence of MetS was shown in the intervention groups. In the PREDIMED study [45], the MedDiet with nuts significantly reduced MetS prevalence at 1 year, mostly because of increased reversion of prior MetS due to redistribution in waist girth in spite of no weight loss, suggesting fat redistribution. Moreover, in a subgroup of this study including the Reus PREDIMED Centre some components of the MedDiet, such as olive oil, legumes and red wine were associated with lower prevalence of MetS [46]. On the other hand, results of a study in overweight, insulin-resistant patients also suggest that, by comparison with a low-fat diet, a MUFA-rich diet prevents the redistribution of body fat from peripheral to visceral adipose tissue without affecting total body weight [47]. Finally we have recently demonstrated that postprandial abnormalities associated with MetS can be attenuated with high MUFA diets [48].

In conclusion, although more data are mandatory the high-fat MedDiet, whether energy-restricted or not, appears to be a useful tool in the lifestyle management of the MetS.

**MEDITERRANEAN DIET, OLIVE OIL AND DIABETES**

The incidence of type 2 diabetes mellitus, a disease difficult to treat and expensive to manage, is increasing rapidly worldwide. Lifestyle modification, in particular recommendations to follow an appropriate dietary pattern, has generally been accepted as a cornerstone of treatment for people with type 2 diabetes, with the expectation that an appropriate intake of energy and nutrients will improve glycaemic control and reduce the risk of complications. Because diabetes is a frequent outcome in patients with sustained MetS, it is reasonable to assume that the MedDiet might also prevent the development of diabetes in predisposed persons or beneficially influence the metabolic abnormalities associated with the diabetic status.

In this context, two prospective studies from Southern European cohorts suggest a lower incidence of diabetes with increasing adherence to the MedDiet in previously healthy persons [50] or survivors of a myocardial infarction [51]. In contrast, in the absence of weight loss, the low-fat diet used in the Women’s Health Initiative trial [52] was ineffective to prevent the development of diabetes.

Diets high in SFA consistently impair both insulin sensitivity and blood lipids, while substituting CHO or MUFA for SFA reverts these abnormalities [53]. Postprandial lipemia and glucose homeostasis are also improved after meals containing MUFA from olive oil compared to meals rich in SFA [54, 55]. Thus, an examination of the association of dietary and membrane fatty acids with insulin secretion in the cross-sectional Pizarra study [56] showed that dietary MUFA contributed to the variability of β-cell function, with a favorable relationship of MUFA with β-cell insulin secretion, independently of the level of insulin resistance.

The question as to what was the best nutrient to replace energy sources from SFA in the diabetic diet, CHO or MUFA, was also hotly debated. Since the late 1980’s, many feeding trials have compared the effects of isoenergetic high CHO and high MUFA diets on insulin sensitivity in healthy subjects and on glycemic and lipid control in diabetic patients [57, 58]. Garg’s meta-analysis [57] favored high MUFA diets, but most of the studies reviewed therein were performed with metabolic diets having wide differences in total fat content between the two experimental diets, ranging from 15% to 25% of energy. The studies reviewed by Ros [58] were performed on an outpatient basis with natural foods, olive oil as the main source of MUFA, and <15% energy difference in total fat content between diets; the conclusion was that both dietary approaches provided a similar degree of glycemic control. Nevertheless, high MUFA diets generally had more favorable effects on proatherogenic alterations associated with the diabetic status, such as dyslipidemia, postprandial lipemia, small LDL, lipoprotein oxidation, inflammation, thrombosis, and endothelial dysfunction [58]. Although we will discuss this point later, of particular interest is the ability of the olive oil-rich MedDiet to improve mild systemic inflammation, as shown by the reduction of C-reactive protein and inflammatory cytokines in the study of Esposito et al. [43] in subjects with MetS and by the PREDIMED study [30] in diabetic patients and other subjects at high risk for CHD.

In summary, there is good scientific support for MUFA diets, especially those based on olive oil, as an alternative approach to low-fat diets for the medical nutritional therapy in diabetes.

**PROTECTIVE MECHANISMS OF MEDITERRANEAN DIET AND OLIVE OIL**

Multiple mechanisms have been proposed to explain the beneficial effects of the MedDiet rich in olive oil (Table 1). Excessive oxidative stress and inflammation are closely associated with the pathogenesis of many human diseases (such obesity, MetS, diabetes, cardiovascular diseases, neurodegenerative diseases and aging). The potential reversal of those conditions can be achieved by reducing the levels of inflammation through the consumption of an anti-inflammatory dietary pattern. Usually this may occur through the reduction of systemic vascular inflammation and endothelial dysfunction without having a drastic effect on body weight. Phenolic compounds present in olive oil have anti-inflammatory activity; therefore, they can modulate signal transduction pathways to elicit their beneficial effects in human diseases. These mechanisms include modulation of pro-inflammatory gene expression such as cyclooxygenase, lipooxygenase, nitric oxide synthases and several pivotal cytokines, mainly by acting through nuclear factor-kappa B and mitogen-activated protein kinase signaling. Beyond this, epidemiological and interventional studies have revealed a protective effect of the MedDiet, and olive oil in particular, against mild chronic inflammation and its metabolic complications [59-61].
Inflammation at the cellular level can be described as an increase in the nuclear factor \( \kappa \)B (NF-\( \kappa \)B) in the nucleus and with a concomitant decrease in its inhibitors \( \kappa \)B-alpha and/or \( \kappa \)B-beta [62]. NF-\( \kappa \)B is a pleiotropic transcription factor activated by low levels of reactive oxygen species (ROS) and inhibited by antioxidants [63]. This factor regulates the expression of several cytokines, chemokines, cell adhesion molecules, immunoreceptors and inflammatory enzymes [64], molecules that are involved in disease such as atherosclerosis and insulin resistance. In most cells, NF-\( \kappa \)B (p50/p65) is present in an inactive form in the cytoplasm, bound to an inhibitor \( \kappa \)B. Certain stimuli result in the phosphorylation, ubiquitination and subsequent degradation of \( \kappa \)B proteins thereby enabling translocation of this transcription factor into the nucleus. In this context, an interesting aspect was the demonstration that supplementing an endothelial cell culture with oleic acid reduces the transcriptional activation of this factor in these cells, similar to what is done by \( \alpha \)-linolenic acid, and the opposite of the inflammatory effect of linoleic acid. Thus, Hennig et al. [65] exposed porcine endothelial cells to 18-carbon fatty acids. Both linoleic and stearic fatty acids activated endothelial cells more markedly than did either oleic or \( \alpha \)-linolenic fatty acids. Also, compared with control cultures, treatment with stearic and linoleic acids decreased glutathione concentrations, which suggested an increase in cellular oxidative stress. This increase in oxidative stress with the subsequent activation of NF-\( \kappa \)B could be one of the mechanisms of the inflammatory properties of 18:0 and 18:2 fatty acids.

Earlier studies have confirmed that fat consumption induced the activation of inflammatory markers [66]. In this regard, we previously demonstrated that the MedDiet, enriched in virgin olive oil, attenuated peripheral blood mononuclear cells (PBMCs) NF-\( \kappa \)B activation compared with a Western SFA rich diet, and the effect of an n-3 PUFA-enriched diet was intermediate in young healthy

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<tr>
<th>Metabolic Diseases</th>
<th>Type of Effect</th>
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<tr>
<td>Obesity</td>
<td>Decrease obesity rates (23-25, 33)</td>
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<td></td>
<td>Favorable effects on weight (26, 27, 30)</td>
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<td></td>
<td>Satiating effect (31)</td>
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<td></td>
<td>Reduce waist circumference (32)</td>
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<td></td>
<td>Reduce prevalence and incidence (40, 41, 46)</td>
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<tr>
<td>Metabolic Syndrome</td>
<td>Reduction in waist girth (45)</td>
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<tr>
<td></td>
<td>Prevent the redistribution of body fat from peripheral to visceral adipose tissue (47)</td>
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<td></td>
<td>Improve postprandial lipemia (48)</td>
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<tr>
<td>Diabetes Mellitus</td>
<td>Reduce incidence (50, 51)</td>
</tr>
<tr>
<td></td>
<td>Improve insulin sensitivity and blood lipids (53)</td>
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<td></td>
<td>Improve postprandial lipemia (54)</td>
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<tr>
<td></td>
<td>Improve glucose homeostasis (55)</td>
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<td></td>
<td>Favourable relationship with ( \beta )-cell insulin secretion (56)</td>
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<th>Protective Mechanisms</th>
<th>Type of Effect</th>
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<tr>
<td>Inflammation</td>
<td>Prevent the activation of NF-( \kappa )B (67-69)</td>
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<td></td>
<td>Decrease CRP, interleukin 6,7 and 18 plasma levels (30, 43)</td>
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<td>Reduce the expression of mRNA TNF-( \alpha ) (80)</td>
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<td>Repress in vivo expression of pro-inflammatory genes (94-98)</td>
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<td>Adhesion molecules</td>
<td>Reduce VCAM-1 and E-selectin gene expression (71, 72)</td>
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<td></td>
<td>Reduce ICAM-1 plasma levels (67)</td>
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<tr>
<td>Oxidation</td>
<td>Reduce oxidized LDL plasma levels (30, 74, 75)</td>
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<tr>
<td></td>
<td>Improve postprandial oxidative stress parameters (93)</td>
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<tr>
<td>Endothelial function</td>
<td>Attenuate plasma markers of endothelial activation (86)</td>
</tr>
<tr>
<td></td>
<td>Improve endothelium-dependent vasodilatory response (84)</td>
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<tr>
<td></td>
<td>Improve vasomotor function (91)</td>
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population [67, 68]. These findings suggest that virgin olive oil could be a possible contributor to prevent the activation of NF-κB system, within the frame of the MedDiet. Besides olive oil, the MedDiet contents other source of potentially cardioprotective nutrients from fruits and vegetables which could also enhance this beneficial effect. In contrast, the opposite effect has been observed after the chronic intake of a Western diet rich in saturated fatty acids, corroborating previous data after the acute intake of a butter meal. The effect of a high CHO diet enriched in n-3 fatty acids on the NF-κB activation was intermediate. In this sense, previous data have suggested that n-3 α-linolenic acid found mainly in plants and walnuts may reduce cardiovascular risk through a variety of biological mechanisms, including inhibiting vascular inflammation.

In the same line, but at functional level, Brunelleschi et al. [69] explored the effects of an extra-virgin olive oil extract, particularly rich in minor polar compounds, on NF-κB translocation in monocytes and monocyte-derived macrophages isolated from healthy volunteers. In a concentration-dependent manner, olive oil extract inhibited p50 and p65 NF-κB translocation in both un-stimulated and phorbol-myristate acetate challenged cells, being particularly effective on the p50 subunit. Interestingly, this effect occurred at concentrations found in human plasma after nutritional ingestion of virgin olive oil and was quantitatively similar to the effect exerted by ciglitazone, a PPAR-γ ligand. However, olive oil extract did not affect PPAR-γ expression in monocytes and monocyce-derived macrophages [69]. These data suggest the hypothesis of a protective effect of extra-virgin olive oil by indicating its ability to inhibit NF-κB activation in human monocyte/macrophages. On the other hand, NF-κB has been shown to regulate the expression of several adhesion molecules in response to inflammatory stimuli, including P-selectin, E-selectin, intercellular adhesion molecule 1 (ICAM-1) and cell adhesion molecule 1 (VCAM-1) [70], all implicated in atherosclerosis development. Carluccio et al. [71] observed, in an endothelial cell culture model, that the incorporation of oleic acid into cellular membrane lipids reduced the expression of VCAM-1. Furthermore, it has been observed that the expression of VCAM-1 and E-selectin in human umbilical vascular endothelial cells (HUVECs), following the addition of minimally oxidised LDL, was less with LDL obtained from persons who had followed a diet rich in olive oil than from persons whose diet was rich in saturated fat [72]. This anti-inflammatory action of MUFA also explains the fact that the enrichment of LDL particles with oleic acid, during the consumption of different types of diet, reduces their capacity to induce monocyte chemotaxis and adhesion. In accordance with these results, a previous study has shown that LDL obtained from a MUFA-rich diet induced a lower rate of monocyte adhesion to endothelial cells [73]. The mechanism by which LDL from carbohydrates and MedDiet induces a lower expression of VCAM-1 and E-selectin is unknown; however, several hypotheses have been suggested, for instance, the interaction of mononuclear leukocytes with vascular endothelial cells is most likely mediated by a complex amalgam of interacting regulatory signals in the inflammatory response characteristic of early atherogenesis. In another study including healthy subjects, virgin olive oil reduced plasma levels of ICAM-1 [67]. This anti-inflammatory effect has also been observed in MetS patients who modified their diet for two years. In the group that followed a MedDiet model, the prevalence of this syndrome was reduced, improved insulin sensitivity and lowered the levels of C-reactive protein (CRP) and interleukin 6, 7 and 18. Such findings have recently been corroborated by Estruch et al. [30] who evaluated the short-term effects of two ad libitum MedDiets (supplemented with either 1 l/week of virgin olive oil or 30 g/day of nuts) and an ad libitum low-fat diet on intermediate markers of cardiovascular disease. Compared with participants in the low-fat group, after 6 months those in the MedDiet groups had decreased levels of C-reactive protein. In addition, olive oil consumption also reduced levels of IL-6, VCAM-1 and ICAM-12. Moreover, people who eat the MedDiet that includes virgin olive oil reduce their levels of oxidized LDL, as suggested by the results of a subgroup analysis of the PREDIMED study carried out in 372 participants at high risk for cardiovascular disease, including diabetes [74]. Furthermore, new data suggest that virgin olive oil intake was associated with higher levels of plasma antioxidant capacity after 3 years of intervention [75].

However, when explaining possible mechanisms it is important to recall that fasting is not the typical physiological state of the modern human being, which spends most of the time in the postprandial state. Therefore, the assessment of the postprandial lipemic response may be more relevant to identify disturbances in metabolic pathways related to inflammation and oxidative stress than measures taken in the fasting state. With regard to the postprandial state, several previous studies have demonstrated that a breakfast enriched in saturated fat resulted in an increase in biomarkers of inflammation and oxidative stress [76-78]. In this regard, the identification of increased expression of TNF-α, a proinflammatory cytokine, in the adipose tissue of obese mice and humans has been correlated with the degree of adiposity and associated with insulin resistance. This fact is crucial given that insulin resistance will drive towards an increase in oxidative stress, endothelial dysfunction and impairments in lipoprotein metabolism and blood pressure. Therefore, targeting TNF-α and/or its receptors has been suggested as a promising treatment for insulin resistance and type 2 diabetes [79]. In this scenario our group observed that a breakfast rich in olive oil or walnuts decreased postprandial expression of mRNA TNF-alpha in PBMCs from healthy men compared with a butter-enriched breakfast [80]. However, the effects of the three fatty breakfasts on the plasma concentrations of these proinflammatory parameters showed no significant differences. The fact that we only found differences in the expression of TNF-alpha at mRNA levels in PBMCs following the intake of the three breakfasts may be due to that the synthesis and secretion processes of these proteins do not happen simultaneously, and to the short half-life of cytokines [81, 82].

In the last years another interesting observation is that dietary fat may affect the endothelium [83-85], and factors related to the arterial wall [86]. Several studies have shown that the acute administration of a high-fat meal induces a transitory disruption of endothelial function. Moreover, the effect of chronic consumption of a high-fat diet on endothelial function has also been evaluated. One study showed that a Mediterranean-style diet administered during 28 days to healthy subjects, attenuated plasma markers of endothelial activation, suggesting an improvement in endothelial function [86].

Similarly, the chronic consumption of low-fat diets and Mediterranean-style diets improve endothelial function compared to a high-fat Western-type diet in hypercholesterolemic patients [87]. In this line, Esposito et al. demonstrated that the consumption of a Mediterranean-style diet by patients with the MetS was associated with improvement of endothelial function, by assessing the vascular responses to L-arginine, the natural precursor of nitric oxide [43]. More recently Radilis et al. observed that the close adherence to a MedDiet diet improves endothelial function in subjects with abdominal obesity [88]. On the other hand, previous studies also demonstrated that postprandial lipemia induces endothelial dysfunction [89, 90]. According to this fact, Fuentes et al. studied the chronic effect of three diets with different fat compositions (high-SFA; high-MUFA; and a low-fat diet enriched in alpha-linolenic acid) on postprandial endothelial function and inflammatory biomarkers in twenty healthy men. This study demonstrated that the endothelium-dependent vasodilatory response was greater after the ingestion of the high-MUFA diet. Moreover this diet also induced lower postprandial sVCAM-1 levels and higher bioavailability of NOx compared with the other two diets [84]. In the same line, we have recently showed that a high-MUFA diet improves endothelial cell, improving vasomotor function, with a higher availability of...
nitric oxide synthase and decreasing plasma sICAM-1 levels compared with a high-SFA diet and two low-fat, high complex carbohydrate diets, supplemented with 1.24 g/day of long chain n-3 PUFA or placebo, in MetS patients [91]. Therefore, those data carried out in the postprandial state support previous evidences suggesting that dietary patterns similar to those of the Mediterranean-style diet exert positive effects on components of the MetS and other conditions associated with, including endothelial dysfunction [43, 92]. In the same population, the high-MUFA diet improved postprandial oxidative stress parameters as measured by glutathione levels and the glutathione/oxidized glutathione ratio. In addition, this diet induced lower postprandial plasma levels of lipoperoxides, protein carbonyls concentration and superoxide dismutase activity compared to subjects adhering to the other three diets [93]. Furthermore, postprandial plasma hydrogen peroxide levels were unfavourable increased during the high-SFA diet compared to the other three diets [93]. These findings suggest that the postprandial state is important for understanding possible cardiovascular effects associated with the MedDiet particularly in subjects with the MetS. In addition, these findings support recommendations to consume a HMUFA diet as a useful tool to prevent cardiovascular diseases in MetS patients.

On the other hand, it has been recently demonstrated the effects that phenolic fraction of olive oil exert at transcriptional level in vivo. In this regard, Camargo et al. [94] studied postprandial gene expression on peripheral blood mononuclear cells. To this end, two virgin olive oil-based breakfasts with high and low content of phenolic compounds were administered to 20 MetS patients following a double blinded, randomized, crossover design. They demonstrated that intake of virgin olive oil rich in phenol compounds is able to repress in vivo expression of several pro-inflammatory genes, thereby switching activity of peripheral blood mononuclear cells to a less deleterious inflammatory profile. In the same context, the dismutation activity of a MedDiet with virgin olive oil, rich in polyphenols, decreased plasma oxidative and inflammatory status and the gene expression related with both inflammation (INF-gamma (INFGamma), Rho GTPase-activating protein15 (ARHGAP15), and interleukin-7 receptor (IL7R)) and oxidative stress (adrenergic beta2-receptor (ADRB2)) in PBMCs from healthy volunteers [95]. Moreover the same authors demonstrated the hypothesis that 3 weeks of nutritional intervention with virgin olive oil supplementation, at doses common in the MedDiet, can alter the expression of genes related to atherosclerosis development and progression [96].

In the same line, Llorente-Cortés et al. [97] have confirmed in a population at high cardiovascular risk, that the MedDiet rich in olive oil influences expression of key genes involved in vascular inflammation, thrombosis and, in general, on atherosclerosis susceptibility. Moreover, it has been previously demonstrated in mice that olive oil up-regulates uncoupling protein (UCP) genes in brown adipose tissue and skeletal muscle [98], which is important given that UCP have been related with the regulation of body fat in mammals across its participation on the system of thermogenesis [99]. It is well reported that mitochondrial biogenesis could, in part, underlie the central role of adipose tissue in the control of whole-body metabolism and the actions of some insulin sensitizers and that mitochondrial dysfunction might be an important contributing the symptoms of MetS [100]. In a recent study Hao et al. observed that the hydroxytyrosol (HT) treatment resulted in an enhancement of mitochondrial function, including an increase in activity and protein expression of mitochondrial complexes I, II, III and V; increased oxygen consumption; and a decrease in free fatty acid contents in the adipocytes. These data suggest that HT is able to promote mitochondrial function by stimulating mitochondrial biogenesis. This mitochondrial targeting property may provide a possible mechanism for the efficacy of the MedDiet for lowering the risk of cardiovascular disease and also suggests that HT may be used as a therapeutic intervention for preventing and treating diabetes mellitus and obesity [101].

In conclusion, based in the above evidences presented, we could assume that the MedDiet rich in nutrients with favorable anti-inflammatory properties, such as virgin olive oil, may protect from metabolic diseases that are related to chronic inflammation and overproduction of reactive oxygen species, such as obesity, MetS and diabetes.

**SUMMARY AND FUTURE DIRECTION**

In summary, olive oil is a foodstuff with a wide range of healthy effects, typical of functional foods. Some of these effects are related to its high content of MUFA, although others depend on its richness in microcomponents, especially abundant in virgin olive oil. This food product, thanks to its double set of benefits, may protect from metabolic diseases that are related to chronic inflammation and overproduction of reactive oxygen species, such as obesity, MetS and diabetes. However, despite the significant advances of the last years, the final proof about the specific mechanisms and contributing role of the different dietary models and nutrients to its beneficial effects requires further investigations.

In the future, the integrated application of approaches that are becoming available in functional genomics, metabolomics, lipomics, proteomics techniques, and bioinformatics analysis, will lead to a more highly integrated understanding of its positive effects on health. In this context the recent advances in human nutrigenomics and nutrigenetics, two fields with distinct approaches to elucidate the interaction between diet and genes but with a common ultimate goal to optimize health through the personalization of diet, will provide powerful approaches to unravel the complex relationship between nutritional molecules, genetic polymorphisms, and the biological system as a whole. On the other hand efforts should be put into identifying those micronutrients in olive oil that have the greatest beneficial effects on health.

In conclusion after decades of epidemiological, clinical and experimental research, it has become clear that consumption of Mediterranean dietary patterns rich in olive oil have a profound influence on health outcomes. Thus, there is good scientific support for recommend MedDiets, especially those based on olive oil, as an alternative approach for the medical nutritional therapy in obesity, MetS and diabetes.

**CONFLICT OF INTEREST**

None of the authors had any conflict of interest.

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