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Nutritional Therapy in Diabetes: Mediterranean Diet

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1. Introduction

Diabetes mellitus is a chronic illness which has an outstanding impact on public health due to its increasing prevalence, poor prognosis, and due to the high impact on cardiovascular health. Such is its importance, that diabetes is actually considered an independent predictor of cardiovascular disease (which includes coronary heart disease and stroke). Moreover, the cardiovascular risk of individuals with diabetes is considered to be equivalent to the risk of nondiabetic individuals with pre-existing cardiovascular disease. Therefore, persons with diabetes mellitus have an increased susceptibility to atherosclerosis and an increased prevalence of atherogenic risk factors, notably hypertension, obesity, and abnormal lipids. This compendium of the abnormalities can be found in people with metabolic syndrome (MetS) which is now regarded as a prelude to diabetes and such as diabetes, MetS is a substantial predictor of cardiovascular disease and all-cause mortality (Ford, et al. 2002).

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 in order to prevent acute complications and to reduce the risk of long-term complications. Thus, it has been demonstrated that medical nutrition therapy is important in preventing diabetes, managing existing diabetes, and preventing, or at least slowing, the rate of development of diabetes complications. 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. 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, 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 (Hu 2002; Trichopoulou, et al. 2003; Trichopoulou, et al. 1995). Thus, the MedDiet pattern is built on the basis of a consumption of fat primarily from

foods high in MUFA (olive oil as the principal source of fat), and emphasizes the consumption of fruits, vegetables, legumes, nuts, and fish, as well as a moderate consumption of alcohol. In this regard, the MedDiet pattern has been associated with higher survival due to lower all cause mortality (Knoops, et al. 2004). 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 (Sofi, et al. 2008). In addition, a recently cross-sectional assessment of baseline data from a cohort of high-risk participants in the PREDIMED study, a large-scale feeding trial of primary cardiovascular prevention (Sanchez-Tainta, et al. 2008), 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 (Psaltopoulou, et al. 2004; Trichopoulou, et al. 2005a; Trichopoulou et al. 2003; Trichopoulou, et al. 2005b) and ATTICA (Panagiotakos, et al. 2009a; Panagiotakos, et al. 2006) study cohorts and the Spanish EPIC (Agudo, et al. 2007) and SUN (Nunez-Cordoba, et al. 2009) study cohorts, are providing new information suggesting that increasing adherence to the MedDiet relates to a reduced prevalence of risk phenotypes. In this regard, the MedDiet pattern is being reconsidered as the one of the more holistic approaches for the control of metabolic diseases including at the same time salutary and pleasure components.

The principal goals of medical nutrition therapy for subjects with metabolic syndrome, 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. In this context, 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 (Perez-Jimenez, et al. 2007). Thus, phenolic compounds have shown antioxidant and antiinflammatory properties, prevent lipoperoxidation, induce favorable changes of lipid profile, improve endothelial function, and disclose antithrombotic properties (Lopez-Miranda, et al. 2007; Lopez-Miranda, et al. 2010; Perez-Jimenez, et al. 2005; Perez-Jimenez, et al. 2006; Ruano, et al. 2007; Ruano, et al. 2005). Therefore, all those evidences suggest that MedDiet could serve as an antiinflammatory dietary pattern, which could help fighting diseases that are related to chronic inflammation, such as MetS and type 2 diabetes. In this context, it has been clearly demonstrated that many components of the MedDiet have been considered to be important in the treatment and modulation of cardiometabolic diseases. In the present chapter, we review the state of the art illustrating the relationship between MedDiet rich in olive oil and metabolic diseases, including MetS and diabetes mellitus and to discuss potential mechanisms by which this food can help in disease prevention and treatment.

2. Mediterranean diet and diabetes

In the last decade the incidence of conditions associated with insulin resistance, including metabolic syndrome and diabetes mellitus, is increasing rapidly worldwide. Although pharmacological interventions are available for minimizing or delaying the comorbidities associated with insulin resistance and the metabolic syndrome, as well as diabetes, initial management for the vast majority of the affected population remains focused on lifestyle modification, consisting of sustainable changes in dietary habits and physical activity. Lifestyle modification, in particular recommendations to follow an appropriate dietary pattern, has generally been accepted as a cornerstone of treatment for people with these conditions, with the expectation that an appropriate intake of energy and nutrients will improve glycaemic control and will reduce the risk of complications. 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 (Phillips, et al. 2006). Epidemiological studies indicate that Western-style dietary patterns promote the MetS, while diets rich in vegetables, fruits, grains, fish and low-fat dairy products have a protective role (Esmailzadeh, et al. 2007; Lutsey, et al. 2008; Pereira, et al. 2005). In the same line, two studies in Southern European populations showed that a greater adherence to the MedDiet was associated with reduced prevalence (Panagiotakos, et al. 2004) and incidence (Tortosa, et al. 2007) of MetS. To date, several feeding trials have assessed the effect of dietary patterns on the metabolic syndrome status (Azadbakht, et al. 2005; Esposito, et al. 2004; Orchard, et al. 2005; Salas-Salvado, et al. 2008). These studies used a behavioral program to implement a relatively low-fat MedDiet (Esposito et al. 2004), intensive lifestyle intervention with inclusion of a vegetable-rich diet restricted in animal fat (Orchard et al. 2005), the DASH diet (Azadbakht et al. 2005), and two MedDiets supplemented with virgin olive oil or nuts (Salas-Salvado et al. 2008) in comparison with standard advices. Three studies (Azadbakht et al. 2005; Esposito et al. 2004; Orchard et al. 2005) used energy-restricted diets that led to some degree of weight loss, while one study (Salas-Salvado et al. 2008) used ad libitum diets. In all these studies, a decreased prevalence of metabolic syndrome was shown in the intervention groups. In the PREDIMED study (Salas-Salvado et al. 2008), the MedDiet with nuts significantly reduced MetS prevalence at 1 year, mostly because of increased reversion of prior MetS due to reduction 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 (Babio, et al. 2009). 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 (Paniagua, et al. 2007b). More recently Jimenez-Gomez et al. have demonstrated that postprandial abnormalities associated with MetS can be attenuated with high MUFA diets (Jimenez-Gomez, et al. 2010).

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 (Giugliano and Esposito 2008). 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 (Martinez-Gonzalez, et al. 2008) or survivors of a myocardial infarction (Mozaffarian, et al. 2007). In contrast, in the absence of weight loss, the low-fat diet used in the Women's Health Initiative trial (Tinker, et al. 2008) was ineffective to prevent the development of diabetes. Furthermore, in the set of the PREDIMED study, it has been tested the effects of two MedDiet interventions versus a low-fat diet on incidence of diabetes. This was a three-arm randomized trial in 418 nondiabetic subjects aged 55–80 years where participants were randomly assigned to education on a low-fat diet (control group) or to one of two MedDiets, supplemented with either free virgin olive oil (1 liter/week) or nuts (30 g/day). Diets were ad libitum, and no advice on physical activity was given. After a median follow-up of 4.0 years, diabetes incidence was 10.1%, 11.0%, and 17.9% in the MedDiet with olive oil group, the MedDiet with nuts group, and the control group, respectively. Multivariable adjusted hazard ratios of diabetes were 0.49 (0.25–0.97) and 0.48 (0.24–0.96) in the MedDiet supplemented with olive oil and nuts groups, respectively, compared with the control group. Interestingly, when the two MedDiet groups were pooled and compared with the control group, diabetes incidence was reduced by 52%. In all study arms, increased adherence to the MedDiet was inversely associated with diabetes incidence. It is also important to highlight that diabetes risk reduction occurred in the absence of significant changes in body weight or physical activity. These results extend those of prior studies showing that lifestyle interventions can substantially reduce the incidence of diabetes in individuals at high risk (Knowler, et al. 2002; Pan, et al. 1997; Ramachandran, et al. 2006; Tuomilehto, et al. 2001). However, in these studies, the interventions consisted of advice on a calorie-restricted diet plus physical activity and, except for one study (Ramachandran et al. 2006), weight loss was a major driving force in reducing the incidence of diabetes (Salas-Salvado, et al. 2011).

Diets high in SFA consistently impair both insulin sensitivity and blood lipids, while substituting carbohydrates or MUFA for SFA reverts these abnormalities (Riccardi, et al. 2004). Postprandial lipemia and glucose homeostasis are also improved after meals containing MUFA from olive oil compared to meals rich in SFA (Lopez, et al. 2008; Paniagua, et al. 2007a). Thus, an examination of the association of dietary and membrane fatty acids with insulin secretion in the cross-sectional Pizarra study (Rojo-Martinez, et al. 2006) 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, carbohydrates or MUFA, was also hotly debated. Since the late 1980's, many feeding trials have compared the effects of isoenergetic high carbohydrates (CHO) and high MUFA diets on insulin sensitivity in healthy subjects and on glycemic and lipid control in diabetic patients (Garg 1998; Ros 2003). Garg's meta-analysis (Garg 1998) 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 (Ros 2003) 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 (Ros 2003). 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. (Esposito et al. 2004) in subjects with MetS and by the PREDIMED study (Estruch, et al. 2006) in diabetic patients and other subjects at high risk for coronary heart disease (CHD). In addition, in a cross-sectional analysis of a population of type 2 diabetic patients, the adherence to a MedDiet was inversely associated with glycosylated haemoglobin and postprandial glucose levels during free living conditions, independent of age, adiposity, energy intake, physical activity and other potential confounders (Esposito, et al. 2009b). This association was apparent even although no strong associations were evident for each of the components of the MedDiet score, except for a modest association with whole grains and the ratio of MUFA to saturated lipids. However its cross-sectional nature does not allow us to make inference about cause and effect. According to these findings, Itsiopoulos et al. have recently demonstrated that a traditional MedDiet improved glycemic control, glycosylated haemoglobin fell from 7.1% to 6.8%, in men and women with well-controlled type 2 diabetes, without adverse effects on weight (Itsiopoulos, et al. 2010). Furthermore a systematic review of the available studies confirmed that adopting a MedDiet may help to prevent type 2 diabetes, and also improve glycaemic control and cardiovascular risk in persons with established diabetes (Esposito, et al. 2010).

Despite the beneficial effect attributed to the MedDiet, the American Diabetes Association (ADA) recommends that patients with newly diagnosed type 2 diabetes be treated with pharmacotherapy as well as lifestyle changes (Nathan, et al. 2006). The rationale for combination therapy is presumably that each form of treatment alone is imperfect. Lifestyle changes are often inadequate because patients do not lose weight or regain weight or their diabetes worsens independent of weight. Pharmacotherapy also often fails with time (Turner, et al. 1999), and some drugs have associated cardiovascular and other risks (Goldfine 2008). In this context Esposito et al. in 2009, conducted a randomized trial to compare the effects of a low-carbohydrate Mediterranean-style or a low-fat diet on the need for antihyperglycemic drug therapy in 215 patients with newly diagnosed type 2 diabetes (Esposito, et al. 2009a). After 4 years, they found that the MedDiet delayed the need for antihyperglycemic drug therapy. There were no differences in the degree to which participants in each group increased their physical activity or decreased their caloric intake, so the effect seems specific to the MedDiet and is probably, although not exclusively, linked to its ability to induce greater weight loss, in accord with results of a recent trial (Shai, et al. 2008). The between-group difference in the proportion of people needing antihyperglycemic drug therapy increased over the course of the trial and favored the MedDiet, whereas the between-group differences in weight loss decreased. Consumption of MUFA is thought to increase insulin sensitivity (Due, et al. 2008; Esposito et al. 2004; Shai et al. 2008), and this component of the diet might explain the favorable effect of the MedDiet on the need for drug therapy. In summary, although more data are mandatory, there is good scientific support for MedDiet diets, especially those based on olive oil, as an alternative approach to low-fat diets for the medical nutritional therapy in MetS and diabetes.

3. Protective mechanisms of mediterranean diet

Several mechanistic links offer potential explanations of protective effect of the MedDiet on type 2 diabetes. 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 endothelium dysfunction without having a drastic effect on body weight. Phenolic compounds are the focus of intense research in the last years, due to the biological properties that they have proven, mainly as potent antioxidants and anti-inflammatory agents; 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, lipoxxygenase, nitric oxide synthases

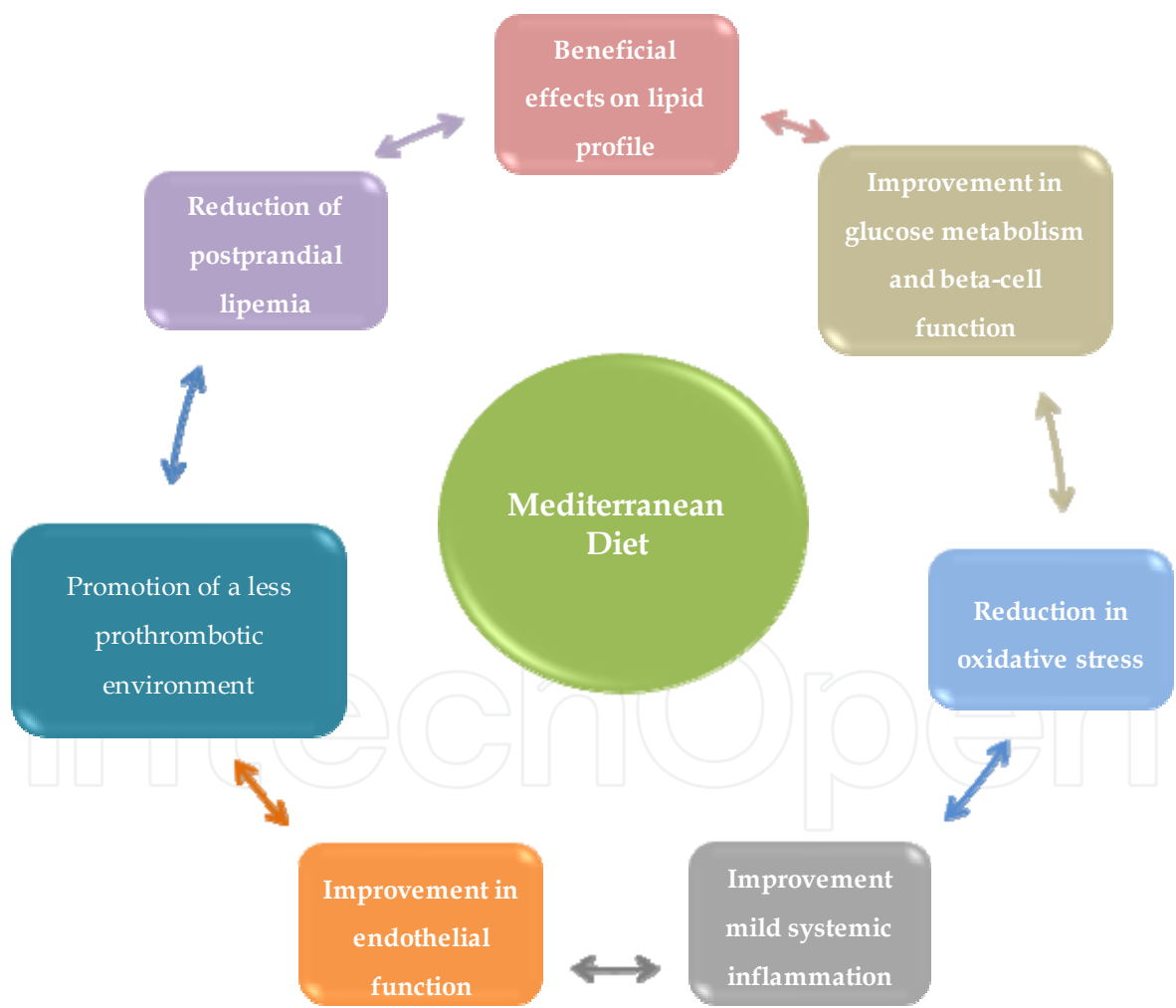


Fig. 1. Health effects of the Mediterranean Diet rich in olive and the potential mechanisms by which this diet can help in disease prevention and treatment.

and several pivotal cytokines, mainly by acting through NF- κ B and mitogen-activated protein kinase signaling. It is of note that phenols are not uniquely represented in olive oil in the traditional MedDiet, but also in other classic foods, such as wine, fruits and vegetables. Beyond this, epidemiological and interventional studies have revealed a protective effect of the MedDiet against mild chronic inflammation and its metabolic complications (Chrysohoou, et al. 2004; Dai, et al. 2008; Panagiotakos, et al. 2009b).

3.1 Inflammation and oxidative stress

The origins of heightened inflammatory activity in diabetes are diverse. In type 1 diabetes, islet inflammation is thought to be a local phenomenon driven by a focal autoimmune attack on islet antigens. By contrast, in type 2 diabetes, activation of inflammation results from systemic etiologic factors, such as central obesity and insulin resistance. Ultimately inflammatory mediators activate a series of receptors and transcription factors such as NF- κ B, toll-like receptors, c-Jun amino terminal kinase, and the receptor for advanced glycation end products, which lead to β -cell dysfunction and apoptosis, impaired insulin signaling in insulin-sensitive tissues, systemic endothelial dysfunction, and altered vascular flow. In this context inflammation at the cellular level can be described as an increase in the NF- κ B in the nucleus and with a concomitant decrease in its inhibitors I κ B- α and/or I κ B- β (Ghanim, et al. 2004). NF- κ B is a pleiotropic transcription factor activated by low levels of reactive oxygen species (ROS) and inhibited by antioxidants (Mantena and Katiyar 2006). This factor regulates the expression of several cytokines, chemokines, cell adhesion molecules, immunoreceptors and inflammatory enzymes (Piva, et al. 2006), molecules that are involved in disease such as atherosclerosis and insulin resistance. In most cells, NF- κ B (p50/p65) is present in an inactive form in the cytoplasm, bound to an inhibitor I κ B. Certain stimuli result in the phosphorylation, ubiquitination and subsequent degradation of I κ 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 α -linolenic acid, and the opposite of the inflammatory effect of linoleic acid. Hennig et al. (Hennig, et al. 2000) 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 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- κ B could be one of the mechanisms of the inflammatory properties of 18:0 and 18:2 fatty acids. Previous studies have confirmed that fat consumption induced the activation of inflammatory markers (Jellema, et al. 2004). In this regard, Bellido and Perez-Martinez have previously demonstrated that the MedDiet, enriched in virgin olive oil, attenuated peripheral blood mononuclear cells (PBMCs) NF- κ B activation compared with a Western SFA rich diet, and the effect of an n-3 PUFA-enriched diet was intermediate in young healthy population (Bellido, et al. 2004; Perez-Martinez, et al. 2007). These findings suggest that virgin olive oil could be a possible contributor to prevent the activation of NF- κ B system, within the frame of the MedDiet. Besides olive oil, the MedDiet contains 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- κ B 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 context, Brunelleschi et al. (Brunelleschi, et al. 2007) explored the effects of an extra-virgin olive oil extract, particularly rich in minor polar compounds, on NF- κ B translocation in monocytes and monocyte-derived macrophages isolated from healthy volunteers. In a concentration-dependent manner, olive oil extract inhibited p50 and p65 NF- κ B 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 monocyte-derived macrophages (Brunelleschi et al. 2007). These data suggest the hypothesis of a protective effect of extra-virgin olive oil by indicating its ability to inhibit NF- κ B activation in human monocyte/macrophages. On the other hand, NF- κ B 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) (Ghosh, et al. 1998), all implicated in atherosclerosis development. Carluccio et al. (Carluccio, et al. 1999) 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 (Bellido, et al. 2006). 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 (Mata, et al. 1996).

The mechanism by which LDL from carbohydrate and MedDiets 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 (Bellido et al. 2004). 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. (Estruch et al. 2006) 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 3 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-1. 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 (Fito, et al. 2007). Furthermore new data suggest that virgin olive oil intake was associated with higher levels of plasma antioxidant capacity after 3 years of intervention (Razquin, et al. 2009). In summary, based in the above evidences presented, we could assume that the MedDiet rich in nutrients with favorable anti-inflammatory properties may protect from metabolic diseases that are related to chronic inflammation and overproduction of reactive oxygen species, such as MetS and diabetes.

3.2 Postprandial state

When explaining possible mechanisms is important to recall that fasting is not the typical physiological state of the modern human being, which spends most 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 (Cardona, et al. 2008; Devaraj, et al. 2008; Ursini, et al. 1998). 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 (Tzanavari, et al. 2010). In this scenario Jimenez-Gomez et al. observed that a breakfast rich in olive oil or walnuts decreased postprandial expression of mRNA TNF- α in PBMCs from healthy men compared with a butter-enriched breakfast (Jimenez-Gomez, et al. 2009). 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- α 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 (Futterman and Lemberg 2002; Kishimoto 2005).

3.3 Endothelial function

In the last years another interesting observation is that dietary fat may affect the endothelium (Berry, et al. 2008; Fuentes, et al. 2008; Goode, et al. 1997), and factors related to the arterial wall (Perez-Jimenez, et al. 1999). 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 (Perez-Jimenez et al. 1999). 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 (Fuentes, et al. 2001). 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 (Esposito et al. 2004). More recently Radillis et al. observed that the close adherence to a MedDiet diet improves endothelial function in subjects with abdominal obesity (Rallidis, et al. 2009). On the other hand, previous studies also demonstrated that postprandial lipemia induces endothelial dysfunction (Anderson, et al. 2001; Bae, et al. 2003). 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 NO_x compared with the other two diets (Fuentes et al. 2008). In the same line, Perez-Martinez et al. 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 (Perez-Martinez, et al. 2010b). 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 (Esposito, et al. 2006; Esposito et al. 2004). 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 (Perez-Martinez, et al. 2010a). Furthermore, postprandial plasma hydrogen peroxide levels were unfavourable increased during the high-SFA diet compared to the other three diets (Perez-Martinez et al. 2010a). These findings suggest that the postprandial state is important for understanding possible cardio-protective effects associated with the MedDiet particularly in subject with the MetS. In addition, these findings support recommendations to consume a high MUFA diet as a useful tool to prevent cardiovascular diseases in MetS patients.

3.4 Coagulation

Both endothelial cells and macrophages contribute to the generation of altered vasoreactivity and a procoagulant state through increased expression of plasminogen activator inhibitor (PAI)-1 and tissue factor and through platelet activation and acute phase reactions that increase levels of coagulation factors such as fibrinogen and factor VIII. Many of these molecules enter the circulation at levels that correlate with the degree of inflammatory activity. It has been well established that consumption of MedDiet as a dietary pattern, and virgin olive oil as its main fat source, is accompanied by a decrease in thrombogenesis, combining a decrease in coagulation factors and by platelet aggregation (Delgado-Lista, et al. 2008; Lopez-Miranda et al. 2007; Cicerale, et al. 2009; De La Cruz, et al. 2010; Gonzalez-Correa, et al. 2008; Lopez-Miranda et al. 2010; Perez-Jimenez et al. 2006;

Rasmussen, et al. 1994; Thomsen, et al. 1995; Tripoli, et al. 2005; Visioli, et al. 2005). To infer the great value that these facts may have on diabetes, we should have in mind that cardiovascular events are the primary cause of death in these patients, and that, a lowering in their procoagulant/prothrombotic status is, nowadays, the main prophylactic and therapeutic weapon to avoid cardiovascular events. In other words, adhering to MedDiet may act as a prophylaxis for the appearance of thrombotic driven cardiovascular events. Reinforcing this hypothesis, some authors have recently published in vitro and animal studies in which they show antiaggregant properties of virgin olive oil comparable in efficacy to those of acetylsalicylic acid (ASA). Even more, virgin olive oil and ASA, when in combination, act synergically to further inhibit platelet activation and aggregation(6, 10). Although the cited studies have been realized mostly in healthy persons, diabetic persons may also benefit from the antithrombogenic effects of MedDiet. As an example, Rasmussen et al showed how non-insulin dependent diabetic patients who were fed a MUFA-rich diet for three weeks decreased their von Willebrand factor (an important procoagulant factor) when compared to a carbohydrate-rich diet. The same authors, in an elegant design, compared the effects of two diets similar in carbohydrate and protein content, one rich in MUFA (30 energy %) and one rich in polyunsaturated fatty acids (PUFA) (30 energy %). After three weeks, the diet rich in MUFA reduced the levels of von Willebrand factor, confirming the results of their previous study, and stating the favourable effect that MUFA have on this prothrombotic molecule.



Fig. 2. Effects of Mediterranean diet on key features and organs affected by diabetes mellitus. MedDiet: Mediterranean diet. DM: diabetes mellitus. SFA: saturated fatty acid.

3.5 Nutrigenomics

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. (Camargo, et al. 2010) 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 consumption 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, Rho GTPase-activating protein15, and interleukin-7 receptor) and oxidative stress (adrenergic beta(2)-receptor) in PBMCs from healthy volunteers (Konstantinidou, et al. 2010). 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 (Khymenets, et al. 2009). In the same line, Llorente-Cortés et al. (Llorente-Cortes, et al. 2010) 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 (Rodriguez, et al. 2002), 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 (Cypess, et al. 2009). 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 (Wilson-Fritch, et al. 2004). 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 (Hao, et al. 2010).

4. Summary and future direction

Because unhealthy eating habits and a sedentary lifestyle are among the strongest risk factors for metabolic syndrome and type 2 diabetes, modification of eating habits and physical activity constitutes an important component of any successful management program. In this chapter we reviewed the state of the art illustrating the relationship between MedDiet rich in olive oil and metabolic diseases, and to discuss potential mechanisms by which this food can help in disease prevention and treatment. Epidemiological and intervention studies indicate that MedDiet, thanks to its set of benefits, may protect from metabolic diseases that are related to chronic inflammation and

overproduction of reactive oxygen species, such as 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, metabonomics, lipidomics, microbiota, cronobiology, proteomic 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.

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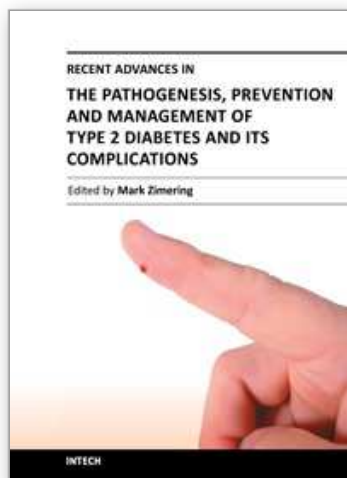
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Type 2 diabetes “œmellitus” affects nearly 120 million persons worldwide- and according to the World Health Organization this number is expected to double by the year 2030. Owing to a rapidly increasing disease prevalence, the medical, social and economic burdens associated with the microvascular and macrovascular complications of type 2 diabetes are likely to increase dramatically in the coming decades. In this volume, leading contributors to the field review the pathogenesis, treatment and management of type 2 diabetes and its complications. They provide invaluable insight and share their discoveries about potentially important new techniques for the diagnosis, treatment and prevention of diabetic complications.

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