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REVIEW ARTICLE

THE MEDITERRANEAN DIET, PART III: COMPOUNDS, COMPONENTS AND CONSIDERATIONS IN RELATION TO THE RISK OF TYPE 2 DIABETES

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ABSTRACT

The dramatic increase in diabetes incidence worldwide has been attributed to various factors, including major lifestyle changes, over the past few decades. One lifestyle-related factor is the increased intake of food with a high glycemic index. The resulting high demand for insulin promotes insulin resistance and β-cell insufficiency. Together with decreased physical exercise, this predisposes individuals to the development of type 2 diabetes. Oxidative stress also plays a role in the pathogenesis of insulin resistance and it has been hypothesized that dietary antioxidants could diminish the risk of type 2 diabetes. Therefore, specific dietary strategies may contribute to improved glucose homoeostasis and help in the prevention of this disease. The epidemiological evidence and molecular details that link the Mediterranean diet, typically rich in antioxidants, with the decreased risk for type 2 diabetes are discussed in this review. It is concluded that prospective observational studies and intervention studies support an inverse relationship between this diet and insulin resistance with the resulting type 2 diabetes.

INTRODUCTION

By the year 2030, the prevalence of diabetes in all age groups worldwide is predicted to be 4.4% with 366 million people suffering from the disease. By comparison, in the year 2000 these numbers were estimated to be 2.8% and 171 million respectively (1). Although the most important increase will concern those over middle age (2), several recent studies have demonstrated an alarming increase of type 2 diabetes in children and adolescents (3, 4, 5). In the United States, the economical costs associated with diagnosed type 2 diabetes for the year 2007 were estimated to be $159.5 million, consisting of medical costs of $105.7 million and indirect costs of $53.8 million (6). With regard to these patients, case-specific mortality rates are increased for ischemic heart, cerebrovascular and renal diseases, evident at all age groups (7). Obviously, the enormous social and personal burden of this disease warrants an aggressive approach.

Various risk factors contribute to the development of type 2 diabetes and have been summarized by Steyn et al. (8). They discuss non-modifiable risk factors, including race/ethnicity, family history, gender, age and genetic determinants. Furthermore, these authors highlight modifiable risk factors, notably dietary and lifestyle habits (8). There is an increasing number of studies on foods that are considered important for health. A prominent position is taken by studies that evaluate the beneficial role of the Mediterranean diet, which is rich in vegetables, legumes, fish, fruit, nuts, olives and olive oil, and avoids red meat, saturated fats and high calorie ingredients. Indeed, many epidemiological studies, including randomized clinical trials, have demonstrated that this diet can reduce the risk of cardiovascular, neoplastic and neuropsychiatric disorders (9).

An alarming increase in obesity, especially in children and adolescents, has been attributed to increased consumption of energy-rich and -dense foods together with physical inactivity (10). This increase in obesity goes hand in hand with an increasing prevalence of type 2 diabetes, and several studies have observed a close relationship between obesity and diabetes (11, 12). These facts suggest that modification of dietary patterns may have a favorable effect on the prevalence of type 2 diabetes and it has been advocated that specific

dietary strategies can improve glucose homeostasis and contribute to the prevention of type 2 diabetes (13, 14). In this review, whether the Mediterranean diet has a beneficial effect on the occurrence of type 2 diabetes is examined. The results of recent epidemiological and some experimental investigations will be reviewed to present the scientific evidence, and the pathology and clinical aspects of diabetes will be discussed.

DIABETES: PATHOLOGY AND CLINICAL ASPECTS

The pathology of diabetes is described in many (bio)medical textbooks. Nevertheless, for a better understanding of this article a short overview is provided below. The islets of Langerhans make up approximately 2% of the pancreatic mass and are scattered throughout the organ. Each islet consists of 2000 to 3000 endocrine cells. Four main cell types are present in each islet: α-cells (secreting glucagon), β-cells (secreting insulin), δ-cells (secreting gastrin and somatostatin) and F-cells (secreting pancreatic polypeptide). After sugar intake, increased blood glucose is taken up by insular β-cells through insulin-independent glucose transporter protein (GLUT)-2 and stimulates the immediate release of insulin (consisting of two peptide chains) and C-peptide (connecting the two peptide chains) from the secretory granules. The transport of glucose into target cells, such as hepatocytes, skeletal and cardiac muscle cells, requires bioactive insulin. The transmembrane transport of glucose is facilitated by GLUT-4, which is translocated from the Golgi apparatus to the plasma membrane upon activation of the insulin receptor. Thus, GLUT-4 removes glucose from the blood in an insulin-dependent manner. Under normal conditions, an increased blood glucose concentration stimulates the release of insulin, which brings the glucose level back to normal within 1 h. Impairment of insulin production diminishes the transport of glucose to the various body cells resulting in hyperglycemia.

If there is no insulin production due to, for example, autoimmune or toxic damage to pancreatic tissue, the patient suffers from type 1 diabetes (also called insulin-dependent diabetes mellitus) and requires lifelong exogenous insulin. This type of diabetes often becomes evident during childhood, but can also develop at later ages. Type 2 diabetes (also called non-insulin-dependent diabetes mellitus) is characterized by insufficient insulin secretion relative to glucose levels. This disease mostly occurs in adults and is caused by resistance of target tissues to insulin together with deficient post-receptor signalling resulting in diminished glucose uptake via GLUT-4 transport.

The clinical symptoms of type 1 and 2 diabetes are similar. Most prominent are hyperglycemia, polyuria, glucosuria and polydipsia (excessive thirst and fluid intake). Patients can be classified as prediabetic or diabetic and diagnostic criteria include impaired fasting plasma glucose concentration and impaired glucose tolerance after an oral glucose tolerance test (15).

The major complication of both types of diabetes is atherosclerosis eventually leading to increased risk for myocardial infarction and stroke, as well as other circulatory diseases. Vascular lesions may also develop in the kidneys and retina, eventually resulting in renal failure and blindness, respectively. Alterations in the nervous system may lead to, for example, bladder function impairment, peripheral neuropathy, cardiac malfunction and neuropsychiatric disease.

These and other clinical complications cause increased mortality rates among individuals with diabetes (16, 17). A recently published Spanish study demonstrated that patients with diagnosed diabetes had a risk of mortality 2.5 times greater than individuals with normoglycemia. In patients with undiagnosed diabetes and pre-diabetes this relative risk was 2.7 and 1.6, respectively (18).

MECHANISMS LINKING THE MEDITERRANEAN DIET TO LOWER INCIDENCE OF TYPE 2 DIABETES

Various epidemiological studies suggest that a plant-based diet may decrease the risk of type 2 diabetes (19, 20, 21). Prospective cohort studies have identified fruit and vegetables (22), berries, oil, margarine and poultry (23), as well as vitamin C plasma levels (24) to be associated with lower incidence of type 2 diabetes. Important features of this diet are its low glycemic index (GI) and glycemic load, which lower the rate of insulin secretion and facilitate glucose homeostasis (25). Importantly, the Mediterranean diet includes the above-mentioned components together with fish, nuts and red wine, rather than red meat and ingredients that contain saturated fats, such as butter. This diet provides a variety of dietary fiber sources (mainly from vegetables, whole grain products and fruit), monounsaturated fats (mainly from olives and olive oil) and polyunsaturated fats (mainly from fish, nuts and vegetables), whereas alcohol consumption is moderate and consists mainly of red wine during the meal.

Dietary fiber

Food intake causes a gastrointestinal response in the sense that various peptides that regulate gastric emptying, pancreatic secretion and the feeling of satiety are released. Among these peptides are cholecystokinin, glucagon-like peptide-1 and peptide YY (26). Increased fiber intake results in increased satiety-related response that reduces hunger (27). This effect contributes to a reduced weight gain or even weight loss and may prevent obesity and the development of diabetes (28-31).

Adipose tissue in obese people is insulin resistant and exhibits overproduction of various pro-inflammatory cytokines, adipocytokines and free fatty acids that may amplify insulin resistance (32, 33). Moreover, plasma adiponectin (a key regulator of insulin sensitivity) is decreased in obesity, type 2 diabetes and other obesity-related diseases, including atherosclerotic cardiovascular diseases (34). An insulin-sensitizing effect has also been attributed to diets rich in fiber. The glycemic response associated with dietary fiber from plant-based food in the Mediterranean diet is approximately 40% lower than in a control diet (35). Fibers in minimally processed foods are thought to surround the carbohydrate particles to form a physical barrier against rapid absorption, lowering the glycemic response. In contrast, processed foods rich in carbohydrate and low in undisrupted fibers increase post-prandial glucose and have a higher GI, predisposing individuals to type 2 diabetes (36, 37).

Dietary fats

Although the dietary patterns of the countries around the Mediterranean basin show regional differences, olive oil has a prominent place in each of them and is considered a hallmark of this diet. Olive oil is a rich source of the monounsaturated fat oleic acid, which

confers strong antioxidant and anti-inflammatory properties (38). (Poly)phenolic compounds, which occur in olive oil (particularly in extra virgin olive oil), are known for their beneficial actions, as demonstrated in experimental and human intervention studies (39). Notably, olive oil exerts an anti-atherogenic and anticancer action (40, 41). The Mediterranean culinary habits also involve the use of olive oil for the preparation of vegetables, legumes and fish, which contain polyunsaturated fatty acids, especially the omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which decrease the pro-inflammatory arachidonic acid content of cell membranes and promote the synthesis of anti-inflammatory eicosanoids (42). A recently published overview on the prevention of insulin resistance by omega-3 polyunsaturated fatty acids by Fedor and Kelley discussed how fish oil and individual fatty acids such as EPA and DHA prevent insulin resistance in animal models, while in human studies of normal weight and obese individuals, a reduced insulin resistance or no improvement has been measured (43). These observed discrepancies may be due to differences in health characteristics in trial participants, the amount and composition of fish oils used and the laboratory methods for insulin resistance assessment. Overall, these researchers concluded that omega-3 fatty acid supplementation has clinical significance in the prevention and reversal of insulin resistance (43).

These beneficial health effects are accompanied by the fact that unsaturated fats are more easily oxidized than saturated fats. This might explain why the consumption of foods and oils containing unsaturated fats do not promote obesity (44-46). One prospective Spanish study of 17,238 women and 10,589 men with high adherence to the Mediterranean diet, who were not obese at baseline demonstrated that there was no increased risk of being overweight during a follow-up period of 3.3 years (47). This suggests that the Mediterranean-style dietary pattern may prevent obesity and its metabolic complications such as insulin resistance.

Alcohol and wine

Whereas excessive consumption of alcoholic drinks may have severe detrimental effects, moderate consumption of red wine in quantities of one to two glasses per day may exert beneficial effects, notably with regard to the cardiovascular system (48). Furthermore, a cross-sectional analysis of a sample of 4153 Greek adults revealed that moderate red wine consumption was associated with lower incidence of type 2 diabetes (49). One of the polyphenols contained in red wine is resveratrol, a potent antioxidant and an activator of sirtuins, which are involved in the common diseases of aging (50). *SIRT1* (a gene encoding for the sirtuin family of proteins) stimulates glucose-dependent insulin secretion from the pancreas and stimulates insulin signalling in insulin-sensitive tissues. Moreover, in obese mouse models, *SIRT1* activators and *SIRT1* overexpression have a beneficial effect on glucose homeostasis and insulin sensitivity (51, 52). Understandably, it has been suggested that *SIRT1* is a novel target for the prevention of type 2 diabetes (53), therefore, its relationship with red wine consumption needs further exploration.

Shai et al. reported on a multicenter randomized clinical intervention trial in patients with established type 2 diabetes who abstained from alcohol (54). They received one glass of red (75% of participants) or white wine (13 g ethanol) or non-alcoholic beer (control drink) each day for 3 months. In those individuals who drank alcohol, fasting plasma glucose levels decreased (P = 0.015), although no effect on post-prandial glucose levels could be measured. Though most intervention studies in this field concern red wine (e.g. www.awri.com.au) there is also a beneficial effect of white wine. Joosten et al. conducted a randomized crossover trial in healthy postmenopausal women (55). They received two glasses of white wine (25 g ethanol) or two glasses of white grape juice (control) per day during dinner for a period of 6 weeks. This moderate alcohol consumption improved insulin resistance (P = 0.02), fasting insulin levels (P < 0.01), adiponectin (P = 0.02) and lipid profile (P < 0.0001).

HUMAN STUDIES ON TYPE 2 DIABETES AND THE MEDITERRANEAN DIET

Prospective studies

Epidemiological evidence in the form of prospective nested, case-control studies and prospective cohort studies suggests that several dietary patterns are favorably associated with a reduced risk for type 2 diabetes. Prospective studies have provided evidence that diets rich in whole grains and fiber reduce insulin resistance in non-diabetic individuals and reduce the risk for type 2 diabetes (56-58). This is in good agreement with studies that identified other dietary patterns, characterized by refined grains, high caloric soft drinks, red meat, processed meat, whole milk, butter and potatoes, being associated with increased incidence of type 2 diabetes (21-23, 59-61).Moreover, a systematic review of cohort studies performed in Western countries, published in 2005, concerning the effect of various nutrients on the incidence of type 2 diabetes demonstrated that a decreased risk for the disease comes with the higher consumption of whole grain foods and coffee and that processed meat consumption is associated with an increased risk (62). A large prospective cohort study (N = 161,737 women of the Nurses' Health studies I and II followed over 12-18 years) indicated a relative risk of 0.75 for the highest versus the lowest quintile of whole grain intake (30). These researchers found their results to be similar to those from a systematic review of six cohort studies (N = 286,125 participants), which demonstrated that whole grain consumption lowered the risk of type 2 diabetes by 21%.

Results from two large prospective studies investigating adherence to the Mediterranean diet and type 2 diabetes incidence were published in 2008; the British Whitehall II study (N = 7,731; follow-up 15 years) among civil servants (63) and the Spanish SUN study (N = 13,380; median follow-up 4.4 years) among Spanish university graduates (64). Both studies showed a reduced risk of type 2 diabetes for those participants who ate a Mediterranean-like diet. The British study determined a hazard ratio of 0.74, whereas the Spanish study reported an incidence rate ratio of 0.65. Also in 2008, McNaughton et al. identified a dietary pattern associated with insulin resistance that represents an important risk factor for type 2 diabetes (65). The investigators explained that this diet is characterized by low consumption of medium/high fiber breakfast cereals, jam, French dressing/vinaigrette and wholemeal bread. Furthermore, a prospective analysis of overall dietary habits and the risk of type 2 diabetes in 80,000 US women during the 18-year follow-up suggested that there were nine dietary features favorably associated with the prevention of type 2 diabetes; high consumption of vegetables, fruit,

fish, fiber and nuts, a high ratio of poultry to red meat, a high ratio of polyunsaturated to saturated fats, moderate alcohol consumption and the use of multivitamin supplements (58). Within this context it is noteworthy that Panagiotakos et al. found an inverse relation between adherence to the Mediterranean diet and insulin resistance in the ATTICA study (66).

Intervention studies

Prospective randomized intervention studies, rather than prospective cohort studies, provide a suitable method to study the effects of the Mediterranean diet on the risk of developing type 2 diabetes. Various short-term studies have investigated the effect of different randomly assigned diets in order to achieve weight loss in obese individuals. In general, adherence to a Mediterranean-type diet favorably influenced glycemic control, fasting plasma glucose and insulin levels, fasting pro-insulin (the pro-hormone precursor to insulin) levels in insulin-resistant people, weight loss and weight maintenance (67-69). These outcomes underpin the important effect of diet on risk factors for diabetes. Nevertheless, it needs to be mentioned that only long-lasting multicenter prospective randomized intervention studies with more than 10,000 participants could throw further light on this issue.

ANIMAL MODELS

For the study of pathogenesis, course of illness and efficacy of drug treatment, appropriate animal models of type 2 diabetes are essential. Various studies have reported on spontaneous old-age diabetes in monkeys (70- 72), however, aside from the low incidence of this disease in captive monkeys, the use of non-human primates is inconvenient and costly. For good reasons, rats and mice are easier to work with, but the ideal model, mirroring the characteristics of the disease in humans, including similar etiology, pathophysiology, natural history and complications has not been developed yet (73). An extensive review on this branch of diabetic sciences is beyond the scope of this paper, however, interested readers are referred to an excellent recent paper by Islam and Loots (74).

Islam and Loots discuss how experimentally induced animal models are preferred for most purposes due to their comparatively low cost. They include: (1) adult streptozotocin (STZ)/alloxan-induced rat models; (2) neonatal STZ/alloxan-induced models; (3) partial pancreatectomy models; (4) long-term high-fat (HF) diet models; (5) HF diet-fed STZ models; (6) nicotinamide (NCT)/STZ-induced models; (7) intra-uterine growth retardation (IUGR) models; (8) the STZ-induced progressive diabetes model; and (9) the monosodium glutamate-induced model (74). These various models have pros and cons with regard to specific applications. As far as dietary intervention is concerned, the models of choice are the HF diet-fed STZ and the NCT/STZ model (74, 75). The former model shows pathological type 2 diabetes features comparable to humans. These test animals, in particular the rat model, develop hyperglycemia, hyperinsulinemia, glucose intolerance, insulin resistance and dyslipidemia, and the model has been validated using anti-type 2 diabetes drugs. The latter model (a mouse model), exhibits the pathological characteristics of the majority of Asian people suffering from non-obese type 2 diabetes (74, 77). Using the HF diet-fed STZ model, various nutrient-related experiments have been carried out providing directions for future studies related to common Mediterranean dietary habits, including the anti-diabetic effect of *Allium sativum* and *Citrullus colocynthis* (76-79).

DISCUSSION AND COMMENTS

The epidemic proportions in many developed and developing countries of type 2 diabetes was recognized more than a decade ago (80, 81). The dramatic rise in type 2 diabetes incidence in Pima Indians in Arizona and women in Fiji who changed their traditional lifestyles to a Western-type diet made it likely that dietary factors play an important role in the pathogenesis of this disease (82, 83). Observations of the Pima Indians made it also likely that an increasing risk for developing type 2 diabetes is associated with being overweight and obese (84). The components of the Mediterranean diet have a relatively low energy density, causing a lower energy intake, whereas tastiness and satiety still hold a prominent place. Importantly, its favorable effect on the prevention of type 2 diabetes is at least partly mediated through weight maintenance and weight loss. Mechanistically, a lower energy intake brings about less biochemical activity of the Krebs cycle. Diminished energy intake decreases the likelihood of mitochondrial dysfunction and the production of reactive oxygen and nitrogen species. In contrast, excessive high-energy food intake causes metabolic overproduction of these reactive species, bringing on oxidative stress. This phenomenon triggers the formation of inflammatory molecules that cause abnormal phosphorylation of the insulin receptor and substrate proteins (85). Evans explains that in individuals with an imbalance between the production of oxidative species and antioxidant defense, oxidative stress plays an important role in the pathogenesis of various chronic disorders, including atherosclerosis, insulin resistance and β-cell dysfunction (86). Indeed, a recent publication by Anderson et al. discusses the attenuation of mitochondrial H_2O_2 emission, either by treating rats with mitochondrial-targeted antioxidants or by genetically engineering catalase overexpression in muscle mitochondria in mice (87). These actions completely preserved insulin sensitivity in an HF diet rodent model with insulin resistence. These findings are consistent with the randomized intervention trial published by Esposito et al. on the use of a Mediterranean-type diet rich in antioxidant-containing foods in patients with a metabolic syndrome (88). Relative to the normal-diet control group, the Mediterranean diet significantly decreased insulin resistance, which suggests that Mediterranean-type dishes contain antioxidants that may counteract the aforementioned imbalance and protect against oxidative stress. An important effect of this diet can be attributed to extra virgin olive oil. Its major component oleic acid, a monosaturated fatty acid, but also its polyphenols, have demonstrated anticancer and anti-atherogenic actions, diseases in which oxidative stress plays an important role (39-41).

The Finnish Diabetes Prevention Study is an important ongoing program that has, among other things, been focusing on lifestyle changes to prevent the development of type 2 diabetes in high-risk individuals (http://www.idf.org/national-diabetes-prevention-plans). In 2001, an important randomized study by Tuomilehto et al. was published in which 265 participants were assigned to a lifestyle intervention and 257 participants to a control group (89). This study revealed that in those adults who were overweight, the risk of developing diabetes could be reduced by 58% ($P < 0.001$) by lifestyle changes consisting of physical activity and individual diet coun-

selling aimed at weight loss. During this study with a mean follow-up of 3.2 years, the cumulative incidence of diabetes was 11% in the intervention group and amounted to 23% in the control group. Interestingly, progression to overt type 2 diabetes was predicted by immunological parameters of which C- reactive protein appeared to be the best predictor (90). Furthermore, it appeared that intervention was the most effective among the oldest participants ($P = 0.01$) and in those in whom values for waist circumference, insulin resistance and fasting serum insulin levels pointed to increased risk (91).

The U.S. Diabetes Prevention Program Research Group (http://www.idf.org/idf-north-america-and-caribbean-region) studied the effect of lifestyle modification (i.e. weight loss and exercise) and found it effective in preventing incident type 2 diabetes in high-risk groups in whom weight loss had the greatest effect (91). The impact of lifestyle risk factors on new-onset type 2 diabetes in older adults has been prospectively investigated and recently reported on by Mozaffarian et al. (92). In a large sample of 4883 men and women with a mean age at baseline of 73 years, combined lifestyle factors were favorably associated with a markedly lower incidence of type 2 diabetes. These lifestyle factors included physical activity (leisure-time activity and walking pace), dietary score (relatively high fiber intake and polyunsaturated to saturated fat ratio, intake of food with a relative low GI and low content of transfat), moderate alcohol use and a body mass index (defined as weight in kg divided by height in m^2) of less than 25. Participants whose physical activity level and dietary, smoking and alcohol scores were all in the low-risk group had an 82% lower incidence of type 2 diabetes compared with other participants. The researchers attribute their results to the lower dietary glycemic load caused by physical activity and food choice, which is associated with an improved inflammatory status. These and earlier studies (93) demonstrate the link between diet and lifestyle in relation to the risk of type 2 diabetes.

In conclusion, a Mediterranean-type diet provides a variety of ingredients that prevents obesity and facilitates weight loss. This diet combined with physical activity has anti-inflammatory actions which reduces the risk of developing type 2 diabetes.

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DISCLOSURE

The author has no conflicts of interest to declare.

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