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REVIEWS: CURRENT TOPICS

Protective mechanisms of the Mediterranean diet in obesity and type 2 diabetes

Helmut Schröder*

Lipids and Cardiovascular Epidemiology Unit, Institut Municipal d'Investigació Mèdica, IMIM, Barcelona 08003, Spain

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Abstract

The prevalence of obesity has grown to an alarming level of at least 300 million people worldwide. Additionally, a diabetes epidemic is underway, with an estimate of 217 million people with diabetes worldwide. There are many links between excessive body weight and type 2 diabetes, and one common and fundamental cause of both epidemics is an unhealthy diet. Research to identify and promote diets that protect individuals from obesity and type 2 diabetes is urgently needed. The Mediterranean diet, a concept developed in the 1950s, refers to dietary habits of individuals from the Mediterranean basin. The Mediterranean diet is an eating pattern that successfully combines pleasant taste and positive health effects. The Mediterranean diet does not stand for a homogenous and exclusive model among the Mediterranean basin population but rather represents a set of healthy dietary habits, including high consumption of vegetables and fresh fruits and the use of olive oil as the main source of fat. Evidence from epidemiological studies supports a protective effect of this dietary pattern on weight gain and the development of type 2 diabetes. Several mechanistic explanations link characteristic components of the Mediterranean diet with obesity and type 2 diabetes. This review will discuss potential mechanisms by which the Mediterranean diet protects individuals from both diseases.

Keywords: Obesity; Diabetes; Mediterranean diet; Energy density; Dietary pattern

1. Introduction

The worldwide obesity epidemic seems to be unstoppable in spite of considerable efforts that have been made to combat this disease [1]. At present, more than 300 million people worldwide are obese [body mass index (BMI) of 30 kg/m^2 or higher]. The prevalence of obesity steadily increased over the past four decades in the United States [2], from around 13% to 30% or nearly one third of American adults. In many European countries, a similar trend can be observed, although the absolute level of obesity prevalence has not yet reached the U.S. level [3–9].

The increasing trend in obesity is accompanied by a growing incidence of diabetes [10,11]. Long considered a disease of minor significance, in the 21st century, diabetes is one of the main threats to human health [12]. Type 2 diabetes, formerly called non-insulin-dependent diabetes mellitus or adult-onset diabetes, accounts for most cases of diabetes worldwide. In 2000, an estimated 150 million individuals worldwide are suffering from diabetes; this count is likely to double by 2025 [13]. The close relationship between obesity and diabetes has led to the adoption of the term *diabesity* [14].

The fact that the incidence of obesity and type 2 diabetes has so recently and drastically increased points to changes in lifestyle. The loss of traditional dietary habits, increasing consumption of energy-dense foods and increasing portion sizes, together with less physical activity at work and/or during leisure time, are strongly associated with the explosive increase of these diseases. However, lifestyle factors such as diet and physical activity are modifiable and disease manifestation from these factors is largely preventable.

During the last few years, a great effort has been made to examine the relationship between health and overall diet. Pattern analysis examines the effects of diet rather than focusing on individual nutrients or foods. Conceptually, dietary patterns represent a broader picture of food and nutrient consumption and may therefore be more predictive of disease risk. Epidemiological evidence suggests that several dietary patterns have been favorably associated with

* Tel.: +34 93 221 1009; fax: +34 93 221 3237.
E-mail address: hschroeder@imim.es.

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the prevention of obesity and type 2 diabetes [15–18]. A common characteristic of these dietary patterns is their abundant plant food content.

The Mediterranean diet was first described in the 1960s by Angel Keys, based on his observation of food habits of some populations in the Mediterranean region [19]. The Mediterranean diet observed by Keys was based on a large variety of foods, mostly of vegetable (and not of animal) origin. This dietary pattern, however, varies among regions of the Mediterranean basin. The whole fat content, for example, may vary from less than 30% to about 40%. Nevertheless, a high consumption of foods of vegetable origin, such as fruits, vegetables, legumes, nuts, cereals and olive oil, and, on the other hand, a low consumption of meat and sausages could be considered important characteristics of this dietary pattern. Although the Mediterranean diet has long been celebrated for its impact on cardiovascular health [20], mounting epidemiological evidence indicates a favorable effect on obesity and diabetes [21–27] as well. However, there is little discussion in the literature that explains these healthy effects of the Mediterranean diet, particularly for obesity. Therefore, the objective of the present review was to discuss potential mechanisms by which the Mediterranean diet prevents obesity and diabetes.

2. Epidemiological evidence of the preventive role of the Mediterranean diet on obesity and type 2 diabetes

Few epidemiological studies have addressed the question of whether the Mediterranean diet produces favorable effects in preventing obesity and diabetes. Recently, we reported an inverse association of BMI and the Mediterranean diet in a representative Mediterranean Spanish population [23]. Furthermore, we found a reduced risk of being obese with higher adherence to the Mediterranean diet pattern. Interestingly, this was independent of whether olive oil is included in the Mediterranean diet or not. However, Trichopoulou et al. [22] observed no essential relationship between adherence to the Mediterranean diet and BMI in a large general Greek population sample. Furthermore, a longitudinal analysis of Spanish men and women showed that subjects with a high adherence to the Mediterranean diet have lower crude increments of weight during 2 years of follow-up [21].

Following a Mediterranean-style diet in a randomized intervention trial over 54 months improved endothelial function and significantly reduced waist circumference, plasma glucose, serum insulin and homeostasis model assessment (HOMA) score in metabolic syndrome patients [25]. Toobert et al. [26] examined in a randomized clinical trial the effectiveness of a Mediterranean lifestyle program (low-saturated-fat diet, stress management training, exercise and group support, together with smoking cessation) in reducing cardiovascular risk factors in postmenopausal women with type 2 diabetes. They found greater improvements in HbA_{1c}, BMI and lipid profile in the intervention group as compared with the control group. A recently published study showed a decrease in several cardiovascular risk factors such as glycemia, insulinemia or HOMA, among others, after following a Mediterranean-type diet for 3 months [27]. Spanish investigators showed an improvement in glucose metabolism after administration of a Mediterranean-type diet [24]. These studies point to a favorable effect of Mediterranean-type diets on weight maintenance and risk factors associated with diabetes outcome, although they do not specify the mechanisms by which it occurs.

3. Mechanisms inversely linking the Mediterranean diet to excessive weight

3.1. Effect of the Mediterranean diet on satiation and satiety

3.1.1. Dietary fiber

There is no doubt that an imbalance between energy expenditure and energy consumption causes weight gain. Too much energy-dense food consumption and too little physical activity worsen the obesity epidemic. Regulation of food intake is a complex process, influenced not only by food intake but also by various environmental and psychological factors [28,29]. The effects of food intake on hunger, satiation (the satisfaction of appetite that develops during the course of eating and eventually results in the cessation of eating) and satiety (the sensation that determines the intermeal period of fasting) are of particular importance for energy consumption.

Overconsumption is facilitated through palatable energy-dense food that disrupts appetite regulation [30]. According to the definition of the Institute of Medicine of the National Academies, dietary fiber consists of "non-digestible carbohydrates and lignin that are intrinsic and intact in plants." In general, dietary fiber may help regulate body weight through its intrinsic effects and hormonal responses. Dietary fiber has long been regarded as a satiation and satiety factor and has long been linked to calorie intake [31,32]. Experimental studies showed that high fiber intake increases satiety or reduces hunger in comparison to low fiber intake, control or placebo treatment [31]. Additionally, the majority of studies investigating the effect of high-fiber diets on energy intake and weight loss reported a reduction in both. Diets rich in plant foods, such as the Mediterranean diet, provide a high amount of, as well as a variety of, both soluble and insoluble dietary fiber.

There are several mechanisms by which dietary fiber may exert its effects on satiation and satiety. Foods rich in dietary fiber might promote satiation through prolonged mastication. Experimental animal studies showed that mastication is important for energy metabolism [33,34]. Mastication leads to an activation of hypothalamic histamine neurons. H_1 receptors located in the satiety centers of the ventromedial hypothalamus and the paraventricular

nucleus are suppressed through histamine neuron activation. This affects eating volume and eating speed [34]. Furthermore, histamine neuron activation accelerates lipolysis, particularly in visceral adipocyte, and increases uncoupling protein (UCP) gene expression in mice [35]. Secondly, the increased mastication necessary for fiber-rich foods increases saliva and gastric acid production, which increases gastric distention. Additionally, fiber-rich foods generally contain a large volume of water, which also increases gastric distention. Activation of stretch receptors in the stomach through gastric distension contributes to satiety and satiation [36,37]. However, tolerance development to gastric distension has been reported [37].

Food ingestion causes gastrointestinal responses. Gastrointestinal satiety peptides such as cholecystokinin, glucagon-like peptide 1 and peptide YY have been shown to reduce food intake not only in animals but also in man [38]. Cholecystokinin has been the most extensively studied gastrointestinal satiety peptide. Cholecystokinin is secreted from cells in the small intestine upon ingestion of food and plays a role in the stimulation of pancreatic secretion, regulation of gastric emptying and central inducement of satiety [39]. Evidence points to an important role of cholecystokinin within the brain to regulate hunger and satiety [38]. The presence of nutrients in the lumen of the duodenum causes the release of cholecystokinin. It has been shown that fiber enrichment of a meal augmented the release of cholecystokinin in women [40]. Most important, the increase in cholecystokinin concentrations was associated with greater feelings of satiety in comparison to the low-fiber-diet control group.

The consumption of legumes, either alone or as part of a mixed dish, is characteristic of the Mediterranean diet. Bourdon et al. [41] analyzed the gastrointestinal response to ingestion of a high-fiber test meal, with beans as the source of dietary fiber (11.8 g fiber content). The cholecystokinin response to the bean-rich meal was twice as high as compared with the response to the low-fiber control meal. This may partly be due to the delayed gastric emptying, which prolonged the period of cholecystokinin response. Furthermore, it has been shown that trypsin inhibitor, a common component of most legumes, stimulates the secretion of cholecystokinin [42,43]. These additional effects may be responsible for the significant increase of cholecystokinin release after consuming the test meal.

Although the consumption of nut as an energy-dense food has not been associated with weight gain in epidemiological studies [44], most experimental nut feeding studies reported no association of weight gain with nut consumption despite an increase in energy intake [45]. One proposed mechanism that might explain this fact is the energy expenditure of unsaturated fat. Furthermore, the high content of dietary fiber and proteins of nuts explains their high satiety rating.

3.1.2. Dietary fat

High intake of olive oil is considered a hallmark of the traditional Mediterranean diet. In the olive-growing areas of the Mediterranean regions, olive oil is omnipresent in the diet. It is used for cooking and is added to legumes, salads and vegetable dishes. An increasing body of evidence indicates the health benefits of olive oil consumption [46]. However, besides its generally healthy effects, concerns regarding the potentially adverse effects of olive oil consumption, including weight gain, have been raised. Indeed, vegetable oils, such as olive oil, are the most energy-dense foods. However, epidemiological evidence shows that olive oil consumption was not associated with increased weight gain after 2 years of follow-up in a Spanish cohort [21]. Furthermore, replacing dietary saturated fat with predominantly monounsaturated fat resulted in significant total weight and fat mass loss after 4 weeks of treatment in overweight or obese men [47]. The metabolic fate of dietary fat is oxidation or storage. Hence, the capacity to oxidize fat is important for energy balance. The degree of fat oxidation varies according to the type of fat. Human studies have shown that polyunsaturated fatty acids are better oxidized than saturated fatty acids [48]. Rodriguez et al. [49] have shown that administration of olive oil up-regulates UCP genes in adipose tissue and muscle of rats. Recent data from a double-masked intervention trial revealed that increases in dietary palmitic acid decreased fat oxidation and daily energy expenditure, whereas oleic acid had the opposite effect [50]. Furthermore, administration of olive oil promoted postprandial fat oxidation and diet-induced thermogenesis in abdominally obese women [51]. This may provide a physiological explanation of why olive oil consumption is less prone to promote weight gain. Moreover, one must take into account the context of olive oil consumption in the Mediterranean diet. High consumption of olive oil is closely related to the consumption of vegetables and legumes. Adding olive oil to salads or cooked vegetables and legumes increases not only the energy content of these dishes but also their palatability. The energy content of a typical Mediterranean raw salad consisting of tomato and lettuce (200 g tomato and 40 g lettuce) increases from 40 to 150 kcal through the addition of one tablespoon of olive oil. However, the total energy content of this dish can be considered low when compared with the energy content of one doughnut (100 kcal).

3.1.3. Energy density

The energy density of foods, defined in terms of available dietary energy per weight (energy content/weight of food or kJ/g), is a key determinant of energy intake. Several intervention studies have shown that energy density influences short-term energy intake [52–54]. Energy density of the total diet differs considerably among populations [55]. The average energy density of the diet of the free-living population of the Mediterranean basin is remarkably lower (5.23 kJ/g for men; 4.63 kJ/g for women) than that

reported for the United States (7.98 kJ/g for men; 7.48 kJ/g for women) [23,56].

Strict adherence to the Mediterranean diet has also been associated with high fiber intake, high diet volume (water content) and low energy density. A first course composed of cooked vegetables, legumes or fresh raw salads has a relatively high content of dietary fiber and is low in energy density. Furthermore, because it contains a considerable amount of water, it possesses a high volume. Evidence indicates that short-term food intake is affected more by the weight or volume of food that is consumed than by the energy content of the food [53,57,58].

In a recently published study, Rolls et al. [59] investigated the effects of first-course salads on satiety and total meal energy intake. The first-course salads differed in portion size and energy density. Subjects were required to consume the entire first course but ate as much pasta as they wanted in a second dish. They found that the salad volume (portion size) was the major determinant of ratings of fullness and hunger and, consequently, of the intake of the subsequent dish (pasta). Furthermore, the energy density of the first course did not affect the consumption of pasta, but it was the main factor that determined total energy intake. Eating a high volume of a low energy-dense salad as a first course reduced total energy intake by 12% in comparison with having no first course. These results might be partially explained by the physiological mechanisms described above.

3.1.4. Alcohol consumption

The relationship between alcohol consumption and weight changes is very complex [60]. Therefore, it is not surprising that evidence from epidemiological and intervention studies is inconclusive [60]. Moderate alcohol consumption, particularly of red wine, is one of the characteristics of the traditional Mediterranean diet. Vadstrup et al. [61] observed that moderate wine consumption was not associated with higher waist circumferences after 10 years in men and women. Furthermore, recent data showed that voluntary red wine consumption prevented weight gain in rats fed a high-fat diet. This effect was mediated through a decrease in energy intake [62]. The question of whether a specific component of red wine affects mechanisms of satiety has not yet been answered.

4. Mechanisms inversely linking the Mediterranean diet to type 2 diabetes

4.1. Preventing obesity

The development of type 2 diabetes seems to be a product of the interaction between genetic susceptibility and environmental factors [63,64]. In genetically susceptible persons, excessive body weight commonly accompanies the development of type 2 diabetes. Indeed, several large epidemiological studies have shown that excessive body weight, particularly abdominal fat deposition, is an important risk factor for type 2 diabetes [65–67]. Recently, Wang et al. [68] showed that high waist circumference (an indirect measure for abdominal fat deposition) is a better predictor of type 2 diabetes than BMI (an indirect measure for general obesity). Results of the Health Professionals Follow-Up Study showed that a 1-kg increase in body weight was associated with a 7.3% increase in the risk of type 2 diabetes [67]. Excessive fat and carbohydrate intake increases energy consumption and postprandial oxidative stress. The increase in energy consumption may lead to an increase in abdominal body fat accumulation. This type of body fat, in turn, is linked to the progression of insulin resistance, which is, apart from β cell dysfunction, one of the two fundamental abnormalities involved in the pathogenesis of type 2 diabetes. Up to now, there has been no definite proof in humans of a causal link between abdominal obesity and insulin resistance. However, several plausible mechanisms could explain such a link. The adipose tissue is now recognized to be a highly active metabolic and endocrine organ [69]. Quantitatively, the most important secretion is fatty acids. The increased release of nonesterified fatty acids (NEFA) inhibits insulin-stimulated glucose metabolism in skeletal muscle and stimulates gluconeogenesis in the liver. Furthermore, the adipose tissue secretes a large number of proteins called adipokines [70]. Several of these adipokines adversely affect the insulin-signaling cascade. Tumor necrosis factor α (TNFα) enhances adipocyte lipolysis, with a subsequent increase of NEFA. Furthermore, TNFα exerts direct adverse effects on insulin-signaling pathways [71,72].

In contrast to the elevated levels of NEFA and TNFα in abdominal obesity, concentrations of adiponectin, an adipose-specific protein, are decreased in obese subjects [73]. This fact is of particular importance because there is evidence that adiponectin improves insulin sensitivity and exerts anti-inflammatory protective effects [73]. Recently, Yang et al. showed that the expression of GLUT4, the transmenbrane transporter of glucose, is down-regulated by retinol binding protein-4 (RBP4) [74]. Furthermore, serum levels or RBP4 is elevated in humans with obesity and type 2 diabetes, and RBP4 mRNA was selectively increased in adipose tissue [74]. Excessive energy consumption, including high intakes of fat and carbohydrates, increases postprandial glycemia and lipidemia. Recent data have suggested that beta cell dysfunction is a result of prolonged exposure to elevated glucose and NEFA. Postprandial hyperglycemia induces oxidative stress [75], which, in turn, damages the beta cells, which are sensitive to reactive oxygen species (ROS) [76,77].

The mechanistic links between obesity, particularly abdominal obesity, and insulin resistance suggest a causal relationship of weight gain and pathogenesis of type 2 diabetes. Diets preventing weight gain, such as the Mediterranean diet, exert a protective effect on the development of type 2 diabetes, which is partially mediated through weight maintenance.

4.2. Antioxidant-rich foods

Results from epidemiological studies indicate that a high consumption of fruits and vegetables, either alone or as components of a healthy dietary pattern, reduced the risk of type 2 diabetes [16,17,78–82]. Adherence to the Mediterranean diet is associated with a high consumption of antioxidant-rich foods such as vegetables and fruits [23]. Furthermore, in a Greek cohort, a high antioxidant capacity was found among those who closely adhered to the Mediterranean diet [83]. Recently, Sanchez-Moreno et al. [84] reported that the consumption of gazpacho, a typical Mediterranean dish, reduced F_2-isoprostanes, a marker of oxidative stress, and increased plasma vitamin C in healthy subjects. These data indicate that the Mediterranean diet protects individuals from oxidative stress, defined as the persistent imbalance between the production of highly reactive molecular species (ROS and/or reactive nitrogen species) and antioxidant defense. This fact is of special interest because prolonged increased oxidative stress seems to play a crucial role in the development of insulin resistance and beta cell dysfunction [85,86]. Excessive caloric intake leads to a substrate-induced increase in citric acid cycle activity, which, in turn, generates an excess of mitochondrial NADH and ROS [87–89]. The prevention of the entry of energetic substrates into the mitochondria could be a self-defense mechanism of the cell, which prevents an increase in the formation of mitochondrial NADH. In fact, if the excess NADH is not dissipated, then free radical production increases, resulting particularly to the formation of superoxide anions [88,89]. Insulin resistance might be considered as a compensatory state that protects the cell against further insulin-stimulated glucose and FFA uptake and subsequent oxidative damage. Indeed, there is evidence supporting this hypothesis. In cell culture models, induction of oxidative stress inhibits insulin-stimulated glucose uptake [90,91], and in results of animal studies, antioxidants improved insulin sensitivity. Furthermore, clinical trials have demonstrated that administration of vitamin antioxidants improved insulin sensitivity [92,93]. Results from cross-sectional studies showed that dietary intake of carotenoids and plasma carotenoid concentrations were inversely associated with fasting plasma glucose and insulin resistance [94–97]. Furthermore, low plasma concentrations of vitamin E were found to increase the risk of type 2 diabetes in a prospective cohort [98]. Recently published data from a randomized intervention trial showed that following a Mediterranean-style diet rich in antioxidant-containing foods significantly decreases insulin resistance in patients with the metabolic syndrome, as compared with the normal diet control group [25]. In this sense, it is important to note that the short-term administration of virgin olive oil decreases several markers of oxidative stress [99]. These data from cellular culture models, animal studies, clinical intervention trials and epidemiological studies strongly suggest the central role that oxidative stress plays in the pathogenesis of type 2 diabetes, as well as the role that dietary antioxidants play in protecting individuals from this disease.

4.3. Polyphenol-rich foods

Polyphenolic compounds are widely found in characteristic foods of the Mediterranean diet, such as fruits, vegetables, cereals, legumes and wine [100]. The two main types of polyphenols are flavonoids and phenolic acids [101]. Flavonoids exert a wide range of biological effects, such as the modulation of enzymatic activity, inhibition of cellular proliferation or antioxidant and anti-inflammatory properties [102,103]. Epidemiological evidence suggests a protective effect of fruits and vegetables, rich sources of polyphenolic compounds, on the development of type 2 diabetes [17,80,81,104]. Recently, however, Song et al. did not find a reduced risk of several flavonoids and type 2 diabetes in a large cohort of women after 8.8 years of follow-up [105]. Results of animal studies indicate a glycemia-lowering effect of polyphenols. This effect seems to be mediated through the inhibition of alpha-glucosidase in the gut mucosa [106]. Administration of quercetin inhibited glucose absorption in rats [109]. Furthermore, in a cell culture model, quercetin inhibited glucose transport by GLUT2 [107]. Evidence from culture cell studies suggests that polyphenols may increase glucose uptake by peripheral tissues [108,109]. However, due to the fact that the administered dosage of polyphenols in the abovementioned studies was superior to that found normally, it is unknown whether these results could be reproduced in humans.

4.4. Magnesium-rich foods

Magnesium is an essential cofactor of high-energy phosphate-bound enzymatic pathways [110]. Insufficient magnesium intake leading to hypomagnesemia has been associated with several disorders including type 2 diabetes [111,112]. Various characteristic components of the Mediterranean diet, such as vegetables, legumes and nuts, are rich sources of magnesium; therefore, high adherence to the Mediterranean diet is associated with a high consumption of magnesium. Evidence from epidemiological studies shows a reduced risk of type 2 diabetes with high intakes of magnesium [111,113–115]. These data indicate an important role of magnesium status in the pathogenesis of type 2 diabetes. However, the underlying molecular mechanism(s) by which magnesium intake influences insulin resistance is poorly understood. It has been hypothesized that maintaining intracellular magnesium homeostasis is crucial for adequate cellular responsiveness to insulin [116]. Magnesium is part of the activated MgATP complex that is required for all ATP- and phosphate-transfer-associated enzymes. Reduced intracellular magnesium concentrations lead to a decrease in the activity of these enzymes, which, in turn, might favor insulin resistance. It has been shown that insulin resistance in magnesium-deficient rats might be partially attributed to a decrease of tyrosine kinase activity

of insulin receptors [117]. At the extracellular level, magnesium moderates intracellular calcium uptake through its nonspecific antagonistic effects on calcium channels [118,119]. This fact is of importance because an increased intracellular concentration of calcium impaired insulin signaling through the reduced ability of insulin to activate phosphoserine phosphatase 1 [120].

4.5. Moderate alcohol consumption

Recently published data of meta-analysis of epidemiological studies suggest a protective effect of moderate alcohol consumption on the pathogenesis of type 2 diabetes [121–123]. In comparison with nonalcohol consumers, moderate alcohol drinking was associated with a 30% risk reduction of type 2 diabetes in both genders [121,122]. This risk reduction was not seen for elevated alcohol consumption [121–123]. Taking into account that estimating alcohol consumption in epidemiological studies is complex and problematic, results should be interpreted with caution. However, from a mechanistic point of view, the protective effect of moderate alcohol consumption on type 2 diabetes can be explained through the enhancing effect of moderate alcohol drinking on insulin sensitivity observed in epidemiological studies [124–126]. Sierksma et al. [127] reported an increase in insulin sensitivity accompanied by an increase in plasma adiponectin levels, but without changes in plasma TNFα, in healthy men after moderate alcohol consumption (40 g/day) for 17 days.

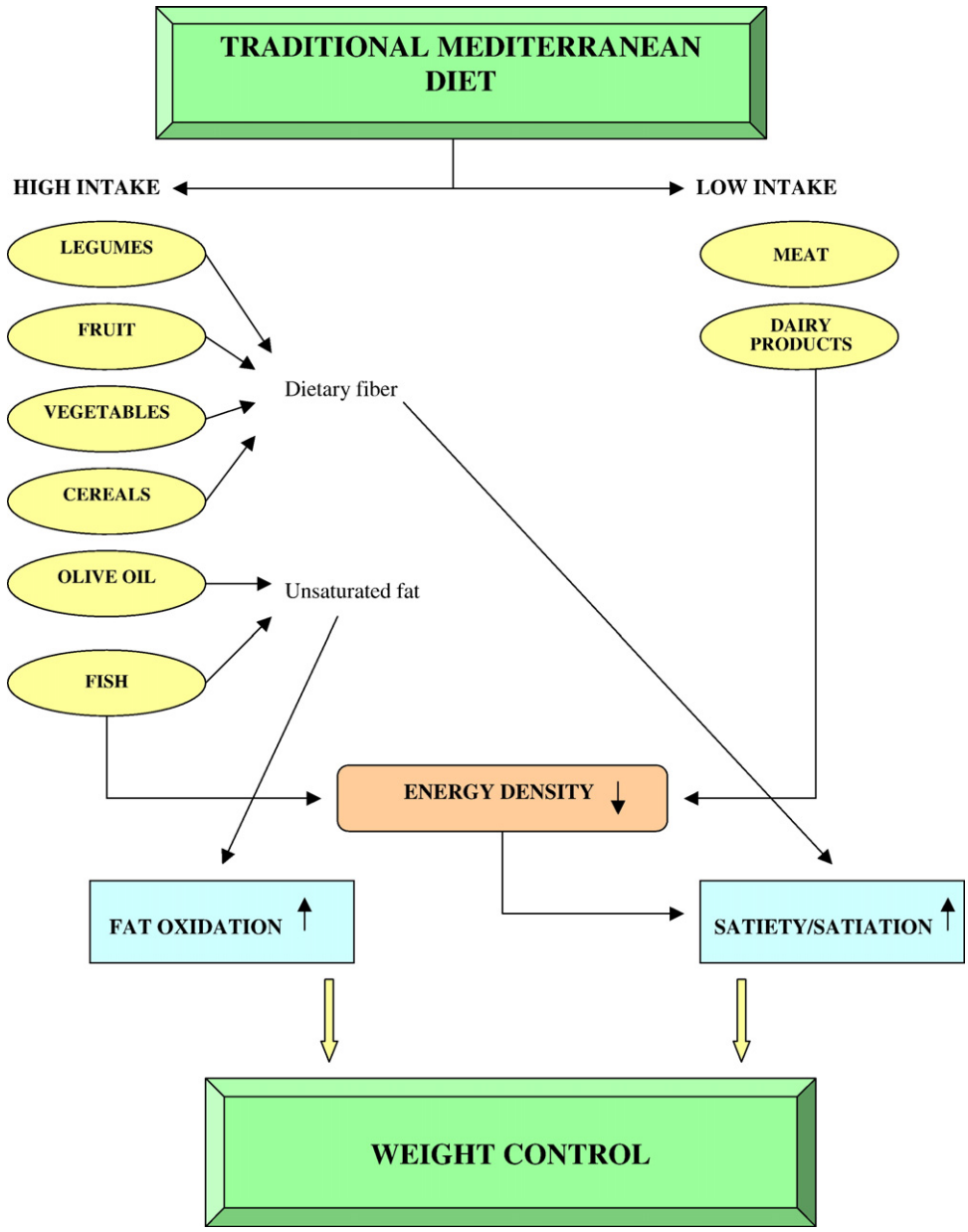

Fig. 1. Proposed mechanisms that link the Mediterranean diet with weight control.

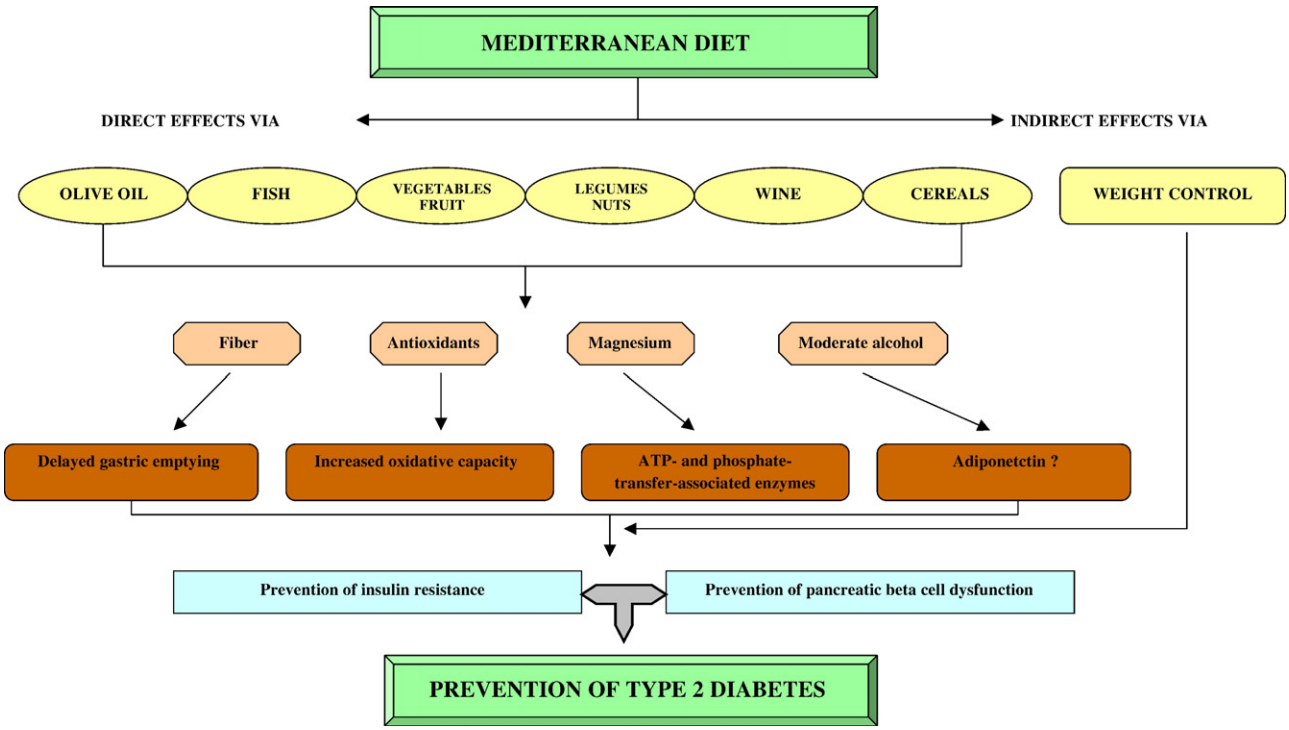

Fig. 2. Proposed mechanisms that link the Mediterranean diet with the prevention of type 2 diabetes.

One might question whether plasma concentration of TNFα represents activity at the tissue level. Furthermore, there are other mechanistic explanations for the protective effects of adiponectin on insulin resistance. Animal studies have suggested that adiponectin reduces NEFA [128,129]. Recent research has demonstrated that adiponectin decreases the hepatic fat content in mice with fatty liver disease. This effect was partially mediated through an increase in hepatic fatty acid oxidation and a decrease in hepatic fatty acid synthesis [130]. Furthermore, Yamauchi et al. [131] showed that adiponectin stimulates glucose utilization and fatty acid oxidation through activation of the 5′ -AMP-activated protein kinase. Recently published data on an intervention study showed that the daily administration of 360 ml of red wine for 14 days significantly increased insulin sensitivity in type 2 diabetic patients [132]. It is of interest to note that this effect was not mediated by or linked to endothelial dysfunction as reported by other authors [133,134].

Despite all the evidence for the existence of a link between moderate alcohol consumption and increased plasma levels of adiponectin, the mechanisms at work have not been established.

4.6. Carbohydrate and dietary fiber

A high consumption of cereals and their products is one characteristic of the traditional Mediterranean diet. To date, there are no published data on the type of cereals (refined or whole) consumed during the late 1950s in Mediterranean regions. It seems very likely that the consumption of whole grains during this time was notably higher than today. However, in the absence of published data, no definitive conclusion concerning this issue can be drawn. An increasing consumption of carbohydrates can be expected with increasing adherence to this dietary pattern [23]. In epidemiological studies, an intake of total carbohydrates did not predict the risk of type 2 diabetes [135]. Carbohydrate-rich foods can be characterized, apart from their fiber content, on the basis of their effects on postprandial glycemia. This effect can be expressed as glycemic index (GI) [136]. Postprandial blood glucose response can also be influenced by the amount of carbohydrates ingested. The glycemic load (GL) of a food, a concept developed in epidemiological studies to better represent the quality and quantity of carbohydrates consumed, is defined as the amount of carbohydrate contained in an average portion of a food multiplied by the GI value of the food [136]. Data from observational studies showed inconsistent results between risk of type 2 diabetes and GI or GL [137–141]. Indeed, there is controversy concerning the usefulness of the concepts of GI and GL in the prevention of type 2 diabetes [142–144]. Recently, Alfenas and Mattes [145] reported no significant difference in the response of plasma glucose and insulin to the consumption of low- and high-GI meals. Furthermore, data from the Inter99 study, an intervention study with the aim of reducing cardiovascular diseases through healthy choices in diet, physical activity and smoking, showed no association of habitual intake of diets that are low and high in both GI and GL with the risk of having insulin resistance. In contrast, dietary fiber was inversely associated with this risk [146]. Insulin resistance, which is not synonymous with type 2 diabetes mellitus, is a

key step in the pathogenesis of this disease. There is consistent epidemiological evidence to support a protective effect of dietary fiber, in particular cereal fiber, on insulin sensitivity and the risk of type 2 diabetes [137–139,146,147]. Several mechanisms may link dietary fiber with the risk of type 2 diabetes. The insulin-sensitizing effects of dietary cereal fiber may be mediated through magnesium, a nutrient found in the outer husk of whole grains (see Section 4.4). Furthermore, the beneficial effect of dietary fiber on glucose metabolism may be the result of a delayed gastric emptying rate and slowed digestion and absorption, which, in turn, slows the rate of glucose absorption and reduces plasma insulin levels [148,149]. An additional mechanistic hypothesis for dietary fiber's capability to protect individuals from type 2 diabetes, as discussed in Section 3.1, is that it helps maintain an appropriate and stable weight. This in turn exerts favorable effects on insulin sensitivity.

4.7. Foods rich in unsaturated fat

Early epidemiological evidence suggested a deleterious effect of total fat consumption on the development of diabetes [150]. More recent large cohort studies that take into account the fat type consumed have shown an increased risk of the development of type 2 diabetes with high intakes of saturated fat. In contrast, an inverse association was reported for unsaturated fat [151–153]. Although total fat intake did not seem to directly increase the risk of type 2 diabetes, an indirect influence of high fat intake that promotes weight gain should be considered [153,154]. A high intake of monounsaturated fatty acids, predominantly from olive oil, is a key characteristic of the traditional Mediterranean diet. There is some evidence that oleic acid, the predominant fatty acid of olive oil, is associated with lower insulin resistance [155,156]. However, contradictory results have also been reported [157,158].

Furthermore, the mechanisms linking the type of dietary fat with insulin resistance are not completely understood. Cell membrane lipid composition is influenced by fatty acid composition of dietary fat. The specific fatty acid profile in cell membranes might affect insulin action in a number of ways, such as insulin receptor binding and the ability to influence ion permeability and cell signaling.

4.8. Conclusion

Several mechanistic links (Figs. 1 and 2) offer potential explanations of the Mediterranean diet's protective effect on obesity and type 2 diabetes. High consumption of vegetables, fruits, legumes, nuts, fish, cereals and olive oil, together with moderate consumption of alcohol, predominantly wine, leads to high ingestion of dietary fiber, antioxidants, magnesium and unsaturated fatty acids. Additionally, this diet is characterized by a low degree of energy density overall, which might be particularly important for the prevention of weight gain. Intervention studies on energy density and appetite control tend to be conducted under short-term laboratory conditions. A number of researchers have suggested potential mechanisms by which isolated components of the Mediterranean diet can prevent weight gain, insulin resistance and beta cell dysfunction (i.e., some nutrients such as dietary fiber, calcium and magnesium influence metabolic pathways or signaling mechanisms). However, a "big picture" approach to food intake and its effect on the development or prevention of obesity and diabetes may be more predictive of disease risk. It is important for individuals to understand the protective effects of healthy foods, particularly on obesity and type 2 diabetes, within the context of a healthy overall diet.

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