

Mediterranean diet in the primary prevention of type 2 diabetes Pathophysiological mechanisms

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ABSTRACT: Despite the on-going advances in treatment and management of type 2 diabetes mellitus, the latter remains a chronic condition that achieves rates of an epidemic, worldwide. The dramatic increase of diabetes, not only plays a role in the increase of the risk for cardiovascular disease, but also imposes a serious economic burden to the society, because of its serious complications. Since no curative treatment exists so far, primary prevention should be the cornerstone of the global response to the disease. There is growing evidence that dietary changes may delay or even prevent diabetes development. Mediterranean Diet, one of the most popular dietary patterns, has been thoroughly studied in relation to various health outcomes, such as cardiovascular disease, metabolic syndrome and diabetes management, with promising results. Here, the role of Mediterranean diet in the primary prevention of diabetes mellitus is reviewed, and results of various

Η Μεσογειακή δίαιτα στην πρωτογενή πρόληψη του σακχαρώδους διαβήτη τύπου 2 Υπεύθυνοι παθοφυσιολογικοί μηχανισμοί

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ΠΕΡΙΛΗΨΗ: Παρά τις συνεχείς εξελίξεις στη θεραπεία και διαχείρισή του, ο σακχαρώδης διαβήτης τύπου 2 παραμένει μια χρόνια κατάσταση που έχει εξελιχθεί σε παγκόσμια επιδημία. Η δραματική αύξηση του διαβήτη, όχι μόνον αυξάνει τον κίνδυνο για καρδιαγγειακά νοσήματα, αλλά επιφέρει μια σοβαρή οικονομική επιβάρυνση στην κοινωνία, λόγω των σοβαρών επιπλοκών του. Δεδομένου ότι μέχρι σήμερα δεν υπάρχει ειδική θεραπευτική αγωγή, η πρωτογενής πρόληψη πρέπει να αποτελέσει ακρογωνιαίο λίθο της συνολικής αντιμετώπισης του προβλήματος. Υπάρχουν αυξανόμενες ενδείξεις ότι οι διαιτητικές αλλαγές μπορεί να καθυστερήσουν ή ακόμη και να αναστείλουν την ανάπτυξη του διαβήτη. Η Μεσογειακή Διατροφή, ένα από τα πιο δημοφιλή διατροφικά πρότυπα, έχει μελετηθεί διεξοδικά σε σχέση με διάφορες εκβάσεις της υγείας, όπως τα καρδιαγγειακά νοσήματα, το μεταβολικό σύνδρομο και ο διαβήτης, με ελπιδοφόρα αποτελέσματα. Στην παρούσα εργασία

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studies are presented, with emphasis on the main proposed biological mechanisms.

Key words: Mediterranean Diet, diabetes, pathophysiological mechanisms, review

1. Introduction

Type 2 diabetes is a chronic disease, deriving by pancreatic b-cells' inability to secrete enough insulin and/or by ineffective insulin activity (insulin resistance) to cover body's metabolic needs.¹ It is considered an epidemic, counting 340 million people worldwide, with continuously escalating direct and indirect costs. It usually occurs in people over 40 years old of age and is due to several factors including genetic and environmental factors (unhealthy diet, physical inactivity, smoking, excessive alcohol use).² Since genetic predisposition is non-modifiable, lifestyle interventions remain the cornerstone of the global response to the disease.

Diet is considered one of the most important factors than can affect health. For the primary prevention of diabetes, various foods and nutrients have been identified to exert a protective –such as fruits– or aggravating –such as red and processed meat– effect on type 2 diabetes mellitus.^{3,4} However, since nutrient research is shifting towards a more holistic approach, for both practical and methodological reasons,⁵ the study of dietary patterns is the new status. Mediterranean diet, initially introduced by Ancel Keys of the Seven Countries Study, in the late 1970's,⁶ is nowadays one of the most studied patterns. Although different Mediterranean-style scores appraising adherence to the pattern have been proposed; overall, Mediterranean Diet is characterized by abundant consumption of plant foods (fruits, vegetables, whole grain cereals, legumes, nuts, seeds, potatoes), olive oil, as the principal source of fat, low to moderate consumption of fish, poultry and dairy products (mainly cheese and yogurt), up to 4 eggs per week, low consumption of meat, its products, highly processed foods, refined grains and sugars and finally low to moderate wine drinking, normally with meals.⁷

ανασκοπείται ο ρόλος της μεσογειακής διατροφής στην πρωτογενή πρόληψη του σακχαρώδη διαβήτη. Ακολουθεί μια συνοπτική παρουσίαση των αποτελεσμάτων των διαφόρων μελετών, με περισσότερη έμφαση στους προτεινόμενους βιολογικούς μηχανισμούς της εν λόγω σχέσης.

Λέξεις ευρετηρίου: Μεσογειακή Δίαιτα, διαβήτης, παθοφυσιολογικοί μηχανισμοί, ανασκόπηση.

2. Mediterranean diet and diabetes development

Although Mediterranean diet has long been celebrated for its beneficial effect against cardiovascular disease (CVD)⁸ and cardiovascular risk factors (i.e, hypertension, dyslipidemia, obesity⁹), the past few years further research worldwide suggests a favorable impact on metabolic parameters and type 2 diabetes as well.

Various epidemiological studies have been conducted towards this direction. Following studies are grouped based on their design.

The first study that assessed the association between adherence to a Mediterranean diet and diabetes was ATTICA study, which was carried out in Athens Metropolitan area and enrolled 3042 participants (aged 20–89 years), free of cardiovascular disease.¹⁰ Cross-sectional analysis of data, after adjustment for various confounders, showed that a 10-unit increase of MedDietScore decreased the likelihood of having diabetes by 0.79-times (95%CI: 0.65, 0.94).¹¹ Another large-scale study is PREDIMED, which is a parallel-group, randomized intervention trial, but has also served as a cross-sectional study. Participants were men (55–80 years old) and women (60–80 years old), without CVD at baseline, with either type 2 diabetes or ≥3 major cardiovascular risk factors (current smoking, hypertension, dyslipidemia, being overweight or with family history of premature coronary heart disease). Cross sectional analyses of PREDIMED database have further confirmed the protective effect of the Mediterranean diet.^{9,13}

However, most studies that have assessed this relationship have a prospective design, Romaguera et al. analyzed data of 27,792 participants, who participated in EPIC study. Higher adherence to Mediterranean pattern reduced by 12% the risk of diabetes (95% CI: 0.79,

0.97), compared with the lower adherence group.¹⁴ Rossi et al, studied the Greek cohort of EPIC, i.e, 22,295 participants; the risk reduction detected was exactly the same ($RR=0.88$, 95% CI: 0.78, 0.99), after adjusting for similar covariates,¹⁵ de Koning et al, studied 41,615 apparently healthy men from the Health Professionals Follow-Up Study. In the multivariate model, the highest compared with the lowest Mediterranean diet quintile had 35% lower risk of developing diabetes within 20 years (95% CI: 0.66, 0.86).¹⁷

Mozaffarian et al, have found that the anti-diabetic effect of Mediterranean diet may expand among patients with a recent myocardial infarction. Multivariate analysis showed that patients with higher adherence had 0.65-times lower risk of developing diabetes (95% CI: 0.49, 0.85).¹⁶ This finding was confirmed by Tobias et al, for women with prior gestational diabetes mellitus.¹⁸

Only one intervention study exists that has looked into Mediterranean diet-diabetes relationship, the aforementioned PREDIMED study. Here, it was revealed that participants in the 2 intervention groups (Mediterranean diet, enriched with virgin olive oil (1 L/week) or nuts (30 g/day) had lower risk of developing diabetes, irrespective of the source of unsaturated fat ($RR=0.49$, 95% CI: 0.25, 0.97 and $RR=0.48$, 95%CI: 0.24, 0.96 respectively), compared to the control group.¹²

Recently, the first systematic work to evaluate the role of Mediterranean diet against diabetes development was performed by Koloverou et al. Primary analyses included 9 prospective studies and 1 clinical trial, yielding to a sample of 136,846 participants. The combined effect was found to be protective. Specifically, it was revealed that higher adherence to the Mediterranean diet was associated with 23% reduced risk of developing type 2 diabetes (combined relative risk for upper versus lowest available group: 0.77, 95% CI: 0.66, 0.89), irrespective of region of origin and the level of adjustment; but it seemed to be more prominent among participants with prior gestational diabetes, or participants at high risk for cardiovascular disease and/or diabetes, according to the following meta-regression analysis.¹⁹

3. Pathophysiological sequale

Various mechanisms have been proposed for the suggested protective effect of Mediterranean diet against the development of diabetes, as several micronutrients,

macronutrients and foods have been associated with diabetes risk.

To begin with, chronic low-grade inflammation has been recognized as the substrate of almost all chronic diseases, including obesity-related metabolic disorders, and in this case type 2 diabetes mellitus.²⁰ One could therefore speculate that a dietary pattern rich in anti-inflammatory nutrients (e.g. n-3 fatty acids, vitamin C, E, D, flavonoids) and poor in pro-inflammatory nutrients (e.g. saturated and trans fatty acids) may act beneficially. Indeed, following the Mediterranean diet for 2 years has been associated with lower levels of C-reactive protein and interleukin-18, two inflammatory markers of cardiovascular risk.²¹ Estruch et al, have also examined the short-term effects of two Mediterranean diets, supplemented with either extra virgin olive oil or nuts versus a control low-fat diet on intermediate markers of cardiovascular disease. Subjects in the intervention group after 3 months had decreased levels of C-reactive protein, compared with the control group.²²

Another plausible mechanism implicates antioxidants, in which Mediterranean diet is plentiful. Patients with diabetes have increased oxidative stress as well as a defect in antioxidant defense mechanisms.²³ It has been reported that the development of insulin resistance and b-cell dysfunction may be mediated by oxidative stress.²⁴ Interestingly, b-cells are more prone to oxidative stress compared to other tissues, as they have less antioxidant defense enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx).^{25,26} In addition to this, hyperglycemia itself further induces free radicals production, resulting in increased oxidative stress in b-cells.²⁷ Due to b-cell ability to directly damage and oxidize DNA, protein, and lipids, as well as to activate many cellular stress-sensitive pathways linked to impaired insulin action and secretion, the progression of the disease as well as its management is exacerbated.²⁴ All these have led to the hypothesis that the antioxidant profile of a diet may suspend oxidative stress accumulation and have a beneficial effect on diabetes development. A meta-analysis of nine prospective studies by Hamer et al, has shown a 13% reduction in diabetes risk ($RR=0.87$, 95% CI: 0.79, 0.98), for the highest compared with the lowest antioxidant intake, mainly attributed to vitamin E.²⁸ In addition, the total antioxidant capacity, i.e, the cumulative effect of all antioxidants present in plasma and body fluids has been studied, as it is believed to provide a better understanding compared to the assessment of dietary components. Specifically, in a random sample of 1,018

apparently healthy individuals, ATTICA researchers have investigated the relationship between diabetes biomarkers and dietary antioxidant capacity, as measured by three different assays: ferric-reducing antioxidant power (FRAP), total radical trapping antioxidant parameter (TRAP) and Trolox equivalent antioxidant capacity (TEAC). An inverse association was observed between FRAP and log-glucose ($r=-0.149$, $p=0.001$), log-insulin ($r=-0.221$, $p=0.001$) and log-HOMA-IR ($r=-0.186$, $p=0.001$) concentration, as well as with TRAP and TEAC.²⁹ Mediterranean dietary pattern, which is abundant in antioxidants, has been examined in relation to oxidative stress levels. Following the Mediterranean diet for two years, irrespective of calorie restriction, has been associated with significant amelioration of multiple risk factors, including reduced oxidative stress, in a randomized controlled trial of 192 overweight men.³⁰ Furthermore, the effect of Mediterranean diet on postprandial oxidant and antioxidant status has been compared with a Western-diet (rich in SFA) and a low-fat, high carbohydrate diet, enriched in n-3 FAs, in a cross-over trial in 25 elderly men and women (each diet for 4 weeks). Two hours after the intake of the Mediterranean diet, it was observed a greater increase in Ischemic Reactive Hyperemia (IRH) and a greater decrease in plasma hydrogen peroxidase (H_2O_2), lipid peroxide (LPOs), nitrotyrosine, oxidized low-density lipoprotein cholesterol (oxLDL) levels and catalase activity ($p<0.05$ for all associations).³¹ Finally, to rule out genetic or shared environmental factors influence, in a well-controlled study of monozygotic and dizygotic twins, the effect of adherence to the Mediterranean diet on the ratio of reduced to oxidized glutathione (GSH/GSSG) was evaluated. A one-unit increment in the diet score was associated with a 7% higher GSH/GSSG ratio ($p=0.03$) after various adjustments. The association persisted within twin pairs, with the one-unit increase in the diet score leading to 10% (95% CI:2.7, 18.0) higher GSH/GSSG. Results did not differentiate between monozygotic and dizygotic twin pairs.³²

The potential anti-diabetic effect of the Mediterranean diet may additionally be attributed to particular properties of specific macro- or micronutrients, which are separately studied in relation to insulin resistance and/or diabetes development. Magnesium is an important micronutrient. It has been reported that decreased intracellular enzymatic activity, attributed to magnesium deficiency, may underline insulin resistance [33]. Extracellular magnesium is also important to prevent a rise in intracellular calcium concentration, which can

further aggravate insulin signaling.³⁴ Magnesium-rich foods, such as vegetables, nuts and legumes, abundant in the Mediterranean pattern, can prevent a magnesium deficiency. Indeed, a recent study showed that Mediterranean diet can assist significantly in the increase of serum magnesium concentrations in a group of patients with coronary artery disease.³⁵

Both carbohydrate quality and quantity are also considered to have a pivotal role. Dietary fiber, especially cereal oriented, is believed to contribute significantly to Mediterranean diet's protective effect.^{36,37} Their beneficial properties could derive from high magnesium concentrations (bran) or delayed gastric emptying rate, which slows down digestion and glucose absorption, mitigates b-cell demands and down streams insulin burden.³⁸ Carbohydrates have been also evaluated under the spectrum of Glycemic Index (GI) and Glycemic Load (GL), which represent the quality and the combined quality/quantity of carbohydrates respectively, and are measures of the increase in insulin levels following glucose uptake. A high GL meal leads to rapid rise in glucose and insulin levels, which in the long term results in beta-cell overload and failure, leading to impaired glucose tolerance and insulin resistance. This theoretic mechanism was confirmed in a systematic review published in 2008, which found a pooled relative risk for diabetes incidence of 1.27 (95% CI 1.12, 1.45) for the highest versus the lowest GL quintile.³⁹ Although Mediterranean diet and low glycemic load diet are usually used as two different diet styles, it is suggested that Mediterranean diet can be considered a low GI and maybe a low GL diet. Even though potatoes, fruits, legumes and cereals, which are high in carbohydrates, are in the basis of the Mediterranean diet, they usually are accompanied by a high dietary fiber load, which decreases the glycemic load of the meal. Additionally, olive oil and vegetables not only minimally affect GL, but also help to decrease it, as well, due to their content in fatty acids and dietary fiber respectively.

Dietary fat has also been of clinical interest regarding its effect on glucose metabolism, as there seems to be a direct link between fatty acids and insulin action. Based on a recent review, saturated fatty acid pattern, as measured in skeletal muscle, which reflects higher intakes of saturated over unsaturated fatty acid, predicts insulin resistance and type 2 diabetes. Conversely, n-6 PUFA pattern favors insulin action, although no association has been observed with n-3 PUFA. Studies assessing dietary fat intake through self-report tools (e.g. questionnaires, food records) are consistent with stud-

ies using serum biomarkers, i.e. the inverse link between n-6 PUFA and diabetes risk. Interestingly risk reduction related to PUFA seems to peak when PUFA replace trans FAs in the diet.⁴⁰ The Nurses' health study has also confirmed the positive association between trans fatty acid intake and risk of diabetes, with a clear dose-response relation.⁴¹ Finally, PREDIMED trial has further evaluated the different effect of MUFA and PUFA, using extra virgin olive oil (source of MUFA) and nuts (source of both MUFA and PUFA) on diabetes development among high cardiovascular risk participants and under the spectrum of Mediterranean diet. Researchers found a similar beneficial effect, which indicates that unsaturated fat is protective, compared to saturated or trans fat, irrespective of its source.¹² The exact mechanism is not yet clear enough, although there seems to be a link between dietary fat composition and cell membrane lipid composition, which in turn affects cell membrane function, including membrane fluidity, insulin receptor binding/affinity and the ability to influence ion permeability and cell signaling.⁴² More recent experimental data also point towards other mechanisms, i.e. gene expression and enzyme activity regulation by free fatty acids (FFAs). For example, PUFAs (e.g. linoleic acid and n-3 FAs) have been found to suppress lipogenic gene expression and enhance oxidative metabolism. On the other hand, SFAs, especially palmitic acid, have an adverse effect.^{43,44} Finally, experimental studies report that Toll-Like Receptor (TLR) signaling, which is a key mediator between inflammation and insulin resistance, is determined by the type of FA (for example, it is initiated by saturated lauric acid).⁴⁵

Mediterranean diet is also characterized by moderate alcohol consumption, especially with meals. A meta-analysis of 20 cohort studies reported a U-shape relationship between alcohol and diabetes development, with moderate and high intake being protective and hazardous respectively.⁴⁶ Modest alcohol consumption has been associated with lower fasting plasma insulin and glucagon^{47,48} and enhanced peripheral insulin sensitivity,⁴⁷ which may be attributed to changes in fat tissue endocrine function, inflammatory pathway or glucose and fatty acids metabolism. The ATTICA study has associated moderate alcohol consumption (1–2 drinks) with lower triglycerides and CRP levels and higher HDL-cholesterol levels.⁴⁹ A lower triglyceride-to-HDL cholesterol ratio, both components of metabolic syndrome, has also been reported.⁵⁰ Increase of insulin-sensitizing, anti-inflammatory adiponectin, has been reported among middle-aged women as well.⁵¹ Plasma Fetuin-A,

a liver secreted glycoprotein which inhibits insulin receptor tyrosine kinase activity, participates in the altered insulin signaling induced by moderate alcohol consumption.⁵² Ethanol may also attenuate the positive association between glycemic index or glycemic load and diabetes, when alcohol consumption exceeds 15 g/d.⁵³ Finally, the anti-diabetic effect of modest drinking may be mediated by the observed improvement in arterial blood pressure.⁴⁹ As far as the alcohol type is concerned, wine has been suggested to offer the greatest benefit, probably due to its high content in anti-inflammatory polyphenols, especially resveratrol, which additionally enhances insulin sensitivity.⁵⁴

Last but not least, it has been suggested that Mediterranean diet may protect, contributing to weight control,⁴² which is crucial, taking into consideration that visceral obesity is an important risk factor for type 2 diabetes.⁵⁵ Increased fat mass in the abdomen leads to increased release of non-esterified fatty acids, inhibiting insulin-stimulated glucose metabolism in skeletal muscle and stimulating gluconeogenesis in the liver, which may aggravate hepatic metabolism. Furthermore, weight loss is associated with a decrease in adipokine level,⁵⁶ which adversely affects the insulin-signaling pathway.⁴² Adherence to the Mediterranean diet assists in weight management also through food intake regulation, resulting from higher satiety and satiation, due to dietary fiber⁵⁷ and better fat oxidation due to the high unsaturated/saturated ratio (i.e. fish, olive oil vs. meat, dairy).⁵⁸

Apart from the last mechanism, i.e. weight control, which can be achieved by various dietary patterns, the rest mechanisms, which implicate the anti-inflammatory and antioxidant profile, high fiber intake, resveratrol, magnesium, high unsaturated/saturated fat ratio, can be hardly found, particularly in combination, in other dietary patterns. For example, a low-fat diet could be very low in fish, nuts and olive oil, whereas a low-carb diet could be low in fruits, dairy and legumes; that is why Mediterranean diet is considered unique.

4. Conclusions

There is compelling evidence that diabetes can be delayed or even prevented by lifestyle interventions. The importance of diet in the context of diabetes medical therapy is unanimously accepted. Mediterranean diet has proven its cardiovascular risk benefits, and it is suggested to have additional health benefits, including an anti-diabetic effect. It is rich in plant-based

foods, extra virgin olive oil and nuts, whereas it eliminates saturated fat consumption. Mediterranean diet is a balanced dietary pattern, which does not exclude any food, but emphasizes on the optimal frequency of consumption of various foods. The synergistic effect of its individual components may be responsible for its beneficial property in mitigating type 2 diabetes development. Mediterranean diet can be easily adopted by not only Mediterranean populations, if appropriately adjusted to reflect local food availability as well as individual's preferences, which ensure long-term adherence. Therefore, steps towards more Mediterranean nutritional choices are encouraged. For example, improving fat quality should be considered part of a dietary lifestyle strategy to prevent type 2 diabetes. In practice, replacing saturated fats with non-hydrogenated vegetable oils rich in MUFA and/or PUFA may be considered as a public health strategy, aiming not only at controlling diabetes, but promoting general cardiovascular health. Choosing fruits, whole-grain bars or nuts for snacks, instead of ready to eat biscuits and chocolates is another easy and feasible choice. Conclusively, it is not suggested that Mediterranean diet is a panacea, but since no consensus exists on the best anti-diabetic diet, Mediterranean dietary pattern could constitute a beneficial nutritional choice for the primary prevention of the disease.

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