Effects of the Mediterranean Diet on Type 2 Diabetes' Incidence and Treatment: A Systematic Review

Panayota Kailatzi¹, Margarita Matte² and Styliani G. Tziaferi³

Abstract

The incidence of Type 2 diabetes is increasing rapidly worldwide, bringing about an enormous economic burden for societies. Dietary habits play an important role in the manifestation and treatment of this disease. Results from epidemiological studies and clinical trials, suggest that adherence to the Mediterranean diet may exert beneficial influence on glycemic control and prevention of this condition. We conducted a systematic review aiming to determine the impact of the Mediterranean diet on glycemic control and diabetes incidence. Electronic databases, PubMed and Google Scholar, were searched for available publications that assessed the effect of the Mediterranean diet on type 2 diabetes. Thirty nine studies met the inclusion criteria, sixteen explored the impact of the Mediterranean diet on type 2 diabetes incidence, fifteen explored the impact of the Mediterranean diet on type 2 diabetes treatment, nine explored the impact of the Mediterranean diet on diabetes indices, as components of Metabolic syndrome and four examined the impact of the Mediterranean diet on cardiovascular risk factors, including type 2 diabetes. Current guidelines and recommendations from all the major scientific associations, strongly encourage a Mediterranean-like dietary pattern for primary and secondary prevention of major chronic diseases, including type 2 diabetes.

Keywords: Mediterranean diet, type 2 diabetes, glycemic control, HbA1c, insulin resistance, glucose homeostasis, cardiovascular disease, metabolic syndrome

1 Introduction

Type 2 diabetes (T2D) remains the major cause of morbidity and mortality world-wide. According to International Diabetes Federation, 382 million people suffered from diabetes

¹National and Kapodistrian University of Athens.
²National and Kapodistrian University of Athens.
³University of Peloponnese.

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in 2013, while this will rise to 592 million by 2035 [1]. Individuals with T2D have a potent risk for a range of complications that can lead to disability and premature death such as renal failure, neuropathy, blindness, hypertension, peripheral vascular and cardiovascular diseases (CVD) [2, 3]. As a result, the management of diabetes mellitus poses a huge medical and economic burden, making it a current public health priority [4].

Although genetic predisposition and environmental influences seem to be the most important factors responsible for the development of T2D, the increased prevalence of this condition seems to result mainly from the lifestyle changes in modern societies. It is well established that diabetes is a nutrient- gene- interaction disease [5-8]. The westernized dietary patterns, physical inactivity, and the raising rates of overweight and obese people are some of the modifiable factors that contribute to the increasing incidence of T2D. Behavior change interventions such as dietary habits may promote healthful lifestyles, reducing the incidence of T2D and improve glycemic control [9]. Diet quality plays an important role to the disease manifestation. High-quality diets with low glycemic index and glycemic load and rich in fruits and vegetables are associated with reduced risk of chronic diseases such as MetS, CVD and T2D. This is attributed to weight balance, low insulin response, lower blood lipids, blood pressure, blood glucose and inflammation [10-14].

Foods are rarely eaten in isolation but, instead, in combination with other food groups, thus the combined effect of food groups may create an additive effect on health [15]. Analyses of the overall diet rather than of individual food groups takes this potential food synergy into account. The Mediterranean diet (MeDiet) is the traditional dietary pattern of Mediterranean region residents [16]. This diet is comprised of abundant plant foods (vegetables, fruits, seeds, nuts and cereals), high consumption of whole grains, olive oil, legumes, moderate to high consumption of fish, moderate to low consumption of meat, meat products, milk and dairy products and moderate intake of alcohol (red wine) [16-19].

The MeDiet is one of the best known dietary patterns for its beneficial effects on human health. Adherence to the MeDiet is usually measured with MeDiet scores, including a variety of components, with higher values in these scores reflecting higher adherence to the MeDiet. Recent studies have shown that conformity to the MeDiet protects individuals from major chronic diseases like heart disease, cancer, Parkinson and Alzheimer. Results from epidemiological studies and clinical trials demonstrate the beneficial role of the MeDiet regarding the development of T2D and its treatment. High consumption of vegetables, fruits, whole grain cereals and moderate consumption of alcohol provide antioxidants, anti-inflammatory factors and dietary fiber, which have been implicated in improvements in glucose regulation and the progression of complications associated with diabetes. Moreover, high consumption of fish and olive oil provides a high intake of polyunsaturated and monounsaturated fatty acids that beneficially influence insulin resistance [20-29].

Nevertheless, urbanization and globalization have altered the diet and nutrition towards the opposite direction despite the nutritional recommendations for a healthy diet and lifestyle [30]. Even in Mediterranean countries, dietary habits have partially changed into a more Westernized dietary pattern. Therefore, diet evaluation for the prevention of T2D is of significant public health importance [1, 22, 25-29, 31]. The aim of this study was to systematically review all the available studies that have evaluated the impact of the MeDiet in human T2D, including diabetes prevention, treatment and metabolic and cardiovascular outcomes.
2 Methods

We searched Pubmed and Google Scholar databases for relevant articles about the effect of the MeDiet on T2D incidence and treatment from February 2014 to May 2014. We used the keywords Mediterranean diet, type 2 diabetes, glycemic control, HbA1c, insulin resistance, glucose homeostasis, cardiovascular disease, metabolic syndrome, as well as combinations of these. In addition, the reference lists of the retrieved articles helped us to find relevant articles that did not allocate through database searching procedure. We narrowed the search to studies published in English between 2003 and 2014, and limited to those conducted in humans. We excluded studies that analyzed adherence to a non-specific dietary pattern. We also excluded studies with less than 3 months follow-up and those with gestational or type 1 diabetes population. We focused the search on articles referring to the MeDiet as a whole dietary pattern and excluded studies that only investigated one aspect of the MeDiet. Moreover, reports with restricted calorie intake or those that aimed to reduce body weight, were discarded.

3 Results

A total of 129 articles were identified in the initial search, of which we excluded 41 on the basis of the title or abstract due to the deliberation of only one of the two aspects (T2D or MeDiet). Of the remaining 88 articles were discarded 49 for the following reasons: a non-specific dietary pattern instead of a MeDiet was evaluated (n=8), the study population had gestational or type 1 diabetes (n=3), the follow-up was less than 3 months (n=3), including 2 studies that were published before 2003, studies with restricted calories or those aimed to reduce body weight (n=8), studies regarding specific foods of MeDiet (n=25) and those that were not written in English (n=1). Thirty nine studies met the inclusion criteria (Figure 1). Of these, we identified 18 observational studies (7 prospective cohort studies, 8 cross-sectional studies, 1 retrospective study, 1 case-cohort prospective study and 2 both cross-sectional and prospective studies), 12 intervention studies (2 of them were cross-over and 10 randomized trials), and 8 reviews.

From the total of 39 studies (Table 1), 31 took place in European countries, of them, 26 conducted in the Mediterranean region, four in north Europe and one was multicenter. Five studies conducted in USA, two in Australia and one in Asia. The number of subjects ranged from 12 to 41,614 participants. Greater adherence to the MeDiet was associated with older age [32, 46, 57, 58], being female [34, 35, 46, 57, 58], better education [33,35], higher incomes [36], smaller waist circumference [36], non-smoking [36, 46, 57, 58], more physically active individuals [57], multivitamin users [46], ERT users [46], slightly greater BMI [58], hypertension [58] and previous acute myocardial infarction [58]. In contrast, the study of Panagiotakos et al [55], found no difference between the two sexes, while in another study [34], age, physical activity, education and consumption of antiplatelet β-blocker agents had no difference between conformity groups.

3.1 Diabetes Incidence

Given the dramatic increase of T2D prevalence nowadays, strategies aiming to prevent the disease manifestation are of major public health priority. The association between MeDiet adherence and the incidence of T2D was assessed in 7 prospective studies [32, 33, 35, 37,
The most available prospective studies support the protective role of the MeDiet against T2D development. The protecting reduction risk ranges from 9% to 83% for patients closely adhered to the MeDiet, compared to those with the lowest adherence, after adjustment for several confounding factors such as smoking, BMI, age, sex, family history of T2D, physical activity, etc. Moreover, a high MeDiet score together with a low GL, offer protection of about 20% against diabetes. Interestingly, the MeDiet not only has a beneficial effect on healthy adults, but also on individuals with recent myocardial infarction. Specifically, Mozaffarian et al. [58], found that prevention of weight gain, smoking cessation and consumption of the MeDiet, offer a protective effect on T2D incidence on this patient group. It should be noted that dietary pattern scores such as the alternative HEI (Healthy Eating Index), the DASH (Dietary Approaches to Stop Hypertension) [37] and the Healthy eating pattern [49] scores were associated with a lower risk on T2D incidence, emerging that a common dietary pattern characterized by plant based foods, fruits, whole- meal bread, low- fat dairy, moderate alcohol and low intake of red meat may beneficially influence the T2D odds.

Cross- sectional evidence regarding the association between adherence to MeDiet and the likelihood of T2D, demonstrate the beneficial role of MeDiet to T2D incidence. It is noteworthy that both Panagiotakos et al. [55] and Sanchez- Tainta et al. [25] discovered that following the MeDiet is inversely associated not only with the clustering of diabetes, but also with hypertension, obesity, and hypercholesterolemia among high cardiovascular risk and elderly individuals. In another cross-sectional study of Panagiotakos et al. [62], 3042 participants took part in order to evaluate the incidence of T2D in relation to both physical activity and dietary patterns. The study revealed that a 10- point increase in the MeDiet score was associated with 21% lower odds of acquiring diabetes. The study adds that commitment to the MeDiet together with light physical activity can reduce diabetes risk by 35%, compared to sedentary individuals.

One large case cohort, multicenter prospective study showed that individuals with a high MeDiet score were 12% less likely to develop diabetes than those with low MeDiet scores. Additionally, a two- point increase in the MeDiet score was associated with a 4% reduction in the risk of T2D. It should be noted that the association between the two variables was attenuated in obese participants, compared to the youngest ones. Finally, two randomized controlled trials searched the relation between MeDiet and the incidence of T2D. Salas Salvado et al., [42] compared the effects of two MeDiets supplemented with olive oil or nuts, versus a low- fat diet on the incidence of T2D in 418 non diabetic participants at high cardiovascular risk. The study found that MeDiet with either olive oil or nuts reduces diabetes incidence by 52%, compared with the low-fat dietary pattern. Similarly, later in 2014 Salas Salvado et al., [65] found that a MeDiet supplemented with extra olive oil and without energy restriction, succeeded in limiting the incidence of T2D among high cardiovascular risk patients.

3.2 Diabetes Treatment

Fifteen studies explored the relationship between MeDiet and glycaemic control. Of them, five were cross- sectional studies [41, 35, 45, 51, 54], two were randomized cross- over intervention studies [36, 41], three were reviews [44] and five were randomized trials [66, 65, 43, 56, 59]. Most of these studies demonstrate the beneficial effect of the MeDiet in
T2D patient's glycemic control and insulin sensitivity. Cross-sectional research results show the salutary effect of the MeDiet to both diabetic and non-diabetic participants. Evidence reveals that non-diabetic participants, consisted with the MeDiet, had lower insulin levels, blood glucose (4), and better fasting indices of glucose homeostasis [54]. Additionally, in diabetic patients with greater attach to the MeDiet, was observed reduced HbA1c and post-meal glucose concentrations [45]. Cross-over intervention studies of Ryan et al [36] and Itsiopoulos et al (9), included of non-diabetic and diabetic participants respectively. Both studies found that insulin sensitivity improved with the MeDiet. Furthermore, Itsiopoulos observed that consumption of the MeDiet fell HbA1c from 7.1% to 6.8%, compared to the usual diet. Liver steatosis reduced with MeDiet, compared with low fat/high carbohydrate diet in participants with NAFLD [36].

Two randomized intervention trials carried out in non-Mediterranean countries, in order to evaluate the effect of the MeDiet on diabetes markers at diabetic population. The study of Lindeberg et al [56] failed to prove any significant correlation between these variables. Particularly, Lindeberg et al estimated the effect of the Paleolithic diet, based on fish, fruits, eggs, nuts, root vegetables and lean meat, compared to the MeDiet on glucose tolerance and postchallenge insulin response in glucose intolerant IHD patients. The study recommends that healthy diets, such as the MeDiet constitute the second best choice for the prevention and control of diabetes condition. On the other hand, Elhayany et al [43], compared two MeDiets, a low carbohydrate MeDiet (LCM) and the traditional MeDiet, to the 2003 American Diabetic Association diet (ADA) between overweight diabetic patients, and found that only the LCM had a significant impact on improving glycaemic control in this population group. Additionally, the recent report of Esposito et al [64] supports that a LCM can improve not only diabetes indices, but also can delay the need for medication use between overweight, diabetic individuals.

3.3 MeDiet and MetS

We identified five primary studies that assessed the association between the MeDiet and diabetes indices, as components of MetS [34, 38, 46, 57, 59] and four reviews [12, 47, 48, 52]. The sum of the reviews ended up that the MeDiet has an anti-inflammatory impact against diseases related to chronic inflammation, including abdominal obesity, MetS and T2D. Traits of MetS such as insulin resistance, hypertension and dyslipidemia are attenuated with the consumption of the MeDiet. Regarding the impact of the MeDiet on the incidence of MetS, Tortosa et al prospectively found that the MeDiet reduces the odds of acquiring MetS together with all risk factors that are responsible for its development, except plasma glucose. Additionally, the prospective study of Rumawas et al [46] found that MetS prevalence was significantly reduced with MeDiet. Moreover, MetS traits were attenuated (less abdominal obesity, less insulin resistance, and less atherogenic dyslipidemia).

Moreover, the cross-sectional study of Viscogliosi et al [34] searched the incidence of MetS and the insulin resistance and fasting glucose levels among non diabetics. They observed that MeDiet protects against MetS and prediabetes, and improves glucose metabolism. Similarly, Gouveri et al [38] observed a reduced incidence of MetS and a subsequent benefit on T2D and CVD development with the commitment to the MeDiet. In contrary, Michalsen et al [59] examined the impact of MeDiet on patients with treated CAD.
with regard to inflammation and metabolic risk factors. Commitment to the MeDiet had no effect on indices of inflammation and metabolic risk factors, including fasting insulin.

3.4 MeDiet and Cardiovascular Disease

Three randomized controlled trials [60, 61, 63] and one review [47], were identified in order to test the effectiveness of the MeDiet on cardiovascular risk factors. Champagne et al [47] carried out a review in 2009 ending up that individuals consuming the MeDiet pattern derive advantage against the development of MetS and CVD. Vincent- Baudry et al [31] conducted an intervention study of 212 overweight and obese participants with moderate CVD risk factors who classified into a MeDiet or a low-fat diet group. The study showed that both diets had a beneficial effect on CVD risk factors, including insulinemia, glycemia, and HOMA score. Particularly, a 9% reduction was observed in CVD risk with the low-fat diet and a 15% reduction with the MeDiet. Furthermore, in another randomized trial, 772 participants at high cardiovascular risk were classified into a MeDiet group with olive oil, a MeDiet group with nuts, or a low-fat group. Both MeDiets improved blood pressure, lipid profiles, reduced insulin resistance and decreased concentrations of inflammatory molecules, compared with the low-fat group. As a result, both MeDiets exert a beneficial effect on CVD risk factors [60]. Finally, Toobet et al [63], investigated the impact of the Mediterranean Lifestyle Program on CVD. He found that stress management, exercise, smoking cessation and the Mediterranean low-saturated fat diet, improved glycemic control, some coronary heart disease risk factors and the overall quality of life.

4 Labels of Figures and Tables

<table>
<thead>
<tr>
<th>Total studies (n=129)</th>
</tr>
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<tbody>
<tr>
<td>Studies excluded on the basis of the title or abstract due to the deliberation of only one of the two aspects (T2D and MeDiet) (n=41)</td>
</tr>
<tr>
<td>88 studies</td>
</tr>
<tr>
<td>Studies excluded due to the non specific dietary pattern(n=8), type 1 diabetes population (n=3), follow-up less than 3 months (n=3), restricted calorie/weight loss (n=8), components of MeDiet only (n=25), in different than English language (n=1)</td>
</tr>
<tr>
<td>39 assessed for eligibility</td>
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</table>

Figure 1: Diagram flow of literature review
Table 1: Studies exploring the effect of the Mediterranean diet on type 2 diabetes mellitus incidence and treatment

<table>
<thead>
<tr>
<th>Author/Year Publication</th>
<th>Country</th>
<th>Type of study</th>
<th>Population</th>
<th>Criteria for inclusion/exclusion</th>
<th>Objective</th>
<th>Methodology</th>
<th>Follow up</th>
<th>Results</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salas-Salvador et al., 2014</td>
<td>Spain</td>
<td>Randomized trial</td>
<td>3541 patients, aged 55 to 80 years</td>
<td>Patients without T2D but at high cardiovascular risk were eligible for the study</td>
<td>To assess the efficacy of MeDiets for the primary prevention of diabetes</td>
<td>Participants were randomly assigned to 1 of 3 nutrition interventions: MeDiet with extra-virgin olive oil (EVOO), MeDiet supplemented with mixed nuts, or a control diet (advice on a low-fat diet)</td>
<td>Median of 4.1 years</td>
<td>- 80, 92, and 101 new-onset cases of T2D occurred in the MeDiet with EVOO, MeDiet with mixed nuts, and control diet groups, respectively - Multivariate-adjusted hazard ratios were 0.6 for the MeDiet with EVOO, and 0.82 for the MeDiet with nuts compared with the control diet</td>
<td>A MeDiet enriched with EVOO but without energy restrictions reduced diabetes risk among persons with high cardiovascular risk</td>
</tr>
<tr>
<td>Lasa et al., 2014</td>
<td>Spain</td>
<td>Randomized controlled trial</td>
<td>191 participants (77 men and 114 women)</td>
<td>Participants with T2D were included</td>
<td>The aim of this work was to compare the effect of two Mediterranean diets versus a low-fat diet on several parameters and indices related to glycemic control in type 2 diabetic subjects</td>
<td>Participants were assigned to 1 of 3 nutrition interventions: two Mediterranean diets supplemented with virgin olive oil (n=67) or mixed nuts (n=74) and a low-fat diet (n=50). Insulin resistance was measured by HOMA-IR index, adiponectin/leptin and adiponectin/HOMA-IR ratios</td>
<td>1 year</td>
<td>- Increased values of adiponectin/leptin ratio (P=0.043, P=0.003 and P&lt;0.001 for low-fat, olive oil and nut diets, respectively) and adiponectin/HOMA-IR ratio (P=0.061, P=0.027 and P=0.069 for low-fat, olive oil and nut diets, respectively) were observed in the three groups - Decreased values of waist circumference (P=0.003, P=0.001 and P=0.001 for low-fat, olive oil and nut diets, respectively) were observed in the three groups - In both Mediterranean diet groups, but not in the low-fat diet group, the variation above was associated with a significant reduction in body weight (P=0.003, P=0.003 and P=0.021 for low-fat, olive oil and nut diets, respectively)</td>
<td>Mediterranean diets supplemented with virgin olive oil or nuts reduced total body weight and improved glucose metabolism to the same extent as the usually recommended low-fat diet</td>
</tr>
<tr>
<td>Esposito et al., 2014</td>
<td>Italy</td>
<td>Randomized trial</td>
<td>215 overweight, middle-aged men and women with newly diagnosed T2D</td>
<td>Participants with T2D were included</td>
<td>To assess the long-term effects of dietary interventions on glycemic control, need for diabetes medications, and remission</td>
<td>Participants were randomized to a low-carbohydrate MeDiet diet (n = 108) or a low-fat diet (n = 107). After 6.1 years</td>
<td>- The primary end point was reached in all participants after a total follow-up of 6.1 years in the low-fat diet</td>
<td>In patients with newly diagnosed type 2 diabetes, an LCMD resulted in a greater reduction of...</td>
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</table>
of type 2 diabetes 4 years, participants who were still free of diabetes medications were further followed up until the need of a diabetic drug. Remission of diabetes (partial or complete) and changes in weight, glycemic control, and cardiovascular risk factors were also evaluated group and 8.1 years in the low carbohydrate MeDiet group. - Median survival time was 2.8 years and 4.8 years, respectively. - Low carbohydrate MeDiet participants were more likely to experience any remission (partial or complete), with a prevalence of 14.7\% during the first year and 5.0\% during year 6 compared with 4.1\% at year 1 and 0\% at year 6 in the low-fat diet group. HbA1c levels, higher rate of diabetes remission, and delayed need for diabetes medication compared with a low-fat diet.

Georgoulis et al., 2014 Greece Review - -

To examine current scientific knowledge on the association between the MeDiet and diabetes mellitus - -

According to epidemiological data, a greater adherence to the MeDiet, is inversely associated with T2D risk in the general population, in individuals at high cardiovascular risk and in patients with established CVD. - International studies also demonstrate the beneficial role of the MeDiet in T2D management, with patients allocated to a MeDiet exhibited greater improvements in glycemic control and CVD risk factors, compared with those following a control diet. - There is evidence that MeDiet may also have a beneficial role in the primary and secondary prevention of CVD and a favorable effect on liver and sexual function in diabetic patients.

Mounting evidence suggests the beneficial effect of the MeDiet on T2D prevention and treatment.
Effects of the Mediterranean Diet on Type 2 Diabetes' Incidence and Treatment

Esposito et al., 2014

To review the impact of MeDiet on T2D

Prospective studies report a lower risk of T2D in healthy people or at risk patients with the highest adherence to a MeDiet

MeDiet improved HbA1c levels from 0.1% to 0.6%

No trial reported worsening of glycemic control with a MeDiet

Adopting a MeDiet may help prevent T2D. Moreover, lower carbohydrate MeDiet seems good for HbA1c reduction in persons with established diabetes

Dominguez et al., 2013

To evaluate the macronutrient distribution, assessed with MDS or MEDAS scoring systems. To evaluate disease incidence or mortality, associated with adherence to MeDiet

Adherence to MeDiet was associated with a decreased incidence of T2D, CVD, and all-cause mortality

Rossi et al., 2013

To investigate the association between MeDiet and GL with diabetes incidence

A low GL diet that also adequately adheres to the principles of the traditional MedDiet may reduce the incidence of T2D

Adherence to MeDiet was associated with a decreased incidence of T2D, CVD, and all-cause mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Study Design</th>
<th>Number of Participants</th>
<th>Excluded Participants</th>
<th>To Evaluate</th>
<th>Individuals Completed</th>
<th>Mean Time</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esposito et al., 2014</td>
<td>Italy</td>
<td>Review</td>
<td>-</td>
<td>-</td>
<td>To review the impact of MeDiet on T2D</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Dominguez et al., 2013</td>
<td>Spain</td>
<td>Cross-sectional/prospective cohort study</td>
<td>20,155 individuals for cross-sectional analyses, &amp; 9,109 individuals for longitudinal analysis, university graduates-former students, non-obese with mean age 38.4 years</td>
<td>Excluded participants: - with energy intake out of &lt;800 or &gt;8000kcal/day for men and &lt;500 or &gt;6000kcal/day for women - with cancer, CVD, and diabetes at baseline, - with missing information - without at least a 2-year follow up</td>
<td>To evaluate the macronutrient distribution, assessed with MDS or MEDAS scoring systems. To evaluate disease incidence or mortality, associated with adherence to MeDiet</td>
<td>Individuals completed a validated FFQ, together with other questionnaires that collected sociodemographic, lifestyle and clinical characteristics. Participants returned completed questionnaires every 2 years</td>
<td>6.2 years</td>
<td>-Perspective studies report a lower risk of T2D in healthy people or at risk patients with the highest adherence to a MeDiet - MeDiet improved HbA1c levels from 0.1% to 0.6% - No trial reported worsening of glycemic control with a MeDiet</td>
</tr>
<tr>
<td>Rossi et al., 2013</td>
<td>Italy</td>
<td>Prospective cohort study</td>
<td>22,295 participants</td>
<td>Excluded participants who: - did not respond or could not be traced during follow up - had diabetes, cancer and/or stroke and/or CVD - had missing values of the covariates of interest</td>
<td>To investigate the association between MeDiet and GL with diabetes incidence</td>
<td>Participants completed a validated FFQ at enrolment. Adherence to MeDiet and dietary GL were calculated from MDS score</td>
<td>11.34 years</td>
<td>-Adherence to MeDiet was associated with a decreased incidence of T2D, CVD, and all-cause mortality - Participants in the highest quartile of adherence to the MD (MDS &gt; 5) exhibited a 12% (95% CI 0.78-0.99) reduced risk of T2DM, compared with those in the lowest quartile (MDS &lt; 4) - Adherence with MeDiet increased with better educated participants - Older participants reported a diet with a lower GL, compared with younger ones - MeDiet reduced diabetes risk independently of GL levels</td>
</tr>
</tbody>
</table>
Viscogliosi et al., 2013  
**Italy**  
**Cross sectional**  
**120 individuals with mean age 59.8±10.2 years**  
Excluded participants:  
- who changed their dietary habits within the last year  
- with diabetes  
- with history of CHD, stroke, ischemic attack  
- with cardiovascular events and chronic diseases except blood hypertension, obesity, dyslipidemia, IFG  
- taking anti-inflammatory agents, statins or other lipid-lowering agents  
- current or former smokers  
- with daily consumption of more than 2 glasses of alcohol for women and more than 3 for men for a period of 6 consecutive months  

To investigate whether the commitment with MeDiet affects the prevalence of MetS, impaires fasting glucose, insulin resistance and microinflammation  
- Commitment with MeDiet was calculated with a validated 14-item questionnaire  
- venous blood sample for FBG, triglycerides, HDL-C, fasting insulin, CRP  
- face to face interview for medical patient/family history, lifestyle habits and home therapy  
- The overall adherence to the MeDiet was low (most subjects succeeded 6-9 points on a 0-14 point scale)  
- No differences in mean age, physical activity, education and consumption of antiplatelet and β-blocker agents were found across categories of adherence  
- Participants with higher adherence to MeDiet were more likely to be women  
- Subjects with MetS were less likely to consume olive oil and vegetables  
- BMI and the overall MeDiet were strongly associated with the presence of MetS  
- IFG was independently predicted by age, BMI and overall MeDiet  
- Adherence to MeDiet may protect against MetS and prediabetes and exert a beneficial role on glucose metabolism  

Abiemo et al., 2013  
**USA**  
**Cross sectional/prospectiv e cohort study**  
**5390 multi-ethnic men and women aged 45-84 years, free of diabetes and CVD**  
Subjects with CVD or T2D excluded from the study  

To investigate if conformity to the MeDiet is related cross-sectionally with lower insulin resistance and prospectively with reduced risk of T2D incidence  
- The average MeDiet score was 5 on a 0-10-point scale  
- Participants with higher conformity to the MeDiet were more likely to be female, more educated, had higher greater consistency with MedDiet was associated with lower insulin levels among non-diabetics, and with lower blood glucose before adjustment for obesity, but not...
Effects of the Mediterranean Diet on Type 2 Diabetes' Incidence and Treatment

Ryan et al., Australia
Randomized, cross-over intervention study
12 non-diabetic subjects (6 female/6 male) with biopsy proven NAFLD
Subjects included if:
- There was evidence of steatosis on ultrasound scanning and histology
- Presence of MetS
- Consumption of no more than 7/10 standard alcoholic drinks per week for women/men
- Excluded those with T2/2D

To examine the effect of the MeDiet on steatosis and insulin sensitivity
MedDiet group compared to a LF/HCD group. All subjects undertook both diets. Insulin sensitivity was determined with a 3-h hyperinsulinemic-euglycemic clamp study, hepatic steatosis assessed with H-MRS.

6 weeks intervention - 6 weeks washout - 6 weeks intervention

At baseline, the 12 subjects were obese, had elevated mean fasting serum concentrations of glucose, insulin, triglycerides, ALT and GGT.
- Insulin sensitivity at baseline was low (M=2.7±1.0 mg/kg/min)
- Mean weight loss was not different between the two diets.
- There was a significant relative reduction in hepatic steatosis after MeDiet compared with the LF/HCD.
- Insulin sensitivity improved with the MedDiet whereas after the LF/HCD there was no change.

Even without weight loss, MeDiet reduces liver steatosis and improves insulin sensitivity in an insulin resistant population with NAFLD.

Koning et al., USA
Prospective cohort study
41,615 male health professionals
Excluded participants with T2D, CVD, heart attack, stroke, angina, or coronary artery bypass graft, cancer, or implausible energy intake (<800 or >4200 kcal/day).

To compare associations of diet-quality scores, which were inversely associated with CVD, with incident T2D and to test for differences in absolute risk reduction across various strata
The HEI 2005, the alternative HEI (aHEI), the recommended Food Score, the alternative MedDiet (aMedDiet) Score, and the DASH score were calculated from FFQs quintiles and continuous intervals.

Questionnaires were mailed to participants every 2-4 years from 1986 to access lifestyle and health status. FFQs were completed ≤20 years

Several diet-quality scores were associated with a lower risk of T2D and reflect a common pattern characterized by high intakes of plant-based foods, moderate alcohol, low intakes of red and processed meat, sodium, sugar-sweetened beverages and trans fat.
A 1-SD increase was associated with 9–13% reduced risk of T2D
- DASH score was associated with lower risk independently of other scores
- Risk reduction was greater among overweight or obese subjects, compared with normal-weight ones (p < 0.01)

Panayota Kailatzis et al.

Gouveri et al., 2011
Greece
Retrospective
2074 adults, 900 men and 1174 women (age, 46.6±14.9 years)

To investigate the association between MeDiet and MetS in a representative sample of the Athenian population in the early 1980s.

A cross-sectional epidemiologic survey of CVD and their risk factors, was conducted in a representative sample of the adult Athenian population in the early 1980s. MetS was defined according to criteria of the National Cholesterol Education Program-Adult Treatment Panel III. MeDiet was assessed according to guidelines of the Division of Nutrition/epidemiology, Athens University Medical School.

49.3% followed MeDiet with similar rates across age groups
- MetS was diagnosed in 24.0% of those following Med Diet, compared with 27.9% of those not following it
- Participants with CVD or T2D were less likely to follow Med Diet
- MeDiet was associated with a 20% reduction in MetS, after adjustment for age, gender, smoking, light physical activity, serum levels of low-density lipoprotein cholesterol and γ-glutamyl transferase, diabetes mellitus, CVD, family history of hypertension, and/or hyperlipidemia

Adherence to MeDiet may attenuate the prevalence of MetS and, consequently, the increasing burden of diabetes mellitus and CVD, especially in urban populations.

Romaguera et al., 2011
Denmark, France, Germany, Italy, the Netherlands, Spain, Sweden and the Case-cohort prospective study
11,994 incident T2D case subjects and a stratified subcohort of 15,798 participants

Were excluded:
- individuals without stored blood or with prevalent diabetes status at baseline,
- participants within the lowest and highest 1% of the cohort distribution of the ratio of reported total energy intake:

To study the association between adherence to the MedDiet and risk of developing T2D, across European countries.

A case-cohort study including 11,994 incident T2D case subjects and a stratified subcohort of 15,798 participants selected from a total cohort of 340,234 participants with 3.99 million person-years of follow-up from 4 million person-years

Individuals with a high MeDiet score range (11-18 points) were 12% less likely to develop diabetes than individuals with low MeDiet scores (0-6 points)
- The alcohol, meat, and olive oil

Adherence to MedDiet was associated with a small reduction in the risk of developing T2D.
Effects of the Mediterranean Diet on Type 2 Diabetes' Incidence and Treatment

U.K requirement

eight European cohorts participating in EPIC study. The relative MedDiet score was used to assess adherence to MedDiet. Cox proportional hazards regression, modified for the case-cohort design, was used to estimate the association between rMedDiet and risk of T2D, adjusting for confounders.

Australi Randomized cross-over study

27 people, aged between 47 and 77 years, with confirmed T2D. Exclusion criteria: presence of disabling stroke, cancer not in remission, renal failure, or liver disease. To examine the impact of a traditional Mediterranean-type cuisine on HbA1c and vascular risk in T2D. Participants were randomly assigned to consume either the intervention diet ad libitum or their usual diet for 12 weeks and then cross over to the alternate diet. Biochemical data and anthropometric characteristics were assessed at baseline, and at the end of both diet periods. Dietary adherence was monitored using plasma carotenoid and fatty acid analysis, complemented by diet diaries.

Spain Cross-sectional study

385 participants, 53.4% women (mean age 69.6 years). Included participants with T2D. To analyze the association between adherence of a MeDiet in patients with T2D and levels of HbA1c. Information on diet was collected with a validated 14 point scale of adherence to the MeDiet and blood samples were obtained to assess HbA1c.

Spain Randomized controlled trial

418 non diabetic subjects aged 55-80 years. Participants without prior CVD but having at least three cardiovascular risk factors: smoking, Participants were randomly assigned to education on a low-fat diet (control group) or to one of two MedDiets supplemented with either extra virgin olive oil or mixed nuts, versus a low-fat control diet on incidence of Diabetes incidence was 10.1%, 11.0% and 17.9% in the MedDiet with olive oil group, the MedDiets without calorie restriction seem to be effective in the prevention of diabetes in subjects.
hypertension, dyslipidemia, overweight (BMI ≥25 kg/m²), and family history of premature CVD, were included in the study. Excluded those with prevalent diabetes, with severe chronic illness, alcohol or drug abuse, BMI ≥40 kg/m², and history of allergy or intolerance to olive oil or nuts.

MedDiets, supplemented with either free virgin olive oil (1L/week) or nuts (30g/day). Diets were ad libitum. The main outcome was diabetes incidence diagnosed by the 2009 American Diabetes Association criteria. Questionnaires about lifestyle variables, medical condition, medication use, conformity to MedDiets and leisure physical activity, time, administered annually. Participants were randomly assigned to one of the three diets. The main outcome measures were glycemic control and biomarkers for cardiovascular risk. Adherence to MedDiets was evaluated from Food Frequency Questionnaire (FFQ) administered at 6 months.

Weight, BMI and waist circumference were reduced in all dietary interventions with no significant difference between the groups. HbA1c, blood lipids and HOMA decreased in all groups, fasting insulin levels increased over time. The reduction in HbA1c was significantly greater in the LCM diet than in ADA diet. HDL cholesterol increased only on the LCM diet. The reduction in serum TG was greater in the LCM and TM than in the ADA diet. Many epidemiological studies show the beneficial effect of the MedDiets on T2D and glucose metabolism in general. Results from epidemiological studies and clinical trials evaluating the role of the MedDiets, regarding the development and treatment of T2D, indicate the protective role of this pattern.
<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Design</th>
<th>Sample Size</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>Study Object</th>
<th>Adherence Measure</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esposito et al., 2009</td>
<td>Italy</td>
<td>Cross-sectional</td>
<td>901</td>
<td>Diagnosis of T2D for at least 6 months but &lt;10 years, age 35-70 years, BMI ≥ 24.0 kg/m², HbA1c ≥ 6.5% and treatment with diet or oral glucose-lowering drugs</td>
<td>Need for insulin use, concomitant chronic diseases, including kidney, liver and CVD diseases, recent acute illness or change in diet, treatment or lifestyle within the 3 months before the initial assessment</td>
<td>To explore whether a MedDiet improves glycemic control in diabetes</td>
<td>Nutrient intakes were assessed using FFQ. Adherence to MedDiet was measured with a 0-9 point scale questionnaire</td>
<td>- Diabetic patients with the highest scores (6-9) had lower BMI, waist circumferences, a lower prevalence of the MetS and lower HbA1c and post-meal glucose levels than diabetic patients with the lowest scores (0-3).</td>
</tr>
<tr>
<td>Rumawas et al., 2009</td>
<td>USA</td>
<td>Prospective</td>
<td>2730</td>
<td>Without T2D and MetS traits and 1918 participants free of MetS</td>
<td>Participants with prevalent MetS at baseline were also excluded</td>
<td>To examine the prospective association between the MedDiet and metabolic syndrome</td>
<td>Adherence to MedDiet was measured with MSDPS. Dietary intake was assessed by using the Harvard semiquantitative FFQ. The association between MSDPS and MetS traits homeostasis model assessment - insulin resistance, glucose, waist circumference, triglyceride, HDL, cholesterol and systolic and diastolic blood pressure was examined</td>
<td>- Participants in the highest quintile category were older, more likely to be women, multivitamin users, and ERT users, more likely to have a greater change in BMI over follow-up, and less likely to be current smokers</td>
</tr>
</tbody>
</table>

**Effects of the Mediterranean Diet on Type 2 Diabetes' Incidence and Treatment**

In T2D, greater adherence to MedDiet is associated with lower HbA1c and postprandial glucose levels.
Panayota Kailatzi et al.

Babio et al., Spain Review

To analyze the effect of diet on MetS and its components

Review of the available literature in relation to MedDiet and MetS

- Several components of MedDiet patterns have been inversely related with BMI. They are considered to be modulators of insulin resistance, can exert beneficial effects on blood pressure, improve atherogenic dyslipidemia or attenuate the inflammatory burden associated with MetS

Champagne et al., USA Review

To review the usefulness of a Mediterranean-based diet in individuals with T2D

This article reviews data available on the MedDiet related to its use in a diabetic population

- Mediterranean diet may be used in dietary interventions for the treatment of overweight and obesity, conditions associated with the development of T2D
- MedDiet has been found to be inversely related to the MetS, often a feature of diabetic individuals
- Consuming MedDiet, there was a positive response of insulin, blood glucose, blood lipids, and other metabolic factors predicting CVD risk and outcomes
- The review of the literature points to using the MedDiet as a viable option for people with T2D. Advisors should stress not only adherence to a fairly MedDiet but also a lifestyle that includes sufficient physical activity

Giugliano et al., Italy Review

To present evidence illustrating the relationship between MedDiets and metabolic diseases, including obesity, T2D, and the MetS, and to briefly discuss potential mechanisms by which these diets can help in disease prevention and treatment

Mounting evidence indicates a favorable effect of MedDiet on obesity and T2D
- MedDiet is attenuating the inflammatory burden associated with T2D
- A lower prevalence of the MetS is associated with dietary patterns rich in fruits, vegetables, whole grains, dairy products, and unsaturated fats
- Both epidemiological and interventional

Mounting evidence suggests that MedDiets could serve as an anti-inflammatory dietary pattern, which could help fighting diseases that are related to chronic inflammation, including visceral obesity, T2D and the MetS
Effects of the Mediterranean Diet on Type 2 Diabetes' Incidence and Treatment

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Design</th>
<th>Number</th>
<th>Eligible participants</th>
<th>Exclusion criteria</th>
<th>Methods</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sanchez-Tainta et al., 2008</td>
<td>Spain</td>
<td>Cross-sectional</td>
<td>3204 asymptomatic, high cardiovascular risk individuals</td>
<td>Eligible participants were community-dwelling men, 55-80 years old, and women, 60-80 years old, who have diabetes or who meet at least three or more other CVD risk factors</td>
<td>Exclusion criteria were: previous history of CVD, any severe chronic illness, drug or alcohol addiction, and history of allergy or intolerance to olive oil or nuts</td>
<td>To estimate the association between adherence to a MedDiet and the prevalence of hypertension, dyslipidemia, diabetes and obesity, or their clustering in a large sample of asymptomatic high-risk patients</td>
<td>Adherence to MedDiet was inversely associated with individual risk factors and, above all, with the clustering of them. The multivariate adjusted odds ratio to present simultaneously the 4 risk factors for those above the median value of the MedDiet score was 0.67. The multivariate odds ratios for successive categories of adherence to MedDiet were 1, 1.03, 0.85, 0.7 and 0.54. The healthy eating pattern reduced risks of diabetes and major coronary events. Such dietary patterns offer considerable health benefits to individuals.</td>
</tr>
<tr>
<td>Brunner et al., 2008</td>
<td>UK</td>
<td>Prospective analysis</td>
<td>7731 participants with mean age of 50y</td>
<td>Excluded participants who were members of outlying dietary clusters, and energy misreporters</td>
<td>Dietary patterns were identified in order to study their relations to incident major coronary events and diabetes as well as mortality. Follow-up carried out by means of screening contacts every 5y. Usual dietary intake was assessed by using a 127-item FFQ. Coronary death or nonfatal myocardial infarction and incident diabetes were verified by record tracing and oral-glucose-tolerance tests</td>
<td>The healthy eating pattern reduced risks of diabetes and major coronary events. Such dietary patterns offer considerable health benefits to individuals.</td>
<td>Following the MedDiet was inversely associated with the clustering of hypertension, diabetes, obesity, and hypercholesterolemia among high-risk patients.</td>
</tr>
</tbody>
</table>
Panayota Kailatzi et al.

**Martinez-Gonzalez et al., 2008**
Spain  
Prospective cohort study  
13,380 Spanish university graduates without diabetes at baseline

Excluded participants who had diabetes at baseline and those who reported a baseline history of CVD

To assess the relation between adherence to a MedDiet and the incidence of diabetes among initially healthy participants

Dietary habits assessed at baseline with a 137-item FFQ with a 9 point index. Adherence to MedDiet was appraised according to the score created by Trichopoulou et al. Every 2 years, follow-up questionnaires on diet, lifestyle, risk factors, and medical conditions, were sent to participants. New cases of diabetes confirmed through medical reports and an additional detailed questionnaire posted to those who self reported a new diagnosis of diabetes by a doctor during follow-up

A median of 4.4 years

- Participants with high adherence to the MedDiet (MDS > 6) exhibited a 83% (95% CI 0.04-0.72) reduced risk of T2DM, compared with those with low adherence (MDS < 3)
- The incidence rate ratios adjusted for sex and age were 0.41 for those with moderate adherence (score 3-6) and 0.17 for those with the highest adherence (score 7-9) compared with those with low adherence (score < 3)
- A 2-unit increase in the MDS score was associated with a 35% (95% CI 0.44-0.95) reduced risk of T2DM

Adherence to a MedDiet is associated with a reduced risk of diabetes

**Tzima et al., 2007**
Greece  
Cross-sectional study  
1762 participants with excess body weight, meaning overweight (BMI: 25-29.9kg/m²) and obese (BMI: >30kg/m²), 20-89 years old

Included people without any clinical history of CVD, or any other atherosclerotic disease, as well as chronic viral infections. Participants did not have cold or flu, acute respiratory infection, dental problems or any type of surgery during past weeks. All people living in institutions were excluded from the study

To investigate if overweight and obese adults “close” to MedDiet present better insulin, lipids profile and better pressure levels, compared to individuals close to a more Westernized diet

Adherence to MedDiet was assessed through a FFQ. Blood pressure, fasting glucose, insulin and blood lipids were measured. Insulin sensitivity was also assessed by the HOMA approach

- Individuals with excess bodyweight in the highest tertile of diet score, were more insulin sensitive than those in the lowest tertile, had 13% lower levels of total cholesterol and 3mmHg decrease of systolic blood pressure levels when adjusted for age, sex and BMI
- Multivariate analysis after taking into account several confounders demonstrated that insulin sensitivity, total cholesterol and systolic blood pressure were

Adherence to a MedDiet is associated with a reduced risk of diabetes

Overweight and obese people, attached to the MedDiet, had a limited profit against cardiovascular risk factors.
Effects of the Mediterranean Diet on Type 2 Diabetes' Incidence and Treatment

Esposito et al., Italy Review

To review the association between MedDiet and MetS.

Dietary patterns close to MedDiet, rich in fruit and vegetables, and high in monounsaturated fats are negatively associated with features of the MetS (abdominal obesity, insulin resistance, hypertension, dyslipidemia). The favorable benefit/hazard ratio makes MedDiet particularly promising to reduce the cardiovascular burden associated with the MetS.

Schroder et al., Spain Review

To discuss potential mechanisms by which the MedDiet prevents obesity and diabetes.

High fiber diets, such as MedDiet, increase satiety and reduce hunger. Olive oil consumption was not associated with increased weight gain but with lower insulin resistance. The average density of the MedDiet is remarkably lower than that reported for the US. Diets preventing weight gain, such as the MedDiet, exert a protective effect on the development of T2D. MedDiet protects individuals from oxidative stress, that is responsible for pathogens of T2D. Polyphenol-rich foods seem to exert a protective effect on the development of T2D. High adherence to the MedDiet is associated with a high consumption of magnesium and reduced risk of T2D.

Several mechanistic links offer potential explanations of the MedDiet's protective effect on obesity and T2D.
Moderate alcohol drinking, such as in the MedDiet, was associated with a 30% risk reduction of T2D. Dietary fiber, in particular cereal fiber, exert a protective effect on insulin sensitivity and the risk of T2D.

Panagiotakos et al., 2007
Greece
Cross-sectional
3042 participants
Subjects with history of CVD or any other atherosclerotic disease, with chronic viral infections, those who had a cold or flu, acute respiratory infection, dental problems or any type of surgery during the past weeks were excluded. Subjects with type 1 diabetes were also excluded.

To investigate the associations between adherence to MedDiet and fasting indices of glucose homoeostasis, T2D and IFG were defined according to the established ADA criteria. Insulin resistance was evaluated by HOMA-IR. Dietary habits were assessed through a validated FFQ and a diet score (range 0-55) was developed (higher values means greater adherence to the MedDiet).

The overall prevalence of T2D was 7.9% in men and 6.0% in women.

Mean diet score was 26.3±6.8 in normoglycemic, 25.7±6.4 in IFG, and 22.2±5.8 in diabetic subjects.

In normoglycemic subjects in the upper tertile of the diet score, was observed 7% lower glucose, 5% lower insulin and 15% lower HOMA-IR compared to subjects in the lower tertile.

In diabetic/IFG subjects in the upper tertile of the diet score, was observed 15% lower glucose, 15% lower insulin and 27% lower HOMA-IR levels compared to those in the lower tertile.

After multiple regression analysis, was observed, only in normoglycemic subjects an inverse relationship between diet score and fasting plasma glucose, insulin and HOMA-IR levels.

Adherence to MedDiet was related to better fasting indices of glucose homoeostasis in normoglycemic people, but not in diabetic or pre-diabetic.

Panagiotakos et al., 2007
Cyprus
Cross-sectional
150 subjects, aged 65 to 100 years
People with clinical history of CVD and those living in institutions were excluded from the study.

To investigate the association of MedDiet on clinical status of elderly people, a diet score that assess the inherent characteristics of the MedDiet was developed (range 0-55). Mean diet score had no differences between men and women.

Adherence to MedDiet is associated with reduced odds of having T2D.
### Effects of the Mediterranean Diet on Type 2 Diabetes' Incidence and Treatment

55). Lifestyle habits were evaluated and clinical characteristics were measured. Adoption of the MedDiet was evaluated against the presence of hypertension, diabetes, hypercholesterolemia and obesity.

- The level of adherence to MedDiet was 64%.
- More than 9 out of 10 of the participants reported that they followed the reported dietary habits for at least 30–40 years of their life.
- MedDiet score was inversely correlated with BMI, total cholesterol, triglycerides, glucose, and systolic blood pressure levels.
- Taking into account age, sex, smoking habits and physical activity status, was observed that 10-unit increase in the diet score was associated with 17% lower odds of having one additional risk factor.
- Stratified the analysis by gender, the reduction in the odds was 21% in women and 14% in men.
- A 10-unit increase in the diet score was associated with a 6% lower odds of having hypertension, 9% lower odds of having hypercholesterolemia, 6% lower odds of having diabetes and 12% lower odds of being obese.

### Lindeberg et al., Sweden 2007

<table>
<thead>
<tr>
<th>Randomized controlled intervention trial (type 1)</th>
<th>29 male IHD patients with waist circumference &gt;94cm and increased blood glucose or known diabetes</th>
</tr>
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<tbody>
<tr>
<td>Included patients with an ongoing acute coronary syndrome, a history of myocardial infarction diagnosed by creatine kinase MB isoenzyme or troponin elevation, percutaneous coronary intervention or coronary artery bypass surgery or angiographically diagnosed coronary stenosis ≥ 30%,</td>
<td></td>
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<tr>
<td>To examine the effect of the Paleolithic diet model, compared to the Mediterranean-like diet on glucose tolerance and postchallenge insulin response in glucose-intolerant IHD patients</td>
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<tr>
<td>Participants were randomized to receive a Paleolithic diet, based on lean meat, fish, fruits, vegetables, root vegetables, eggs and nuts, or a Mediterranean-like diet based on whole grains, low-fat dairy products, vegetables, fruits, fish, oils and margarines. Outcome variables were changes in glucose intolerance and cardiovascular risk factors.</td>
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<tr>
<td>3 months</td>
<td>- There was a 26% decrease of AUC glucose 1–2 h in the Paleolithic group and a 7% decrease in the MedDiet group.</td>
</tr>
<tr>
<td>- The larger improvement in the Paleolithic group was independent of change in waist circumference.</td>
<td></td>
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<tr>
<td>- In the study population as a whole, a Paleolithic diet may improve glucose tolerance, independently of decreased waist circumference. Subjects who followed the MedDiet did not significantly improve their glucose tolerance despite decreases in weight and waist circumference.</td>
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</tbody>
</table>
Exclusion criteria were BMI < 20 kg/m², serum creatinine > 130 μmol/L, poor general condition, dementia, unwillingness/inability to prepare food at home, participation in another medical trial, chronic inflammatory bowel disease, type 1 diabetes and treatment with hypoglycaemic agents, warfarin or oral steroids. Other drugs were not restricted and treatment with statins and beta blockers was usually initiated and/or changed during the trial.

To assess the relationship between adherence to the MedDiet and the subsequent development of MetS, baseline assessment of participants consists of a self-administered questionnaire, gathering information on lifestyle factors and including a 136-item FFQ. Biennially mailed follow-up questionnaires were used to collect information about diet, lifestyle and medical conditions. MetS was defined according to the International Diabetes Federation criteria.

Baseline, there was no relationship between change in AUC glucose 0-120 and changes in weight or waist circumference.

Healthy diets based on wholegrain cereals and low-fat dairy products are only the second best choice in the prevention and treatment of T2D.
Effects of the Mediterranean Diet on Type 2 Diabetes’ Incidence and Treatment
83

- The average age was 59 years, and 13% of participants were women.
- Patients were on average overweight (mean BMI: 26.3 kg/m²) and 13% were obese.
- Greater intake of MedDiet was associated with older age, being female, slightly greater BMI, hypertension, previous acute myocardial infarction and former rather current smoking.
- Independent risk factors for new-onset diabetes or IFG included older age, hypertension, use of beta-blockers, lipid-lowering medications (protective) and diuretic use.
- Independent lifestyle risk factors included higher BMI, greater BMI gain during follow-up, current smoking, a lower MedDiet score and wine consumption of more than 1 l/day.

Michaelsen et al., 2006

German Randomized, controlled trial

101 patients (59.4±8.6 years, 23% female) with established and treated CAD

Excluded individuals with an ACS or CABG within the previous 3 months, diabetes mellitus type 1, manifest cardiac arrhythmias, heart failure, life-threatening comorbidity and BMI > 33 kg/m²

To investigate the effect of MedDiet on markers of inflammation and metabolic risk factors in patients with treated CAD

Participants were assigned to a MedDiet group with 1-year program of 100 h of education, or to a written advice-only group. Before and after intervention, serum hs-CRP, fibrinogen, fasting insulin, homocysteine, serum lipids and plasma fatty acids were measured

1 year

- The MedDiet group individuals, increased the intakes of fish, fruits/vegetables and moderately of canola/olive oil and increased plasma concentrations of long-chain n-3 polyunsaturated fatty acids.
- Median hs-CRP and mean fibrinogen, homocysteine, fasting insulin, triglycerides and serum cholesterol remained unchanged in both groups.

Adoption of a MedDiet by patients with medically treated CAD has no effect on markers of inflammation and metabolic risk factors.
Eligible participants were community-dwelling men, 55 to 80 years old and women, 60 to 80 years old, who fulfilled at least 1 of 2 criteria: T2D or 3 or more CHD risk factors (current smoking, hypertension, LDL cholesterol level ≥4.14 mmol/L, HDL cholesterol level ≤1.04 mmol/L). Exclusion criteria were history of CVD, any severe chronic illness, drug/alcohol addiction, history of allergy or intolerance to olive oil or nuts, or low predicted likelihood of changing dietary habits according to the stages-of-change model.

To compare the short term effects of 2 MedDiets versus those of a low-fat diet on intermediate markers of cardiovascular risk, participants were assigned to one of two MedDiets (with virgin oil or with mixed nuts) or to a low-fat diet. Those allocated to MedDiets received nutritional education. A 14-item questionnaire assessed the degree of adherence to the MedDiet. FFQ and a 47-item questionnaire about education, lifestyle, history of illness, and medication use were used. Anthropometric and blood pressure measurements were performed, and samples of fasting blood and spot urine were obtained.

Compared with the low-fat diet, the 2 MedDiets decreased systolic (-5.9 mm/Hg and -7.1 mm/Hg, respectively for MedDiet with olive oil and MedDiet with nuts) and diastolic blood pressure, blood glucose levels (-0.39 mmol/L and -0.30 mmol/L, respectively for MedDiet with olive oil and MedDiet with nuts), and cholesterol-HDL cholesterol ratio (-0.38 and -0.26, respectively for MedDiet with olive oil and MedDiet with nuts) and increased HDL cholesterol levels.

Fasting insulin levels and HOMA scores were also lower in participants without diabetes in the 2 MedDiet groups. Total cholesterol and triglyceride levels decreased only in the MedDiet with nuts. The MedDiet with olive oil reduced C-reactive protein levels by 0.54 mg/L compared with the low-fat diet.

To investigate the effects of a MedDiet or a low-fat diet on cardiovascular risk factors, participants met at last one of the following criteria: fasting plasma cholesterol concentration of 6.5-7.7 mmol/L, triglyceride concentration of 2.1-4.6 mmol/L, glucose concentration of 6.1-6.9 mmol/L, systolic and diastolic blood pressure between 140-

After the 3-month dietary intervention, changes in many risk factors were evaluated. Dietary questionnaires and plasma nutritional markers were used to test compliance.

The mean age of the subjects was 50.8±10.8 and 51.6±10.3 in the MedDiet group and the low-fat group, respectively.

Both diets significantly reduced CVD risk factors.
Effects of the Mediterranean Diet on Type 2 Diabetes' Incidence and Treatment

Panagiotakos et al., 2005
Greece
Cross-sectional

3042 subjects with no evidence of CVD or any other chronic disease

Participants with type 1 diabetes, history of CVD or any other atherosclerotic disease were excluded.

To evaluate the prevalence of T2D in a Greek adult population, in relation to physical activity and dietary habits

Diabetes was defined according to the established ADA criteria. Dietary habits were assessed through a validated FFQ and a diet score measured the adherence to the MedDiet. Weekly energy expenditure was assessed by considering frequency, duration and intensity of sports-related physical activity.

- BMI, total and triacylglycerol-rich lipoprotein (TRL) cholesterol, triacylglycerols, TRL triacylglycerols, apolipoproteins A-I and B, insulinemia, glycemia and the HOMA score were significantly lower after 3 months.
- There was a 9% reduction in CVD risk with the low-fat diet and a 15% reduction with the MedDiet.
- The projection prevalence of diabetes was 7.6% in men and 5.9% in women.
- Diabetic people were less likely to smoke, less physically active and less educated than the participants without diabetes.
- Diabetic people were less devoted to the MedDiet compared with participants without diabetes.
- The prevalence of diabetes in a person with no physical activity was 4.6% and in low physical active people was 4.2%. The relative risk reduction was 9.5%.
- Increasing age, smoking habits, family history of diabetes, elevated systolic blood pressure and triglycerides levels were significantly associated with the presence of diabetes.
- 24% of men and 30% of women were unaware of their condition.

- Light physical activity and greater adherence to the MedDiet was associated with significantly lower odds of having diabetes.

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- Increasing age, smoking habits, family history of diabetes, elevated systolic blood pressure and triglycerides levels were significantly associated with the presence of diabetes.
- 24% of men and 30% of women were unaware of their condition.

- Light physical activity and greater adherence to the MedDiet was associated with significantly lower odds of having diabetes.
Inclusion criteria were female sex, diagnosis of T2D for at least 6 months, postmenopausal, independent living, having a telephone, able to read English, not developmentally disabled and living within 30 miles of the intervention site. Exclusion criteria were being >75 years of age or planning to move from the area within the study’s time span.

To test the effectiveness of the Mediterranean Lifestyle Program (MLP) (Mediterranean low-saturated fat diet, stress management training, exercise, group support and smoking cessation) in reducing cardiovascular risk factors in postmenopausal women with T2D, participants were randomized to either usual care control or treatment (MLP) conditions. MLP participants took part in an initial 3-day retreat followed by 6 months of weekly meetings to learn and practice program components. Biological end points were changes in HbA1c, lipid profiles, BMI, blood pressure, plasma fatty acids, and flexibility. Impact on quality of life was assessed.

HbA1c decreased from 7.43 to 7.07 mg/dl for the MLP women, HbA1c remained at 7.4 mg/dl for the control subjects, this would translate into a 14% reduction in risk of diabetes complications. A drop of 0.37 in BMI observed in the MLP women and an increase of 0.20 in BMI for the control group. Quality of life improved significantly for the MLP women. Postmenopausal women with T2D can make comprehensive lifestyle changes that may lead to clinically significant improvements in glycemic control, some coronary heart disease risk factors and quality of life.
5 Discussion

The MeDiet has been widely reported to be a model of healthy eating for its contribution to a favourable health status, better biochemical profile and a better quality of life. In the present review, the role of the MeDiet in T2D prevention and treatment, as well as its potential protective mechanisms against the MetS and CVD, were briefly presented [28, 29]. According to epidemiological data, a greater adherence to the MeDiet, as assessed by various MeDiet indices, is inversely associated with T2DM risk in the general population, in individuals at high cardiovascular risk and in patients with established CVD. Interventional studies also demonstrate the beneficial role of the MeDiet in T2D management, with patients allocated to a MeDiet exhibiting greater improvements in glycemic control and CVD risk factors, compared with those following a control diet [12, 22, 25, 26].

Although this review provides useful information, all studied outcomes must be interpreted with caution because of some weaknesses. The wide variety of available MeDiet scores makes it difficult to compare the results of studies, in which different scores are used. This observation, along with the fact that diet varies significantly across populations, suggest that an analysis of this type cannot provide universally applicable results [67]. In addition, MeDiet indices may not precisely describe the overall MeDiet, since most available scores focus on selected aspects of the diet and involve some level of arbitrary decision in the type and number of components to be included as well as their scoring system [68]. Secondly, the availability of few controlled trials designed to evaluate the metabolic and cardiovascular outcomes of the MeDiet specifically in MeDiet, as well as the fact that most clinical studies focused on surrogate markers for early CVD risk assessment, signify major limitations of the present review. Moreover, some major randomized controlled trials, which showed that intensive lifestyle interventions can reduce the incidence of T2D in individuals at high risk for T2D in the general population, did not decrease the risk of CVD and CVD-associated mortality [69,70].

Although some relevant differences among the studies are present and further long-term intervention trials are crucial in evidencing the long-term efficacy in the T2D prevention and treatment, strategies aiming to promote adherence to MeDiet dietary pattern are of considerable public health interest [71,72].

6 Conclusion

In conclusion, this review seems to be clinically relevant in terms of public health, particularly for reducing the risk of premature death in the general population, and is strictly concordant with current guidelines and recommendations from all the major scientific associations that strongly encourage a Mediterranean-like dietary pattern for primary and secondary prevention of major chronic diseases [26]. Indisputably, the development and implementation of national policies for the prevention of T2D and its complications with optimum efficiency and minimum cost is the only way to reduce the personal and socio-economic burden of the disease and its complications.
References


Effects of the Mediterranean Diet on Type 2 Diabetes' Incidence and Treatment


[23] Jensen A., Sherman S. In patients at high CV risk, a Mediterranean diet plus olive oil reduced diabetes more than advising a low-fat diet, Ann Intern Med, 160 (12), (2014), JCI2


[38] Romaguera D., Guevara M., Norat J et al. Mediterranean Diet and Type 2 Diabetes Risk in the European Prospective Investigation Into Cancer and Nutrition (EPIC) Study. The InterAct project. *Diabetes Care.* (2011) **34**: 1913-1918


Effects of the Mediterranean Diet on Type 2 Diabetes' Incidence and Treatment


