A Review of the Effects of Mediterranean Diet on Prevention of Type 2 Diabetes amongst Overweight Patients

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Abstract. Objective: this review aims to analyze six recently published to compare the Mediterranean diet (MedDiet) with different control diets including American Diabetes Association diet, low-fat diet, low-carbohydrate diet on the treatment and management of type 2 diabetes (T2D) in overweight adults, to evaluate the limitations for improving randomized controlled trials design on this field. Methods: full text and published articles were searched via following databases: Medline on OvidSP, CINAHL, Web of Science Core Collection, and Google Scholar. The select interval of this review was controlled from November 2009 to January 2017. All headings, abstracts, contents and references were selected with following mutual terms: “Mediterranean”, “MedDiet”, “type 2 diabetes”, “dietary pattern”, “insulin resistance”, “insulin sensitivity”, “RCTs” and “intervention”. And then 114 studies were selected, but some of the unrelated articles (n=109) were filtered by setting excluding criteria via Endnote: non-English publications (n=2); the intervention period was less than three months (n=0); duplicate publications (n=13); non-RCTs studies (n=94). Finally, only six eligible studies were included. Results: encouraging the use of extra virgin olive oil to reduce the intake of monounsaturated fatty acids in Mediterranean diets and increase exercise has a positive effect on the prevention of type 2 diabetes. In addition, the use of a low-carbohydrate Mediterranean diet can also prevent T2D. Conclusions: overweight and obese patients are more encouraged to adopt the Mediterranean diet to control their T2D.

1. Introduction
Type 2 diabetes (T2D) is a widespread chronic disease. There is an increasing trend in T2D amongst adults with overweight and obese patients having more risk of getting it. By 2040 the incidence will rise to 642 million worldwide¹. In order to control this trend, the American Diabetes Association (ADA) (2016) has suggested an appropriate approach: energy intake restriction combined with lifestyle modification helps overweight or obese adults with T2D². Recently, the low-fat, low-
carbohydrate (CHO) calorie-restricted, or Mediterranean Diet (MedDiet) were recommended by ADA (2016) for weight loss in overweight patients who had or are at high risks of T2D. Moreover, there are many systematic reviews encouraging a MedDiet pattern, which may improve glycaemic control and cardiovascular risk factors in the prevention of cardiovascular disease in adults T2D\textsuperscript{345}. Furthermore, epidemiological evidence has shown a positive influence on obesity and diabetes\textsuperscript{67}. MedDiet was first defined in the 1960s\textsuperscript{8}, it contained plenty of vegetables, fruit, nuts and legumes, intake of olive oil, substantial intake of fish, a modest consumption of dairy products and a low intake of simple sugars and red meat\textsuperscript{9}. Many systematic reviews encourage a MedDiet pattern for the prevention and management of risk of the main cardiovascular diseases, especially T2D\textsuperscript{1011}. While a study claimed that adoption of the MedDiet together with nutritional advice on health eating could not meaningfully control the fasting glucose, even the figures showed beneficial improvements in those patients at risk of T2D\textsuperscript{12}. Moreover, MedDiet was one of the recommended diets via Meta-analyses of different dietary approaches such as Low-carbohydrate, low glycaemic index high-protein diets like Vegetarian and vegan diets\textsuperscript{1113}. An adjusted MedDiet, using monounsaturated fatty acids to replace the polyunsaturated fatty acids, helped a decline of 7% in the total death ratio in ageing Europeans\textsuperscript{19}. To select an appropriate and effective intervention, epidemiologists have recommended that the ideal was to make use of the outcomes of randomised controlled trials (RCTs) of treatment and prevention\textsuperscript{15}. However, the suitable nutritional intervention for overweight participants with T2D is unclear so far\textsuperscript{16}. Additionally, few reviews have evaluated the effects of different healthy diets on T2D\textsuperscript{1117}. Hence, this systematic review analysed six RCTs studies to compare the modified MedDiet with different control diets on the treatment and management of T2D in overweight adults, to evaluate the limitations for improving RCTs design on this field.

2. Methods
Full text and published articles were searched via following databases: Medline on OvidSP, CINAHL, Web of Science Core Collection, and Google Scholar. The select interval of this review was controlled from November 2009 to December 2016 due to the recent review\textsuperscript{5}, which previously analysed all and only RCTs regarding the MedDiet prevention on T2D before November 2009. All headings, abstracts, contents and references were selected with following mutual terms: “Mediterranean”, “MedDiet”, “type 2 diabetes”, “dietary pattern”, “insulin resistance”, “insulin sensitivity”, “RCTs” and “intervention”. And then 114 studies were selected, but some of the unrelated articles (n=109) were filtered by setting excluding criteria via Endnote: non-English publications (n=2); the intervention period was less than three months (n=0); duplicate publications (n=13); non-RCTs studies (n=94). Finally, only six eligible studies were included.

3. A critical review of six RCTs studies
Six RCTs have evaluated the effects of different modified MedDiets, as compared with ADA diet, low-fat diet, low-CHO diet, on indices of glycaemic control and weight change in subjects with T2D. To be specific, the modified MedDiets main focuses on low-carbohydrate MedDiet and MedDiet using virgin olive oil. Four of six studies using haemoglobin (HbA1c) as the primary outcome, HbA1c of 48mmol/mol (6.5%) was recommended as the criteria for diagnosing diabetes\textsuperscript{18}. Additionally, all studies also used the weight change as secondary outcome except\textsuperscript{19}. Both outcomes were analysed by this review (as shown in table 1).
Table 1. Summary of the six studies critically reviewed regarding the different dietary interventions on T2D

| Author/Duration | Sample Characteristics | Measurements | Intervention & Control Groups | Results (95% CI, P-value) | Limitations |
|-----------------|------------------------|--------------|--------------------------------|---------------------------|-------------|
| Esposito et al., (2009) 4 years | Antihyperglycemic drug therapy patients Newly diagnosed T2D Age 30-50 years Overweight (BMI≥25kg/m2) HbA1c≤11% | -Self-monitor diet (using food models) and PA -Provided dietary education that emphasized healthy eating and being physically -Taught to prepare their own meals at home. | -Low-CHO MedDiet (<50% of daily calories from CHO) -Low-fat Diet (<30% of daily calories from fat) | -MedDiet led to more favourable changes in glycaemic control and weight change: HbA1c HR: 0.63 [CI, 0.51 to 0.86] -Weight HR: 0.70 [CI 0.59 to 0.90], (P=0.001) -Delayed the need for diabetic drug therapy: -26.0% [CI, -31.1 to -20.1] | -Unblinded for drug therapy patients -Self-reported dietary intake |
| Elhayany et al., (2010) 12 months | Age 30-65 years community-based T2D diagnosed within 1-10 years Overweight (BMI: 27-34kg/m2) Last HbA1c: 7-10% No diabetic medication change before 3 months | -Patients were followed up by the same dietitian every 2weeks for 1 year. -Advised to engage in 30-45 min of aerobic activity at least 3 days a week. -FFQ, 24h food recall and PA questionnaire | -Low-CHO MedDiet (35% LGI-CHO, 45% fats rich MUFAs, 15-20% proteins). -MedDiet (50-55% LGI CHO, 30% fats rich MUFAs, 15-20% proteins) -ADA Diet (50-55% CHO, 30% fats and 20% proteins) | -Low-CHO MedDiet should recommend, it was helpful for glycaemic control & CVD risk -Only-Low-CHO MedDiet improved HDL level (12%,0.1 mmol/l ± 0.02), P<0.002 -Low-CHO MedDiet was superior to glycaemic control -HbA1c Low-CHO MedDiet (2-0%) was greater than ADA (-1.6%), p < 0.022. -No difference in weight loss 10.1, 7.4, and 7.7 kg, respectively (P>0.05). | -Short follow-up times -High dropout rates (31%) -Self-reported dietary intake |
| Salas-Salvador et al., (2010) 4 years | Age 55-80 years Community-dwelling Nondiabetic &CVD CVD risk factors ≥3 Overweight (BMI≥25kg/m2) | -A behavioural intervention for promoting the MedDiet -Dietitians gave personalized dietary advice -Energy restriction and PA was not promoted -14-item questionnaire of adherence to the MedDiet and 137-item validated FFQ -Leisure-time PA questionnaire | -MedDiet+VOO (virgin olive oil, 1 litter /weeks) -MedDiet+ Nuts (nuts 30 g/day) -Low-fat Diet (CG) Recommended to reduce all types of fat (animal and plants) | -MedDiets without calorie restriction might effective in the prevention of diabetes -No difference on weight loss: (P=0.7) -0.2±4.6kg, -0.6±4.2kg and -0.6±4.3kg Primary outcome: diabetes incidence - MedDiet+VOO10.1% [ CI, 5.1–15.1], - MedDiet+ Nuts11.0% [CI, 5.9 –16.1], - Low-fat Diet (CG)17.9% [CI, 11.4 – 24.4] -Adjusted HR of diabetes (vs. CG) - MedDiet+VOO 0.49 [CI, 0.25–0.97] - MedDiet+ Nuts 0.48 [CI, 0.24–0.96] | -Unblinded -Less generalization -Wide CIs |
| Babio et al., (2014) | 1919 | Age 55-80 years | Nondiabetic | No prior CVD | CVD risk factors ≥3 | Overweight (BMI≥29.8kg/m²) | 4.8 years |
|---------------------|------|----------------|------------|--------------|---------------------|-----------------------------|-----------|
|                     |      |                |            |              | -14-item questionnaire to enhance the intervention -9-item dietary screener to assess compliance with CG -Recommended reducing all types of fat -Not calorie restriction -Not promoted for PA, filled leisure-time PA questionnaire. | -MedDiet+VOO (1 litter/weeks) - MedDiet+ Nuts (Mixed nuts:30 g/d) - Low-fat Diet (CG) Recommended to reduce all types of fat | -Both interventions had not associated with a reduced incidence of metabolic syndrome: - MedDiet+VOO HR: 1.35 [CI, 1.15–1.58], (P < 0.001) - MedDiet+ Nuts HR: 1.28 [CI, 1.08–1.51], (P < 0.001) -Both interventions might reduce central obesity and hyperglycaemia. | -Less generalization -Benefit bias toward in CG |
| Ceriello et al., (2014) | 24 | T2 Diabetic patients | Overweight (BMI≥29.2kg/m²) | HbA1c ≥8% | 3 months | -Kept a 3D food diary, filled a basic questionnaire -Weekly monitored via telephone by dietitian. -Positive recommendations according to MedDiet -Negative advices about high calorie food intake | -MedDiet using olive oil (MUFAs, 50mL, extra virgin olive oil/day) -Low-fat Diet(CG) Suggested to reduce all types of fat | -MedDiet increased plasma antioxidant capacity &improved basal endothelial function nitro tyrosine, 0.35 ± 0.02, (P >0.05) 8-iso-PGF2α, 41.3 ± 2.2, (P < 0.05) IL-6 170.20 ± 8.3, (P < 0.05) ICAM-1 110.5 ± 10.1, (P <0.05) | -Small sample size -Short follow-up -Less generalization |
| Esposito et al., (2014) | 215 | Mean age 52.2 years | T2 Diabetic patients | Overweight (BMI mean 29.6kg/m²) | HbA1c mean 7.7% | 4 years | -Given detailed dietary advice by nutritionists -Instructed recording the intake via food models -Advised to increase the level of PA: 175 mins/weeks of moderate-intensity PA -Completed a 3-day food record &international PA Questionnaire | -Low-CHO MedDiet ≤50% of calories from CHO and ≤30% calories from fat, included 30–50 g of olive oil) -Low-fat Diet(CG) ≤30% of calories from fat & ≤10% of calories from saturated fat. | -Low-CHO MedDiet resulted in a greater reduction of HbA1c levels -HbA1c unadjusted HR 0.64 [CI, 0.50–0.82]; (P<0.001). -Weight change HR 0.70 [CI, 0.59-0.90], (P<0.05) -Delayed the need for medication: 44% and 70% respectively. HR:0.63 [CI, 0.51–0.86], P <0.001 | -Unblinded -Unclear definition of diabetic remission -Self-reported diaries |

Abbreviations: T2D= Type 2 Diabetes; PA=Physical Activity; FFQ= Food frequency questionnaire; LGI=Low glycaemic index; HDL=High-density lipoprotein; CHO= Carbohydrate; BMI=Body mass index; HbA1c= Haemoglobin A1c; MUFAs =Monounsaturated fats; HR=Hazard ratio; Low-CHO MedDiet =Low carbohydrate Mediterranean Diet; MedDiet=Traditional Mediterranean Diet; vs.=Versus; ADA Diet=American Diabetic Association Diet; CVD=Cardiovascular Disease; VOO=Virgin Olive Oil; CG=Control Group.

3.1. Low-Carbohydrate MedDiet and T2D
Three studies demonstrated that Low-CHO MedDiet caused more favourable changes in glycaemic control and weight loss compared with low-fat MedDiet, ADA Diet and MedDiet (as illustrated in table 1). The content of CHO in those three studies was different, less than 50% calories from CHO and around 35% calories from low glycaemic index CHO. Although the percentage of
fat of calories was not illustrated, MUFAs should be supposed. However, the percentage of protein was not mentioned in those three studies.

One the one hand, the possible interpretation of the positive effect on weight loss adopting Low-CHO was that all the participants were overweight; the restriction of CHO had a positive impact on weight control. All studies included overweight participants whose body mass index (BMI) was more than 25.0 kg/m², the BMI between 25.0 and 29.9 kg/m² is categorised as overweight. Some previous studies also provided it, the incidence of diabetes increases with growing weight levels, advising that weight loss was a significant intervention.

On the other hand, contrasted with a low-fat diet, a Low-CHO MedDiet led to more favourable alterations in glycaemic control (greater reduction of HbA1c levels) and the risk feature of coronary and delayed the need for diabetic medication in overweight participants who were newly diagnosed with diabetes in recent two years. Additionally, Esposito et al., (2014) reported that the Low-CHO MedDiet led to a superior decrease of the higher ratio of diabetes remission compared with the control group. Moreover, Elhayany et al. (2010) designed a 12 months nutritional interference relying on a community-based setting which was effective in promoting most adaptable CVD risk factors in different dietary sets. However, only the Low-CHO MedDiet enhanced the level of high-density lipoprotein (12%, 0.1mmol/l ± 0.02, P < 0.002) and was greater in improving glycaemic control in both the ADA diets (-1.6%) and traditional MedDiet (- 2.0%). It seemed that the Low-CHO MedDiet led to some positive changes in glycaemic control and weight loss.

3.2. MedDiet using virgin olive oil and T2D
MedDiet using virgin olive oil might reduce the hyperglycaemia and prevent T2D obesity in people at high risk of CVD, but they had different opinions on whether MedDiet using olive oil was associated with metabolic syndrome. A specific feature of MedDiet was the plentiful utilisation of virgin olive oil for frying, cooking food, or dressing vegetables. It could cause a high rate of MUFAs to saturated fatty acids. Three of six studies compared MedDiet using virgin olive oil with control diets, all of them engaged virgin olive oil intake, while the percentage of main food components (carbohydrate, protein, and fat) were discussed.

Babio et al., (2014) reported MedDiet with olive oil or nuts had no relation to a reduced frequency of metabolic syndrome (as shown in table 1). However, Salas-Salvado et al., (2010) considered that both MedDiet with olive oil (Hazard Ratio 0.49, 95%CI: 0.25 – 0.97) and MedDiet with nuts (Hazard Ratio 0.46, 95% CI, 0.24–0.96) had a lower risk of diabetes incidence because hazard ratio less than one (as shown in figure 1). Other clinical RCTs also showed that the MedDiet using the olive oil can improve the effects of the MedDiet on these parameters (as shown in the table 1) in metabolic syndromes such as endothelial dysfunction, inflammation and oxidative stress in T2D. Previous studies suggested an inverse relationship between adherence to the MedDiet and the prevalence of metabolic syndrome. However, these studies could not conclude whether the parameters could be attributed to the diets themselves. Further experimental researches are needed to verify the association of the MedDiet on the diabetic metabolic syndrome and the underlying mechanisms.

Salas-Salvado et al., (2010) and Babio et al., (2014) mentioned that MedDiets without calorie control seemed effective in reducing the diabetes incidence in participants with a high risk of CVD. And then, the diabetes incidence was 10.1% (95%, CI 5.1–15.1) and 1.35 (95% CI, 1.15–1.58) respectively in the MedDiet using olive oil. Although Ceriello et al., (2014) provided negative advice about high-calorie food intake, it still suggested that the MedDiet, using olive oil, may have a favourable effect on the management of T2D. Virgin olive oil intake was encouraged in those three articles above, it could be the function of MUFAs. Further studies are needed to evaluate the effects of hyperglycaemia change using different types of olive oil or different percentages of MUFAs.
Figure 1. Hazard ratios of diabetes by intervention groups compared with control group in Salas-Salvado et al., (2010) study.

HR <1 means that the intervention group had higher risk of diabetes; HR >1 means that the intervention group had lower risk of diabetes; HR =1 means no difference of diabetes incidence between the two groups.

Intervention groups: MedDiet with VOO and MedDiet with nuts; Control group: low-fat diet.

Abbreviations: BMI=Body mass index; VOO=Virgin Olive Oil; HR=Hazard ratio; vs.=Versus; CI= Confidence interval.

3.3. MedDiet using virgin olive oil and T2D

Five of six studies selected low-fat diet (less than 30% daily calories from fat) as a control group, only Elhayany et al., (2010) had adopted the traditional MedDiet (50–55% low glycaemic index CHO, 30% fats rich MUFA's, 15–20% proteins) and the ADA Diet (50–55% CHO, 30% fats and 20% proteins) compared with MedDiet using olive oil. The amounts of main food components (carbohydrate, protein, and fat) of Low-fat diet were unclear. Although the low-fat diet did not have a more favourable impact on the prevention of T2D compared with modified MedDiett. However, it might have a slight association with T2D and weight change in overweight patients. At the end of the intervention, patients continued reducing weight by 5% to a similar degree in all diets including low-fat diet and the change in diabetes incidence was similar with intervention groups around 17.9%. Esposito et al., (2014) stated that both the low-fat diet and intervention group delayed the need of diabetic medication by 70% and 40% respectively. A recent previous review published that low-fat diet may be associated with the prevention of diabetes. It was not clear whether the low-fat diet had a slight association with T2D based on a few included studies, further studies are needed to indicate this relationship.

4. Conclusion

Based on the evidence above, adopting low-CHO MedDiet and MedDiet using virgin olive oil and engaging in PA had a positive impact on the prevention of overweight patients within T2D. More specifically, the design of a modified MeditDiet could be that restricting CHO intake and engaging in a moderate amount of MUFA's intake, while the proportion of CHO, protein and fat need more RCTs to explore. To develop an approach modified MedDiet pattern for prevention of T2D, well-designed long-term (more than three months) RCTs are needed. Utilising accurate dietetic assessments and
recruiting varied samples of patients are desired, due to the methodological, realistic and ethical problems that obstruct the capacity of RCT’s to be led. In addition, the impacts of PA on dietary intervention should be clear by designing the control group to reduce it. Clinical studies also are needed to confirm the underlying mechanisms of the prevention of MedDiet on T2D.

5. Discussion

Changes in PA and weight were measured because of their recognised association with diabetes, but they were not intervention aims\textsuperscript{11}. PA was a main independent variable in RCTs studies that might affect the dietary intervention. Therefore, this review also analyses the intervention of PA to evaluate the dietary influence on outcomes. It was noticed that engaging in increasing the level of PA had favourable impacts on weight loss on the majority of studies, which might help the dietary intervention on glycaemic control and weight loss. For example, the patients in Elhayany et al., (2010) study\textsuperscript{16} were advised to engage in 30 to 45 minutes of aerobic activity at the minimum of three days each week, all groups had a weight loss range from 7.4 to 10.1kg.

Nevertheless, Babio et al., (2014)\textsuperscript{26} provided that the modifications in body weight and PA were slight. In fact, Shephard, (2012)\textsuperscript{29} designed an RCT to prove that PA advice was related with lower HbA1c in patients with T2D, but only when combined with dietary guidance. Another systematic review also explored that the moderate intensive PA could reduce the risks of T2D\textsuperscript{30}. Only Ceriello et al., (2014)\textsuperscript{19} had not been involved with weight change as the main outcome because it uses bio-marks to investigate the glycemic change. All studies indicated that there was no difference between groups, excepted Esposito et al., (2009)\textsuperscript{20} which provided that the MedDiet led to more favourable changes in weight loss compared with the low-fat diet: weight hazard ratio = 0.70, (95%CI, 0.59-0.90; P=0.001).

It seemed that reduced the side effects from an additional measure variable (weight change) when other markers of CVD measure risks. Reducing these extra effects between groups and keeping a weight constant in all subject groups could be beneficial to help clarify this concern for future study. In the real world, increasing the time diabetic patients spend being physically active may assist good dietary intervention to reduce the risks of CVD.

5.1. Study limitations

The detailed study limitations were emphasised in table one, but some similar limitations had to be mentioned for further RCTs design. The primary limitation was due to using the Food frequency questionnaire (FFQ) as an assessment tool to measure dietary intake in half of those RCTs studies. However, the FFQ has limited choice items, which could lead to a low accuracy (recall bias) (Shim, Oh, and Kim, 2014). The range of food items was limited from 9 items to 137 items, which means studies had altered sensitivities for MedDiet foods. Studies also adopted a 3D food diary \textsuperscript{19} and 24 hours recall\textsuperscript{16} to reduce recall bias. Moreover, half of them\textsuperscript{20,21} had adopted a non-blinding design, according to Sanson-Fisher et al., (2007), if one of the participants, the assessor and the investigator is conscious of the intervention applied, it could not be admitted that systematic bias has been accepted. Besides, the majority of studies had a specific small sample size ranging from 24\textsuperscript{19} to 259\textsuperscript{16}, diverse demographic and large samples are needed for improving generation, which also restricts the exterior validity of many types of research. Finally, all the assessments of dairy and PA relied on self-reporting, which potentially increased the possibility of social desirability and recall bias (Schoeller, 1995).

5.2. Review limitations

From the purpose of diabetic prevention, the included articles should be divided into two situations due to the recruitment participants whether they have T2d or not. However, only Salas-Salvado et al., (2010)\textsuperscript{22} and Babio et al., (2014)\textsuperscript{26} recruited non-diabetic patients in this review, they used the diabetic Incident as the primary outcome. The rest of the article included diabetic patients to analyse the change in glycaemic control, using HbA1c as the primary outcome. It could reduce the effects of diabetic medicine if it only recruited non-diabetic participants. Besides, those results were only achieved in the setting of an RCT which is challenging from the physical life of T2D patients, where it
was frequently challenging to obtain a substantial life adjustment (Sanson-Fisher et al., 2007). Of course, all six RCTs studies wanted to enhance the practical intervention when all participants in included studies were conducted by nutritionists or dieticians. For example, participants were taught that prepared their own healthy meals at home.

The independent effect of weight change was another confounder in this review. It is challenging to separate the results of weight change from dietary intervention of the markers of CVD risk. Therefore, these positive results from all included studies might incorrectly recognise by dietary intervention only, but those benefits could also from the weight loss’s contribution on overweight population. This probability could be of specific relevance when the result of low-CHO intake was inferred11. Further studies that target to confirm an equivalent caloric intake or retain weight constant in all subject groups, could be beneficial to help clarify this concern. Finally, uncompleted research terms might cause reporting bias if some relevant terms were ignored. Reporting bias may also have been obvious due to articles only published after the year 2009 and accessible in English, the limited period (2009-2017) might impact the numbers of included articles.

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