

# The Mediterranean diet in the treatment of type 2 diabetes and its complications

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**Abstract.** The incidence of type 2 diabetes mellitus (T2DM) has gone upward sharply for the past few years. Therefore, the efficient way to combat it has set off a new wave of research. Compared with traditional medication, dietary interventions can also control the development of T2DM with fewer side effects or prevent the onset. Among these studies with different methods and views, the Mediterranean diet (Med diet) can be crucial to prevent and treat T2DM in lifestyle. On the basis of the summary and analysis of relevant literature, this paper has introduced the risk factors and pathogenesis of T2DM and the ingredients and function of the Med diet, followed by the research status of this dietary pattern for the aspects such as hormone and inflammation regulation in treating T2DM. At the end of this paper, the treatment of T2DM aims to focus on nutritional interventions based on the Mediterranean diet in the future, in order to provide a reasonable dietary pattern for T2DM patients as soon as possible.

**Keywords:** Mediterranean diet, type 2 diabetes, inflammation.

## 1. Introduction

Diabetes is a group of metabolic diseases characterized by chronic hyperglycemia due to a lack of insulin secretion and utilization. Long-term hyperglycemia could injure multiple systems leading to a series of complications, such as acute metabolic disorders, infectious diseases and numerous chronic complications, which threaten the health and lives of humans seriously. At present, with the improvement of people's living standards, the prevalence rate of diabetes mellitus rises dramatically. As stated by the International Diabetes Federation (IDF), the total diabetics globally is predicted to reach nearly 650 million by 2030 and 780 million by 2045, which is a significant increase of 20% approximately [1]. T2DM accounts for about 80% of the cases [2]. It follows that diabetes, especially T2DM become a universal public health problem.

Med diet was first discovered in Greece and Italy in 1960. Med diet consists mainly of plant base food such as fruits, vegetables and olive oil, a moderate number of nuts and a small amount of animal-based food like fish and red meat and wine. According to the researches, the Med diet will lead to a positive effect against cancer, cardiovascular (CV) disease, inflammation and diabetes [3]. The Med diet contains many foods rich in unsaturated fatty acids, vitamins, and flavonoids. Those substances will contribute to the hormone regulation, inflammation regulation, and cardiovascular regulation of

the patients with T2DM. What is more, the Med diet may also have a preventive effect on the complications of type 2 diabetes.

Nowadays, pharmacotherapy should be the first choice for diabetes. However, it has some limitations and potential side effects. These not only reduce the life quality of the patients, but also attach a considerable financial burden to their families and society. Diabetes is responsible for \$966 billion in heavy healthcare costs, a 316% rise during a span of the last 15 years [1]. Hence, more and more scholars advocate using a relatively lifelike and easily implemented medical nutrition therapy (MNT) that focus on dietary interventions [2]. The Med diet is low in calories and high in dietary fiber [4]. It can improve the sensitivity of insulin, which facilitates blood sugar regulation as an appropriate diet for the treatment of diabetes [5].

There is a paucity of relevant literature and research, and the treatment of T2DM with the Mediterranean diet is not systematic. This paper explores the mechanisms of the Mediterranean diet in the therapy of T2DM by collecting, identifying and organizing the existing literature, with a view to the perfection of the theoretical system of medical nutrition therapy and the promotion of its development.

## **2. Risk factors of T2DM**

T2DM is the most prevalent type of diabetes in patients and one of the most prevalent diseases today and the number of patients is increasing. The number of type 2 diabetic patients may increase to 439 million in 2030 [6]. There are numerous reasons that will lead to T2DM. For instance, obesity, diet, and the interaction between environment and genetics [6]. Obesity is one of the most significant factors of T2DM. According to WHO, obesity is the main reason why nearly 90% of people with diabetes patients develop T2DM. An unhealthy lifestyle will lead to obesity, such as the lack of physical exercise, and alcoholism, which will cause an increase of weight and lead to obesity [6]. The storage of fat may cause obesity. The increasing number of Visceral Adipose Tissue (VAT) will enhance the risk of T2DM. A diet high in oil, sugar and calories is also an important factor in causing T2DM. Consuming saturated fats is linked to a higher risk of developing diabetes [7]. In addition, high sugar diet will lead to a rise of blood glucose. Maintaining a high-sugar diet for a long time is likely to increase the prevalence of hyperglycemia and lead to T2DM. Under normal conditions, blood glucose homeostasis is maintained by a combination of insulin and glucagon. When impaired insulin secretion and insulin resistance take place, the balance may be broken. Because of insulin resistance,  $\beta$  cells cannot secrete enough insulin to maintain blood glucose homeostasis, it will promote the risk of T2DM [8]. The interaction between Genetic factors and environmental factors is also an issue which needs to be considered. In some twins, dizygotic twins have a lower heritability or risk of disease than monozygotic twins [6]. What is more, 140 susceptibility factors associated with type 2 diabetes have been identified on chromosomes, such as PPARG, KCNJ11, TCF7L2 and so on [9]. However, it is worth noting that some susceptibility factors are only present in specific human races. For instance, a susceptibility factor (IL-1082A/G) only exists in Asian people but not in European and African. The probable reason may be due to the environment and Genetic background [6].

## **3. The ingredients and function of the Mediterranean diet**

The ability of the Med diet to decline the danger of cardiovascular disease, cancer, and diabetes had been proved in a range of previous researches [8]. The Mediterranean diet is based on the vegetable and fruit. The consumption of red meat should be controlled in low content. It mainly contains a plentiful provide of minimally processed whole grain bread, a wealth of vegetables, some seed, fresh vegetable, nut and olive oil [10]. Bread, vegetable and fruit are the main source of carbohydrate, and nut and olive oil which contain sufficient unsaturated fatty acids are the primary sources of high-quality fat. The energy of the Med diet is approximately 9300 KJ, and the energy of total fat accounted for two-fifth of total energy [8].

The Mediterranean diet can slow down aging and maintains physical and organ health. The main functions of the Med diet are to control blood lipid content and maintain a low level; Prevent the

appearance of oxidative stress, inflammation and platelet aggregation; Alter cancer-causing hormones and growth factors to prevent the creation and spread of cancer; Action on amino acids and intestinal flora-mediated affects the metabolism [11]. In a Meta-analyze comparing the effects of different dietary patterns on blood glucose regulation in T2DM patients, The Mediterranean diet has the most effective ability to regulate blood glucose [12]. Therefore, maintaining the Med diet lifestyle has a positive effect on preventing T2DM, hyperglycemia, obesity, CV diseases and cancer. The next section will focus on the influence of Med Diet on T2DM.

#### **4. The treatment of T2DM by the Mediterranean diet**

The risk factors of T2DM are various. For instance, Obesity, Hyperglycemia, Inflammation and so on. An unhealthy diet and life habits will cause a negative effect to T2DM. Such as high sugar and high-oil diet. However, many researches have demonstrated the positive effects of the Med diet on the prevention and treatment of T2DM. Based on a meta-analyze of the relationship between the Med Diet and T2DM, the application of the Med Diet in patients with T2DM can help with blood glucose regulation, weight regulation, cardiovascular regulation, and inflammation regulation [13]. The prevention of inflammation, the ability of anti-oxidant, the balance of glucose, and the regulation of intestinal flora will be promoted by the maintenance of Med diet. Therefore, The Med diet plays a crucial part in treating and preventing T2DM. The next paragraphs will discuss the mechanism of the Med diet to prevent and treat T2DM in some specific points.

##### *4.1. Hormone regulation by the Mediterranean diet*

Patients with T2DM are not able to regulate their own blood sugar balance. The main reasons are insulin secretion and insulin resistance [8]. The body cannot secrete enough insulin to regulate the increase of glucose, which will cause the development of T2DM. In clinical practice, doctors mainly used a number of drugs to treat type 2 diabetic patients [14]. Although the treatment result of these drugs is significant, they will cause some side effects and cannot improve T2DM from a lifestyle perspective. T2DM can be alleviated by changing the lifestyle. According to the study, patients who received GLP for six weeks had better insulin sensitivity and less insulin resistance. The enhancement of insulin secretion and the expression of insulin genes are made easier by GLP-1. According to the study, patients with T2DM who received GLP for six weeks had better insulin sensitivity and less insulin resistance [15]. Med diet can promote the secretion of GLP-1. The secretion of GLP-1 will increase because the poly-unsaturated fatty acid in extra-virgin olive oil will stimulate G-protein-coupled [13]. GLP not only improves blood glucose regulation but also does not cause hypoglycemia [16]. In addition, GLP-1 can lead to satiety, which will cause a decrease in the intake of food and control food consumption [13].

##### *4.2. Inflammation regulation by the Mediterranean diet*

For the sake of the anti-inflammatory and antioxidant features of the Med diet, it has a positive impact on the treatment of T2DM. One of the pathophysiologies of T2DM's causes is chronic low-grade inflammation and oxidative stress. Inflammation and oxidative stress have a positive relationship, and they will promote each other [17]. The Antioxidants and anti-inflammatory substances such as Ascorbic acid and b-Carotene in type 2 diabetic patients are lower than in normal people [13]. If inflammation is not suppressed and prevented, the condition of type 2 diabetic patients may deteriorate. Med diet is mainly based on vegetables, fruit, and grain. The Med diets contain a lot of anti-oxidant nutrients including Vitamin C, Vitamin A, flavonoids, etc. [10]. The specific anti-inflammatory effects of specific food in the Med diet are not fully understood. However, the complementary impact of nutrients from multiple foods can have a positive impact on anti-inflammation [10].

In recent years, the researches about unsaturated fatty acid in the Med diet are the most widely one and follow by flavonoids. For instance, Unsaturated fatty acids can reduce the probability of inflammatory responses in adipose tissue and decrease insulin sensitivity [18]. Therefore, maintaining a long-term Med diet will reduce the production of pro-inflammatory and chemokines in fat. What's

more, Polyunsaturated fatty acid (PUFA) has a negative relation with inflammation and oxidant stress. Unsaturated fatty acids can reduce the probability of inflammatory responses in adipose tissue. PUFA can regulate the antioxidant signaling pathway, and break the relation between inflammation and oxidant stress [17]. Omega-3 PUFA and Omega-6 PUFA have a positive relationship with human health. Those PUFA are widely present in plants and vegetables, such as plant oils like olive oils, seeds, and nut, which mean that PUFA is widely present in Med diet. Hence, the Med diet pattern is beneficial to the treatment of T2DM [17].

In Med diet, the flavonoids also play a key role in anti-inflammatory. Flavonoids are negatively correlated with oxidative stress, and inflammation. However, current research on this is relatively limited. The flavonoids known to exert anti-inflammatory effects in Mediterranean foods are myricetin and quercetin. These substances are widely present in vegetables and fruit. Quercetin reduces the oxygen consumption of adenosine diphosphate in mitochondria by activating the relevant enzymatic pathways. In addition, under conditions of oxidative stress, quercetin allows better glucose uptake by skeletal muscle cells through upregulation of the glucose transporter GLUT-4 [10]. Hu et al. used meta-analysis to make a summary of the anti-inflammatory mechanism of quercetin, and Hu et al. found different dosages of quercetin affect different pathways and all of them will eventually have a therapeutic effect on T2DM [19]. Myricetin was first extracted from the bark of the prune tree. It was later proved to be widely present in vegetables and berries. Myricetin has similar effects to quercetin, such as hypoglycemic effects and anti-inflammatory effects. Myricetin, glutathione peroxidase and xanthine oxidase activities in kidney tissues are positively correlated, it also improved lipid and glucose metabolism. Chen et al. who used controlled analysis, demonstrated that dihydromyricetin inhibited the activity and expression of T cell protein tyrosine phosphatase [20]. According to Chen et al, dihydromyricetin will decrease the fasting blood glucose and fasting insulin in rats with T2DM. However, the insulin sensitivity index is increased, which proves that myricetin could improve insulin resistance. Myricetin, as a natural compound with hypolipidemic and hypoglycemic functions and few side effects, may provide new ideas for the future treatment of T2DM [20].

#### 4.3. Cardiovascular regulation of Mediterranean diet

A range of cardiometabolic risk factors such as body weight, lipoprotein concentration and function, blood pressure, inflammation, and endothelial health are all influenced by dietary patterns [21]. The main food components of the Med diet include plenty of fresh vegetables and fruits, olive oil, moderate amounts of low-fat white meat such as seafood and poultry, small amounts of red or processed meats and red wine, using low-sodium herbal spices like garlic as a salt substitute.

A meta-analysis of 50 studies and 535,000 individuals on T2DM showed that the Med diet reduced waist circumference by approximately 0.5 cm, triglycerides by approximately 6.2 mg/dL, and heart systolic and diastolic blood pressure by roughly 2.35 and 1.60 mmHg [21]. Another meta-analysis showed that the Mediterranean diet can also increase weight loss by about 2 kg and lower total cholesterol levels from 3.5 mg/dL [21]. This reduces the risk of cardiovascular disease by approximately one-third. Polyphenols are beneficial in terms of reducing insulin resistance and controlling blood glucose [22]. Mediterranean diet coincides with a high consumption of vegetables and fruits, so these positive results should be related to the Med dietary characteristics.

A prospective randomized controlled trial called CORDIOPREV by Elena M. Yubero-Serrano et al. in 1002 patients with coronary atherosclerosis heart disease showed that every patient following a Mediterranean diet had higher flow-mediated dilation (FMD) and endothelial progenitor cell (EPC) levels with lower endothelial microparticles (EMPs) compared to a low-fat diet [23]. This suggests that the Mediterranean diet better regulates endothelial function in almost everyone, including those with severe endothelial dysfunction. The Mediterranean diet ensures the intake of different antioxidants and protective compounds by consuming the right amount of olive oil and different colors and textures of vegetables and fruits at each meal [24]. These components cause decreasing pro-inflammatory cytokines and an upward tendency in anti-inflammatory cytokines. This quantitative shift in these two cell factors results in the suppression of innate immune system activation, further

raising susceptibility to insulin in peripheral tissues and enhancing vascular endothelial function, ultimately slowing the progression of T2DM and reducing CV risk factors.

#### *4.4. The treatment of complications of T2DM*

As a chronic metabolic disease requiring lifelong treatment, T2DM is associated with more complications. Many patients do not attach enough attention to treating and preventing diabetes and allow it to develop, which eventually leads to damage to multiple organs such as kidneys, nerves and blood vessels. Currently, it is common to classify the complications of diabetes into two major categories: macroangiopathy and microangiopathy. Among them, cardiovascular diseases such as diabetic heart disease belong to macrovascular lesions, while peripheral neuropathy, retinopathy and diabetic nephropathy belong to microvascular lesions [25].

In addition, the diabetic foot, which is the leading cause of nontraumatic diabetic amputation, is associated with both neurological abnormalities and vascular lesions.

It is well known that T2DM is a non-insulin-dependent disease and its progression is closely related to the patient's dietary habits. Adhering to a healthy diet that helps with blood glucose control not only prevents diabetes, but also reduces the occurrence of diabetes complications. In a four-year randomized controlled trial of 418 non-diabetic participants at high risk for vascular disease, the scholars found that the incidence of diabetes was more than half, at about 52%, which was lower in those on a Med diet than a low-fat diet. It points out that the Mediterranean diet is beneficial to diabetic management. Otherwise, another meta-analysis also suggests that it is helpful in glycemic control and reduction of CV risk factors in T2DM patients [26]. It is healthy and effective with proper nutritional distribution, which indirectly affects the development of diabetes and its complications through weight control, blood glucose regulation, and cardiovascular protection.

## **5. Conclusion**

This paper introduces the effects of the Med diet on hormone regulation, inflammation regulation and cardiovascular regulation of T2DM. However, there are relatively few studies on how the Mediterranean diet treats type 2 diabetes. To develop a more effective dietary plan for people with T2DM, further investigation and study in this area will be required in the future. The timing of application, specific measures and details related to the Med diet for treating and preventing T2DM are still in the exploratory phase, and relevant guidelines are almost invisible. MNT for T2DM with a predominantly Med diet still requires a large number of cases for long-term follow-up and clinical studies for further validation. Future research should focus more on dietary interventions for T2DM and further clearly define the unique role of the Med diet in this context, with the aim of providing a well-established dietary model for the prevention and treatment of T2DM and even all types of this disease.

## **Author contribution**

All the authors contributed equally and their names were listed in alphabetical order.

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