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The Anti-inflammatory Effects of the Mediterranean Diet in Type 2 Diabetes Mellitus: Evidence and Mechanisms

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Abstract. Type 2 diabetes (T2DM) is a chronic metabolic condition that occurs widely across the world and is strongly linked to persistent low-grade inflammation. However, conventional drug treatment with metformin does not effectively address this inflammatory basis. This article aims to review the anti-inflammatory mechanisms of the Mediterranean diet (MD) and to explore its potential as an adjunctive therapy for T2DM. Research has synthesised evidence from clinical trials, cohort studies and mechanistic experiments, focusing on four key pathways: 1) Polyphenols and antioxidants reduce oxidative stress; 2) n-3 polyunsaturated fatty acids produce anti-inflammatory mediators; 3) Reducing dietary late-stage glycation end products (AGEs) to lower inflammation triggers; 4) Short-chain fatty acids generated by intestinal microbiota may enhance insulin secretion while decreasing systemic inflammation. The results of the study show that strictly following an MD can reduce the risk of T2DM by 19% to 23%, lower fasting blood sugar levels by 0.59 to 0.72 mmol/L, and reduce the levels of IL-6 and adhesion molecules, which supports the contribution of the MD to diabetes prevention and management. However, existing studies have high heterogeneity, publication bias, and some randomized controlled trials are of poor quality. Moreover, there is a total absence of investigation on special populations such as pregnant women. Researching for different anti-inflammatory existing in different individuals that have specific genotype when they use MD and the development of diet for these individuals based on each of their metabolic profiles.

Keywords: Nutritional Epidemiology, Dietary Patterns, Metabolic Diseases

1. Introduction

Type 2 Diabetes Mellitus (T2DM) is one of the most common chronic metabolic disorders that exists today as well as one of the most common chronic diseases in the world. According to the estimate of International Diabetes Federation (IDF), there is about 589 million people in the world who are diabetic. By 2045, it is projected that there will be about 700 million people in the world who will have diabetes [1]. About 90%–95% of people who are diabetic, which exits in the world, are Type 2 Diabetes Mellitus. So, it is important to find the solution for this problem. The reason why the T2DM would increase so rapidly in the world may be caused by the following factors: unhealthy lifestyle which is not beneficial to the human health (such as diet, etc.).

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T2DM is a type of diabetes that affects millions of people around the world. It is characterized by the following feature: existing persistent hyperglycemia. This type of diabetes may cause the following damages to the patient's health. There is evidence that diabetes may be associated with the existence of the inflammation happened in the body of diabetic patient. It is thought that the existence of the increased content of inflammatory biomarker such as CRP, IL-6 and TNF-α in the blood of diabetic patient may be associated with the development of diabetes. Currently, the most commonly used medicine for the patient with T2DM is Metformin. Although this medicine could decrease the blood glucose of patient, it is not effective in treating the diabetic patient with the problem of insulin resistance. So, the doctor usually suggest the patient to change the diet to improve the patient's condition which has improved the insulin resistance.

Any person consuming foods that have anti-inflammatory properties in their diet can enhance their metabolism, physical fitness, and overall health. One type of dietary pattern that has been associated with significant health improvements is the MD. This type of dietary pattern generally includes foods such as fruits, vegetables, whole grains, nuts, fish, and olive oil. Several studies have suggested that consuming this type of dietary pattern within a person's diet can lead to a decrease in the inflammation present within the body as well as an increase in metabolic health.

Therefore, the possibility of the Mediterranean diet decreasing inflammation within the bodies of people with T2DM can be investigated to determine whether or not this dietary pattern can be an effective treatment for this health condition.

This article will investigate ways in which the Mediterranean diet can be integrated into the management of diabetes. Four mechanisms by which the MD can decrease inflammation within the body and subsequently alleviate T2DM will be discussed.

First, antioxidants that are present in the foods that are generally consumed by individuals who follow the MD decrease the amount of oxygen produced within the mitochondria of the body. Second, the metabolites of polyunsaturated fatty acids that are present in the MD help the body to decrease the amount of inflammation present within the body. Third, decreasing the amount of advanced glycation end products that are consumed by patients with T2DM will reduce their likelihood of experiencing inflammation. Finally, short-chain fatty acids that are present within the gut of an individual help to promote the release of insulin while also decreasing their inflammation levels.

The aim of this study regarding metabolic syndrome (MS) and type 2 diabetes mellitus (T2DM) is to assist healthcare professionals in treating patients with diabetes as well as provide healthcare professionals with a second option, besides using metformin, to slow the progression of type 2 diabetes mellitus. This option includes using the MD in the treatment of type 2 diabetes mellitus.

2. Nutritional composition of the MD

The Mediterranean diet (MD) originates from the countries surrounding the Mediterranean sea and it is largely comprised of plant foods and healthy fats with a moderate consumption of protein. The Mediterranean diet is a well-balanced and nutritious diet. There is an array of foods that can be consumed within the MD diet. Among these raw materials, polyphenols from red wine and berries neutralize free radicals, which reduces oxidative stress on pancreatic beta cells and blood vessels, and also improves vascular function (Figure 1). n-3 PUFAs from fish, nuts, and soybean oil have direct anti-inflammatory effects and enhance insulin sensitivity by facilitating glucose absorption by muscle and adipose tissues. In addition, SCFAs from grains, beans, and vegetables help strengthen the gut barrier.

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The MD pyramid below shows that olive oil, vegetables, fruits, and grains make up the largest part of the diet. Dairy products and fish are in the middle levels. Foods with AGEs, like red meat, are at the top and should be eaten the least. Red wine is optional and only for light drinking.

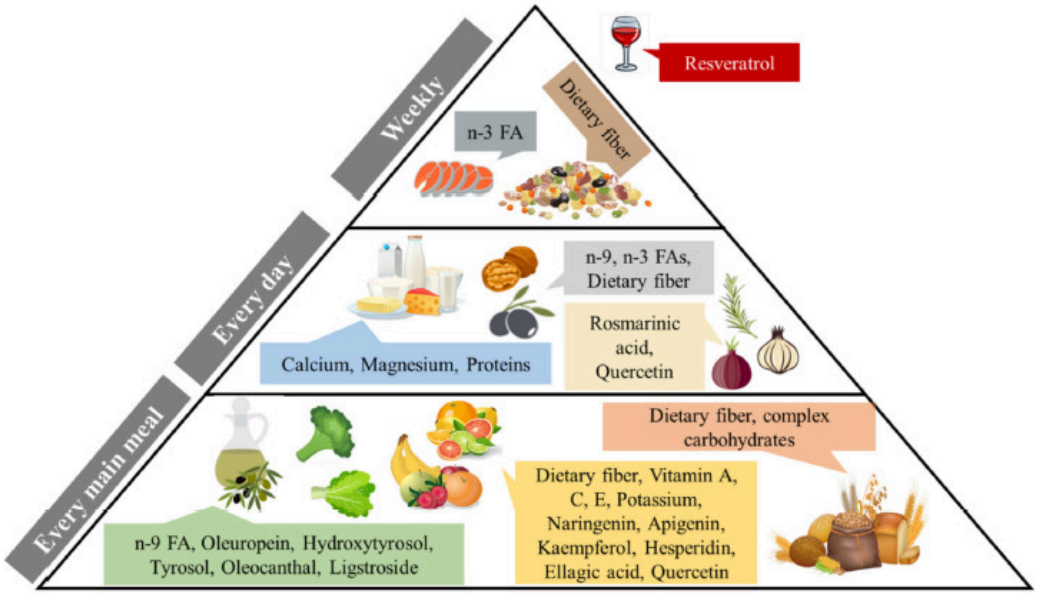

Figure 1. Introduction of MD composition [2]

Evidence from a substantial number of studies strongly suggests that nutrition plays a central role in supporting healthy living and reducing the risk of multiple chronic conditions. More specifically, extensive research has demonstrated that the MD may provide protective benefits against various chronic illnesses, including diabetes, cardiovascular disease, cancer, age-related disorders, as well as overall mortality [3].

3. The association between the MD and T2DM

A table showed some reviews involving more than 100,000 participants enrolled in clinical trials and prospective cohort investigations, including systematic reviews or meta-analyses on the effects of the MD on the occurrence or improved management of T2DM [4]. The data in this table document the DASH and AHEI scores of individuals with T2DM and individuals considered to be at elevated risk of the disease following a MD. The data indicate that, for healthy individuals, strong compliance with the MD may help prevent the development of T2DM, reducing their likelihood of developing the condition by approximately 19% to 23%; for those already diagnosed, the MD can lower fasting blood glucose by approximately 0.59–0.72 mmol/L and reduce insulin resistance. Compared with other diets, such as low-carbohydrate (LC), vegan, or Paleo diets, the MD did not show any disadvantages in improving blood glucose levels, but there is more robust evidence regarding its long-term sustainability and safety. Of course, this table also lists the limitations of the studies, such as high heterogeneity in some studies, publication bias, and low-quality RCTs in certain cases.

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4. Mechanisms of the MD in the prevention and treatment of T2DM

4.1. Polyphenols and antioxidants

Polyphenols are phytochemicals with antioxidant activity. In the MD, they are abundant in extra virgin olive oil and herbs and are regarded as major constituents contributing to its beneficial health effects. Among the numerous anti-inflammatory and antioxidant substances contained in the MD, phenolic constituents occur most extensively, especially flavonoids. Quercetin, a flavonoid, is capable of stimulating the insulin-independent AMP-activated protein kinase (AMPK) signaling pathway within skeletal muscle cells, thereby reducing adenosine diphosphate (ADP) consumption in isolated mitochondria [5].

A 2021 MD intervention clinical trial conducted in the United States demonstrated the role of phenolic compounds in the MD in treating T2DM. The study examined plasma specimens obtained from 19 individuals diagnosed with T2DM. After a 12-week controlled trial, relative to baseline values, the MD markedly elevated circulating concentrations of the citrus bioflavonoids naringin, taxifolin, and flavonol glycosides (increases of 60%, 58%, and 39%, respectively, $p < 0.05$), while circulating concentrations of the inflammatory cytokine IL-6 declined by 49% ($p = 0.016$). The oxidative stress indicator 8-hydroxy-2'-deoxyguanosine (8-OHdG) was also reduced by 32.4% ($p = 0.128$). The conventional diet did not induce these beneficial changes [6].

4.2. Optimization of fatty acid composition

PUFAs are a class of fatty acids characterized by two or multiple carbon-carbon double bonds and are an important component of cell membranes. In the MD, they are primarily derived from deep-sea fish, nuts, and plant-derived oils including soybean oil and corn oil. Lipid mediators formed from n-6 PUFAs have inflammation-promoting effects, whereas those produced from n-3 PUFAs have anti-inflammatory or physiologically neutral effects. The fish oil and flaxseed oil in the MD are abundant in alpha-linolenic acid (ALA), an n-3 polyunsaturated fatty acid [7].

PUFAs can reduce pro-inflammatory precursors by competitively displacing arachidonic acid in cell membranes; they can competitively bind to cyclooxygenase to inhibit the production of pro-inflammatory mediators; their metabolites, resolvins and protectins, can actively initiate the inflammatory resolution process; and they can downregulate the expression of pro-inflammatory genes by activating nuclear receptors such as PPAR-γ, ultimately achieving an anti-inflammatory effect.

A 2025 systematic review conducted in London evaluated 15 clinical trials of individuals aged between 23 and 80 years to determine the health benefits of the Mediterranean Diet (MD) rich in olive oil. It was discovered that participants' concentrations of intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and P-selectin were reduced in the MD diet [8].

Therefore, the conclusion is that MD Diet has a positive anti-inflammatory activity and it helps to reduce the incidence of cardiovascular diseases in the studied subjects.

4.3. Reducing dietary AGEs intake

The Maillard reaction is a reaction that happens when foods rich in reducing sugars are heated at temperatures greater than 120 ºC, leading to the formation of AGEs. These AGEs reach the liver and bind to the RAGE receptors that are present on the cells. In this way, inflammatory signals such as

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NF-κB, oxidative stress and inflammatory cytokines are activated. Therefore, the high content of sugar in the diet leads to a chronic inflammatory state that promotes diabetic complications.

An in vitro cellular assay of macrophages exposed to AGEs, and their RAGE receptors was carried out in 2018 [9]. It was found that the AGEs led to the release of TNF-α from macrophages. Individual AGEs did not cause this release. Therefore, the AGE must be bound to proteins to cause an inflammatory reaction. MD diet avoids the consumption of foods rich in AGEs, such as red meat, and favors foods with low contents of AGEs. Thus, following MD diet reduces the risk factors of T2DM.

4.4. Modulating the gut microbiome

SCFAs are metabolic products generated by the action of beneficial bacteria in the gut during the digestion of dietary fiber, such as that present in whole grains, legumes and vegetables. Some examples of SCFAs are butyrate, acetate and propionate. By strengthening the intestinal barrier and preventing the translocation of endotoxins, these products avoid these toxic substances reaching the bloodstream and causing inflammation. In addition, SCFAs, particularly acetate and propionate, favor the release of hormones such as GLP-1 and PYY. In addition, SCFAs, particularly acetate and propionate, avoid the translocation of endotoxins, preventing the inflammation caused by these toxic substances. Finally, SCFAs, especially acetate and propionate, reduce systemic inflammation by activating the NF-κB pathway, improving the sensitivity of the body to insulin and regulating blood glucose.

One experimental study published in 2017 aimed to determine the effect of a fiber-rich and experimental diet rich in the SCFA acetate on the inflammation present in mice with gout. It was found that the inflammation was reduced at a faster rate in mice fed a high fiber diet in comparison to mice fed a standard diet. In addition, the reduction in NF-κB activity and the increase in the anti-inflammatory mediators contributed to the resolution of the inflammation observed in mice fed either a high fiber diet or acetate alone. In summary, the results of this study showed that a diet rich in fiber or the SCFA acetate could help to reduce inflammatory processes and inflammation induced by the accumulation of MSU crystals [10].

5. Conclusion

In conclusion, type 2 diabetes remains one of the world's biggest public health problems and Type 2 diabetes mellitus pharmacologic treatments are inadequate in their ability to manage this disease. This article discusses how the MD diet can be used to manage and treat Type 2 diabetes. This article examines how the MD works to help patients with Type 2 diabetes and how it can reduce the symptoms and complications of the disease. This article provides various studies as evidence to support the claims made in this article.

However, there are a multitude of advantages to the MD diet for Type 2 diabetes patients and it cannot be recommended for everyone. Further research can be done into the effects of the MD diet on pregnant women and any other population. Further research can be done into the anti-inflammatory effects for those with MD genetic makeup and how the MD diet may be customized to fit the metabolic profiles of individuals with the condition.

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