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The Mechanisms of the Mediterranean Diet on the Prevention of Type 2 Diabetes Mellitus

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Abstract:

Type 2 diabetes mellitus has become a serious global health problem. Since it cannot be cured at present, its prevention is very important. A daily diet is one of the keys to preventing type 2 diabetes mellitus. Among many diets, the Mediterranean diet, as a healthy plant-based diet, has attracted much attention. This paper studied the effect and mechanisms of Mediterranean diet on the prevention of type 2 diabetes mellitus. Through literature review, this report found that the Mediterranean diet has many effects on preventing type 2 diabetes mellitus, including anti-inflammatory, preventing obesity, alleviating insulin resistance and preventing cardiovascular disease. and found the main mechanism of nutrients in the Mediterranean diet in these aspects, including polyphenols, polyunsaturated fatty acids, monounsaturated fatty acids, dietary fiber, and short-chain fatty acids. This report finally conclude that the Mediterranean diet has a significant and multifaceted effect on the prevention of type 2 diabetes mellitus.

Keywords: Mediterranean diet; type 2 diabetes mellitus; prevention.

1. Introduction

Diabetes is a kind of chronic metabolic disease,which is a serious public health problem at present.It is estimated that the prevalence of diabetes has reached 11.1% globally in 2024, with about 589 million adults aged 20 to 79 years old having diabetes [1]. In China, where has the largest number of diabetic patients according to the IDF Diabetes Atlas 11th Edition, about 233 million people live with diabetes, giving the prevalence of 13.7% in 2023 [2].

Type 2 diabetes mellitus (T2DM) is the most common type of diabetes, accounting for over 90% of all cases around the globe [1]. T2DM features insulin resistance and insufficient insulin secretion. The underlying causes of T2DM are insulin resistance and pancreatic β-cell failure, which can result in decreased insulin sensitivity and insufficient insulin secretion. These can be alleviated by a proper diet according to previous researches [3]. Some studies have proposed that adherence to the Mediterranean diet can benefit the prevention of T2DM [3].

The Mediterranean diet (MedDiet) is a conventional dietary pattern in countries around the Mediterranean

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Sea. It largely consists of a large intake of plant foods (seeds, fruits, nuts, vegetables, legumes, bread and other whole grain) , olive oil and fish, moderate consumption of low-fat dairy products (mostly cheese and yogurt) and wine, and a small intake of red meat [4]. Previous studies have proposed that the MedDiet can provide primary prevention against T2DM [4]. And some studies have proposed that MedDiet can reduce insulin resistance and help promote insulin secretion, which can play an important role in secondary prevention of T2DM [5].

The PREDIMED study, a randomized controlled trial which is considered the strongest evidence for the association between MedDiet and T2DM development, has compared MedDiet with a low-fat diet to see whether MedDiet can prevent T2DM. The study includes 3541 men and women at high cardiovascular risk and followed them up for an average of 4.1 years. It turns out that MedDiet with extra virgin olive oil (EVOO) can reduce the risk of T2DM by 40% in contrast to a low-fat diet [6]. Without the interventions for increasing physical activity or weight loss, this study has effectively proved the connection between the MedDiet and lower T2DM risk [6].

In China, a nationwide cohort study conducted by Zhen Ying and other colleagues proposed that there is an inverse correlation between Mediterranean diet adherence (MDA) score and T2DM risk [7]. For each 1 point increase in MDA (HR=0.83(95% CI: 0.76-0.90)), the risk is reduced by 17%, which means the higher adherence to the MedDiet, the less likely people are to develop T2DM, indicating MedDiet can help prevent T2DM [7].

There are several studies that mainly show the preventive effect of the Mediterranean diet on type 2 diabetes, but few of them focus on how different nutrients in it contribute to the prevention effects. Based on this, this report is going to explain how the MedDiet works in different aspects of T2DM prevention.

2. Reducing Inflammation

Several studies have proposed that inflammation has strong connections with T2DM. Chronic low-grade inflammation is a common feature of obesity and type 2 diabetes [8].

Inflammation promotes the occurrence and development of diabetes by inducing insulin resistance and β-cell dysfunction [8]. It also plays a driving role in diabetic complications, such as cardiovascular disease [8].

The main cause of inflammation is that adipose tissue secretes a variety of inflammatory factors such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), interleukin-1 (IL-1) and leptin. This secretion can also occur through macrophage infiltration into adipose tissue. Also, IL-1 may be related to islet inflammation, which causes β-cell function damage [8].

Inflammation interferes with insulin signal transduction through c-Jun N-terminal kinase (JNK), NF-κB and other signaling pathways, leading to insulin resistance, thus further leading to T2DM [8]. Anti-inflammation plays a crucial role in preventing T2DM. Polyphenols, polyunsaturated fatty acids such as omega-3 polyunsaturated fatty acids, and monounsaturated fatty acids can help people avoid inflammation.

2.1 Polyphenol

Most foods in the MedDiet contain anti-inflammatory substances. Polyphenols are bioactive compounds that have antioxidant and anti-inflammatory properties [9]. They are the most abundant antioxidants in MedDiet as numerous studies have reported [10]. MedDiet has rich content of fruit, vegetables, nuts, seeds, legumes, and olive oil, where the polyphenols come from [9].A study has analyzed that polyphenols exert anti-inflammatory effects via two mechanisms. Polyphenols (mostly flavonoids) can stimulate the secretion of adiponectin, a protein hormone secreted by adipocytes, and the phosphorylation of AMP-activated protein kinase (AMPK), which can inhibit the signalling pathways of NF-κB. NF-κB is a transcriptional factor that regulates cytokine gene expression and the inflammatory response, and it can be activated by a variety of stimuli. Polyphenols can also inhibit it while suppressing macrophage infiltration. Thus, they lead to reducing the gene expression of pro-inflammatory cytokines such as interleukin-1β (IL-1β), IL-6, and TNF-α [10].

Besides, Evoo and red wine contain polyphenols hydroxytyrosol, tyrosol, oleocanthal and resveratrol.These substances also have anti-inflammatory properties [9]. The reduction in the number of pro-inflammatory cytokines decreases inflammation, thereby reducing the interference with insulin signal transduction, thus preventing T2DM.

2.2 Omega-3 Polyunsaturated Fatty Acid

Several studies have proved that inflammation can be suppressed by omega-3 polyunsaturated fatty acids (ω-3 PUFAs), which means the consumption of ω-3 PUFAs is highly significant for avoiding inflammation. In the MedDiet, most ω-3 PUFAs derive from fish and nuts. Monocytes and macrophages produce lots of cytokines including tumor necrosis factor-alpha (TNF-α), IL-1 and IL-6. These cytokines are closely related to the occurrence of inflammation. ω-3 PUFAs stimulate monocytes and suppress their capacity to synthesize these cytokines [11]. Specifically, they can inhibit IL-1 mRNA, thereby inhibiting the transcription of pro-inflammatory cytokines,

reducing their levels, and consequently attenuating inflammation [11].

In another way, a potent platelet aggregator and leukocyte acti vator called platelet-activating factor (PAF) can be inhibited by it. Arachidonic acid (AA) metabolism can be greatly improved through this [11]. ω-3 PUFAs can then further reduce inflammation.

2.3 Monounsaturated Fatty Acid

One of the characteristics of the MedDiet, which is high in monounsaturated fatty acids (MUFAs), is the high use of olive oil. They are also provided by MedDiet nuts. Sirtuin 1 (SIRT1) is naturally activated by oleic acid (OA), the most prevalent MUFA in the human diet and the primary ingredient in 70–80% of olive oil [12]. An important function of SIRT1, a widely expressed NAD+-deacetylase, is to inhibit oxidative damage and inflammation. Pro-inflammatory cytokine mRNA, such as IL-6 and TNF-α, is expressed less frequently when OA increases its catalytic activity, which inhibits NF-kB activity [12].

Oleic acid can also produce a bioactive lipid called Oleoylethanolamide (OEA) [12]. It possesses antioxidant and anti-inflammatory properties.It can suppress the nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3) inflammasome pathway by inhibiting NLRP3 and caspase-1, bringing about a reduction of the expression of IL-1β [12]. Thus, it reduces inflammation.

3. Obesity Prevention

One of the main risk factors for later metabolic diseases, especially type 2 diabetes, is obesity [13]. Numerous studies demonstrate that obesity can lead to β-cell malfunction and insulin resistance. One important factor in preventing type 2 diabetes is preventing weight. A lower risk of obesity has been associated with MedDiet. Some possible routes linked to obesity have been hypothesized, although the exact mechanisms are still not fully known.

3.1 Obesity Prevention Via Inflammation Reduction

Excess adipose tissue, an organ with metabolic and endocrine activity, and a low level of chronic inflammation are characteristics of obesity. Obesity and inflammation are thought to be linked via the overexpression of pro-inflammatory cytokines in obesity [14].

As previously mentioned, the MedDiet has an abundance of anti-inflammatory substances that can reduce inflammation. A reduction in inflammation can lead to decreased levels of inflammatory factors such as IL-6 and an increase in adiponectin [14]. The former (IL-6 reduction) can inhibit adipocyte hyperplasia and hypertrophy,while the latter (adiponectin increase) can reduce total fat and cholesterol levels, ultimately achieving the effect of preventing obesity [14].

3.2 Monounsaturated Fatty Acids

MUFAs also has a positive effect on preventing obesity. OA can stimulate the AMPK signaling pathway. The rates of fatty acid oxidation can be regulated by AMPK through increasing sirtuin-1 (SIRT1)-mediated peroxisome proliferator–activated receptor γ coactivator 1-α (PGC-1α) transcriptional complex activity. It can also activate protein kinase A (PKA) activity by raising the intracellular concentration of cAMP [15]. This leads to SIRT1 phosphorylation and the promotion of its catalytic deacetylase activity [15]. And the expression of genes involved in the oxidation of fatty acids increases because of the hyperactivity and deacetylation of the transcriptional coactivator PGC-1α [15]. This can increase weight loss.

3.3 Dietary Fiber

MedDiet is also rich in dietary fiber from whole grains, legumes, vegetables, and fruits.

Dietary fiber can reduce energy intake by delaying gastric emptying, increasing satiety, inhibiting appetite hormones (such as ghrelin), and promoting the secretion of anorexic hormones (such as PYY and GLP-1) [16]. Meanwhile, the short-chain fatty acids generated through fiber fermentation modulate hormone secretion, insulin sensitivity, and fat metabolism by activating receptors like FFAR2/3 [16]. It mainly achieves the effect of weight control through these two paths.

3.4 Avoiding Processed Food

Besides, MedDiet avoids processed and ultraprocessed food consumption, which are poor in nutrients and with very low fiber content, undeniably associated with an increased risk of overweight and obesity [17].This is also one reason why the MedDiet can prevent obesity.

4. Alleviating Insulin Resistance

Insulin resistance (IR) is a key reason for T2DM.It is a state where the body's cells become hyposenitive to the hormone insulin. Improving insulin sensitivity is an effective method for the prevention of T2DM.

A randomized crossover controlled study enrolled 27 patients with T2DM. All participants initially received the MedDiet intervention, followed by a conventional diet intervention. Each dietary intervention lasted for 12 weeks, and changes in the patients' glycated hemoglobin (HbA1c)

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levels were observed [18]. The study results showed that, given the participants' mean baseline HbA1c was 7.1% prior to intervention, the average HbA1c level decreased to 6.8% after the MedDiet intervention. In contrast, the average HbA1c level remained at 7.1% following the conventional diet intervention [18]. These findings clearly demonstrate the superior efficacy of the MedDiet in alleviating IR.

4.1 Insulin Resistance Via Inflammation Reduction

The anti-inflammatory effects of the MedDiet can also alleviate IR. The JNK and IκB kinase beta (IKKβ) pathways link inflammation and IR. The reduction in inflammation can decrease the activation of IKKβ and JNK, which can decrease the interaction with insulin receptor substrates (IRS) [19]. This mechanism safeguards the insulin signaling pathway from disruption, thereby mitigating IR [19].

4.2 Polyphenol

Polyphenols comprise multiple varieties, each exerting distinct effects on improving insulin sensitivity. α-glucosidase and α-amylase are the key enzymes responsible for digesting carbohydrates into glucose, and their activity can be suppressed by flavonoids and tannins [20]. Green tea polyphenols and naringenin can inhibit sodium-dependent glucose transporters (SGLTs), which are closely associated with the regulation of blood glucose homeostasis [20]. And catechins can enhance the PI3K and NO signaling cascades, which are responsible for insulin signal transduction [20]. These mechanisms contribute to improved insulin sensitivity collectively.

4.3 Short-Chain Fatty Acid

Short-chain fatty acids (SCFAs) in the MedDiet is also of great importance to improve insulin sensitivity mainly through regulating the structure of intestinal microbiota [21]. SCFAs are mainly from whole grains, and high-fiber foods such as fruits and vegetables. Propionate and butyrate, two types of SCFAs activate the GPR43 and GPR41 receptors on intestinal cells, which promote the secretion of insulin and the release of glucagon-like peptide-1 (GLP-1), an incretin hormone, thereby reducing blood glucose levels and improving insulin sensitivity [21].

5. Preventing Cardiovascular Disease

According to the website of the IDF, cardiovascular disease (CVD) is the most common cause of mortality in diabetic patients. Preventing CVD is a critical step to prevent T2DM or halt its further progression.

A randomized controlled trial enrolled 1,002 patients with type 1 coronary heart disease. They were randomly assigned to either a MedDiet group (n=502) or a low-fat diet group (n=500). The study was conducted over 7 years to observe the incidence density of patient outcomes [22]. And the results showed an incidence rate of 28.1 per 1000 person-years in the Mediterranean diet group, compared to 37.7 per 1000 person-years in the low-fat diet group. The MedDiet demonstrated a significantly superior intervention effect on cardiovascular disease compared to the low-fat diet, highlighting its advantages in combating cardiovascular conditions [22].

5.1 Polyphenol

Polyphenols have two pathways to prevent CVD [23]. On the one hand, they can inhibit mammalian target of rapamycin (mTOR) signaling, which is linked to the occurrence of heart diseases such as hypertension, cardiac hypertrophy, and heart failure [23]. On the other hand, they can also help in the stabilization of atherosclerotic plaques, which prevents enlargement and vascular encroachment [23]. The two pathways prevent CVD respectively through the protection of heart function and the prevention of atherosclerosis [23].

5.2 Omega-3 Polyunsaturated Fatty Acid

ω-3 PUFAs also affect the prevention of major cardiovascular conditions, such as coronary heart disease, stroke, sudden cardiac death, heart failure, and so on. ω-3 PUFAs in fish and nuts (mostly walnuts) compete with arachidonic acid (AA) to produce substrates for cyclooxygenase (COX) enzymes. This competition could lead to vasodilation and decreased platelet aggregation. They can also increase the production rate of nitric oxide (NO), the atheroprotective signaling molecule, which can promote vasodilation. The elevation in NO levels improves arterial compliance, alleviates vasoconstriction responses to angiotensin II and norepinephrine, and enhances vasodilatory responses. All these contribute to vasodilatory responses eventually.

5.3 Monounsaturated Fatty Acid

High levels of MUFAs are beneficial for increasing high-density protein cholesterol (HDL) levels. HDL extracts excess cholesterol from peripheral tissues and arterial walls and delivers it to the liver for excretion or recycling. This mechanism is called reverse cholesterol transport, which prevents the accumulation of excess fat and cholesterol in blood vessels, and ultimately triggers acute events like heart attacks and strokes. HDL also increases the production of NO by upregulating the ex-

pression of endothelial NO synthase (eNOS), and helps promote vasodilation. Both pathways act in concert to prevent atherosclerosis, which helps to stop it from developing into CVD.

6. Conclusion

This report introduces the effect and mechanism of MedDiet in preventing T2DM from the nutrients contained in it, and mainly explains the mechanism of the high content of nutrients in MedDiet, polyphenols, ω-3 PUFAs, MUFAs, SCFAs, and dietary fiber in avoiding inflammation, obesity, IR, and CVD to prevent T2DM. It shows that adhering to the Mediterranean diet plays a significant role in preventing T2DM or its deterioration.

Some limitations exist. First, this report does not cover all mechanisms. For example, SCFAs can also reduce inflammation, actually, but t is not included in this paper, because detailed research on this aspect cannot be found due to the lack of ability. Second, some mechanisms were not explained in detail due to space constraints, such as how avoiding processed food can prevent T2DM; this part was not explained in detail.

Third, there are also other approaches to preventing T2DM that have not been mentioned, such as a healthy gut microbiota, which is related to better glucose metabolism and lower levels of inflammation. Fourth, this report does not further explore the suitability of the MedDiet for non-Mediterranean populations, especially for the Chinese population. Because olive oil is rarely used in the daily diet, the MedDiet is difficult to apply in the Chinese population. Therefore, it is necessary to further modify the MedDiet to better suit the Chinese or to seek a diet in China that bears similarities to the MedDiet, such as the Jiangnan diet, which contains non-refined rice, vegetables, fresh water fish and shrimps, and rapeseed oil.

In conclusion, although there are a few limitations, this report has elucidated the multifaceted effects and mechanisms of the Mediterranean diet in preventing T2DM. In the future, this report can explore the limitations mentioned above, and further explore the mechanism of nutrients in the Mediterranean diet for the prevention of T2DM.

References

[1] Schwarz P. IDF global clinical practice recommendations for managing type 2 diabetes - 2025. Diabetes Research And Clinical Practice, 2025, 22(2): 112-158.

[2] Zhou Y C, Liu J M, Zhao Z P, et al. The national and provincial prevalence and non-fatal burdens of diabetes in China from 2005 to 2023 with projections of prevalence to 2050. Military Medical Research, 2025, 12(1): 28-32.

[3] Salas-Salvadó J, Martinez-González M Á, Bulló M, et al. The role of diet in the prevention of type 2 diabetes. Nutrition Metabolism And Cardiovascular Diseases, 2011, 21(4): 32-48.

[4] Zeraattalab-Motlagh S, Jayedi A, Shab-Bidar S. Mediterranean dietary pattern and the risk of type 2 diabetes: a systematic review and dose-response meta-analysis of prospective cohort studies. European Journal Of Nutrition, 2022, 61(4): 1735-1748.

[5] Newsholme P, Keane K N, Carlessi R, et al. Oxidative stress pathways in pancreatic β-cells and insulin-sensitive cells and tissues: importance to cell metabolism, function, and dysfunction. American Journal Of Physiology-Cell Physiology, 2019, 317(3): 420-433.

[6] Salas-Salvadó J, Bulló M, Estruch R, et al. Prevention of diabetes with Mediterranean diets: a subgroup analysis of a randomized trial. Annals Of Internal Medicine, 2014, 160(1): 1-10.

[7] Ying Z, Fu M, Fang Z, et al. Mediterranean diet lowers risk of new-onset diabetes: a nationwide cohort study in China. Nutrition Journal, 2024, 23(1): 131.

[8] Lontchi-Yimagou E, Sobngwi E, Matsha T E, et al. Diabetes mellitus and inflammation. Current Diabetes Reports, 2013, 13(3): 435-444.

[9] Itsiopoulos C, Mayr H L, Thomas C J. The anti-inflammatory effects of a Mediterranean diet: a review. Current Opinion In Clinical Nutrition And Metabolic Care, 2022, 25(6): 415-422.

[10] Nani A, Murtaza B, Sayed Khan A, et al. Antioxidant and anti-inflammatory potential of polyphenols contained in Mediterranean diet in obesity: molecular mechanisms. Molecules, 2021, 26(4): 98-105.

[11] Simopoulos A P. Omega-3 fatty acids in inflammation and autoimmune diseases. Journal Of The American College Of Nutrition, 2002, 21(6): 495-505.

[12] Santa-María C, López-Enríquez S, Montserrat-de la Paz S, Geniz I, Reyes-Quiroz M E, Moreno M, Palomares F, Sobrino F, et al. Update on anti-inflammatory molecular mechanisms induced by oleic acid. Nutrients, 2023, 15(1): 22-24.

[13] Ruze R, Liu T, Zou X, et al. Obesity and type 2 diabetes mellitus: connections in epidemiology, pathogenesis, and treatments. Frontiers In Endocrinology, 2023, 14(12): 116-152.

[14] Ellulu M S, Patimah I, Khaza'ai H, et al. Obesity and inflammation: the linking mechanism and the complications. Archives Of Medical Science, 2017, 13(4): 851-863.

[15] Tutunchi H, Ostadrahimi A, Saghafi-Asl M. The effects of diets enriched in monounsaturated oleic acid on the management and prevention of obesity: a systematic review of human intervention studies. Advances In Nutrition, 2020, 11(4): 864-877.

[16] Deehan E C, Mocanu V, Madsen K L. Effects of dietary fibre on metabolic health and obesity. Nature Reviews Gastroenterology & Hepatology, 2024, 21(5): 301-318.

ISSN 2959-409X

[17] Dominguez L J, Veronese N, Di Bella G, et al. Mediterranean diet in the management and prevention of obesity. Experimental Gerontology, 2023, 17(4): 112-121.

[18] Itsiopoulos C, Brazionis L, Kaimakamis M, et al. Can the Mediterranean diet lower HbA1c in type 2 diabetes? Results from a randomized cross-over study. Nutrition Metabolism And Cardiovascular Diseases, 2011, 21(9): 740-747.

[19] Shoelson S E, Lee J, Goldfine A B. Inflammation and insulin resistance. Journal Of Clinical Investigation, 2006, 116(7): 1793-1801.

[20] Shahwan M, Alhumaydhi F, Ashraf G M, Role of polyphenols in combating type 2 diabetes and insulin resistance. International Journal Of Biological Macromolecules, 2022, 20(6): 567-579.

[21] Zhang D, Jian Y P, Zhang Y N, et al. Short-chain fatty acids in diseases. Cell Communication And Signaling, 2023, 21(1): 21-28.

[22] Delgado-Lista J, Alcala-Diaz J F, Torres-Peña J D, et al. Long-term secondary prevention of cardiovascular disease with a Mediterranean diet and a low-fat diet: a randomised controlled trial. The Lancet, 2022, 399(10338): 1876-1885.

[23] Rana A, Samtiya M, Dhewa T, Mishra V, et al. Health benefits of polyphenols: a concise review. Journal Of Food Biochemistry, 2022, 46(10): 14-26.

[24] Kosmas C E, Martinez I, Sourlas A, et al. High-density lipoprotein (HDL) functionality and its relevance to atherosclerotic cardiovascular disease. Drugs In Context, 2018, 7(21): 21-25.