REVIEW

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The Reciprocal Relationship between Inflammation and Diabetes: Importance of Medical Nutrition Therapy

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Abstract

Diabetes, which can be defined as an inflammatory disease, is a common condition. While the presence of inflammation can cause diabetes, in reverse it can also be caused by diabetes. Inflammation-related mechanisms can deteriorate the effect of insulin, causing hyperglycemia and insulin resistance. Various factors such as nutrition, physical activity, medication, and insulin are involved in the management of diabetes. The potential mechanisms regarding diabetes, inflammation, and nutrition were examined using the PubMed, ScienceDirect, Medline, EBSCO, Google Scholar, Wiley Online Library, BioMed Central, SpringerLink, Taylor & Francis, and Web of Science databases. In particular, anti-hyperglycemic and anti-inflammatory dietary recommendations are important in terms of maintaining homeostasis in the body. In this way, in addition to body weight control, improvements in biochemical indicators related to diabetes and inflammation are attained. Furthermore, with the improvement in inflammation, future diabetic complications can be prevented by providing glycemic control. Therefore, in this review, the mechanisms underlying diabetes and inflammation are explained and the potential effects of nutritional components on diabetes and inflammation are discussed.

Keywords: Diabetes, insulin, inflammation, cytokine, medical nutrition therapy

INTRODUCTION

Inflammation is a natural reaction of the immune system against injury, infection, and fear. In other words, inflammation is a complex biological response of vascular tissue to harmful stimuli (irritants etc.) to eliminate them. In response of the immune system to physiological and metabolic stress, pro-inflammatory molecules (such as adipokines and cytokines) are produced. These cell signaling components take part in cell-to-cell interaction, allowing cells to move to the site of inflammation in the case of infection and injury. That is why the immune system and inflammation are closely linked. Inflammation can be local or systemic and acute or chronic.[1]

In diabetes, certain changes occur in immune system components (such as macrophages and T-cells). The most prominent changes occur in leukocytes, which take part in the adipose tissue, liver, pancreas, vascular system, and circulation. These immunological changes affect the levels of certain cytokines. Thus, inflammation is contained in diabetes pathogenesis.[2]

Diabetes is a chronic disease that causes low-grade inflammation. In conditions such as heart diseases and metabolic syndrome, which are closely related to diabetes, concentrations of cytokines in the circulation increase. Inflammatory cytokines are generated by various types of cells and released into the circulatory system. Cytokines have regulatory functions by acting locally, centrally or peripherally in various tissues such as adipose and muscle tissues. In the case of low-grade systemic inflammation, there is a 2-to 3-fold increase in systemic plasma tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP) levels. These cytokines play important roles in the development of diabetes.[3]

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Nutrition plays an essential role in diabetes in which inflammation occurs. Omega-3 (n-3) polyunsaturated fatty acids with anti-inflammatory properties, antioxidant vitamins in vegetables and fruits, and whole grain or low glycemic index foods are among the nutritional strategies against diabetes. In addition, it should be aimed to reach and provide a healthy body weight by decreasing the saturated fat intake and enhancing the intake of complex carbohydrates.[4]

Adipose tissue is an important endocrine organ that exhibits pro- or anti-inflammatory effects and releases the bioactive substances known as adipokines. Disruption of the balance between these anti- and pro-inflammatory adipokines causes dysfunction in adipose tissue and is critical in the pathogenesis of metabolic diseases (diabetes etc.).[5]

In this review, the mechanisms underlying diabetes and inflammation are explained and the potential effects of nutritional components on diabetes and inflammation are discussed.

MATERIALS AND METHODS

Literature research was carried out using selected websites containing PubMed, ScienceDirect, Medline, EBSCO, Google Scholar, Wiley Online Library, BioMed Central, SpringerLink, Taylor & Francis, and Web of Science. The information in the article was obtained using keywords such as "inflammation, diabetes, cytokine, pro-inflammatory, anti-inflammatory, adipokine, insulin resistance, hyperglycemia, nutrition, inflammation and diabetes, inflammation and nutrition, diabetes and nutrition." In studies on diabetes, inflammation, and nutrition, animal studies and clinical human studies were reviewed. In addition, review, randomized controlled, and meta-analysis studies were also examined.

Relationship of Pro- and Anti-inflammatory Adipokines with Diabetes

TNF-α: It is an inflammatory indicator greatly related with diabetes. TNF-α, which is also related with obesity and insulin resistance, is produced from adipose tissue and secreted from macrophages, T-cells, and natural killer cells. Chronically increased TNF-α has deleterious effects on glucose metabolism. TNF-α can vary the sensitivity of insulin in various ways, such as reducing insulin receptor (IR) signal pathways, reducing glucose transporter 4 (GLUT 4) function in adipocytes and repressing adiponectin.[3] In a study conducted with diabetic individuals; it was stated that TNF-α negatively affect the functioning of intracellular GLUT and IR.[6]

IL-6: IL-6 is a pro-inflammatory cytokine that can cause disruption of the insulin-mediated phosphorylation process by acting on insulin receptor substrate-1 and -2 (IRS-1 and -2) in liver and skeletal muscles. Therefore, IL-6 can inhibit the action of insulin.[7] Atlı et al.[8] reported that IL-6 concentrations increased in individuals with diabetic and non-diabetic retinopathy.

Adiponectin: Adiponectin, another cytokine related to insulin sensitivity and produced by adipose tissue, also has an important place in relation to diabetes. High adiponectin levels are related to increased insulin sensitivity and lower cardiovascular disease risk. Adiponectin can reduce glucose production (in liver) by suppressing gluconeogenic enzymes such as phosphoenolpyruvate carboxykinase and glucose-6 phosphatase. Therefore, it can improve glycemic control and insulin sensitivity. In addition, TNF-α and IL-6 can diminish the adiponectin expression. Furthermore, adiponectin exerts an anti-inflammatory effect by repressing TNF-α-dependent nuclear factor kappa B (NF-κB) stimulation.[3] In the study conducted in 154 newly diagnosed type 2 diabetic and 1077 newly diagnosed pre-diabetic individuals; adiponectin concentrations were detected to be negatively related with pre-diabetes and diabetes.[9]

Visfatin: It is a cytokine responsible for regulating insulin sensitivity. In addition, insulin resistance has a significant function in inflammation and diabetes pathogenesis. Visfatin binds to the IR. It can also cause a decrease in blood glucose by diminishing the release of glucose by liver and stimulating the glucose utilization in adipose tissue and muscles.[10] According to Mir et al.[11]; visfatin concentrations were detected to be considerably higher in type 2 diabetic individuals.

Resistin: It is a hormone with the potential to cause insulin resistance. It functions in glucose tolerance and glucose homeostasis. In a study involving 124 individuals, serum resistin concentrations were detected to be significantly higher in overweight or obese people with impaired glucose tolerance compared with individuals with normal body weight.[12] Azab et al.[13] Showed that resistin levels were detected to be higher in diabetic people than in those who were not. In addition, a relationship was determined between resistin levels and diabetes-related risk factors (insulin resistance and obesity, etc.). Furthermore, resistin levels were found to be higher in individuals with retinopathy, a complication of diabetes.[13]

IL-1β: It is a cytokine that can disrupt insulin secretion and induce β-cell apoptosis. In addition to affecting β-cell function, it has an effect on type 2 diabetes development by causing a decline in the mass of β-cell.[14] Mojtaba et al.[15] Conducted a study in individuals with diabetes (30 people) and without diabetes (36 people). In this study, insulin resistance, fasting blood glucose, and serum IL-1β concentrations were detected to be significantly greater in diabetic individuals; serum insulin levels and β-cell function were detected to be significantly lower. In individuals with diabetes, serum IL-1β concentrations were negatively correlated with insulin levels and β-cell function, while positively correlated to fasting blood glucose. Additionally, it was concluded that IL-1β (inflammatory cytokine) has a crucial function in insulin secretion by β-cells.[15]

IL-10: It is one of the anti-inflammatory cytokines secreted from macrophages and lymphocytes. It also acts as a role in reducing inflammation induced by TNF-α, IL-6, and IL-1. Additionally, IL-10 has a potential effect to increase insulin sensitivity.[16,17] In a study conducted in Indian population, the association between IL-10 gene promoter polymorphisms and type 2 diabetes risk was assessed and it was concluded that the type 2 diabetes risk increased in those with IL-10 gene promoter polymorphisms.[18]

CRP: CRP, a cytokine produced by the liver, is an indicator responsible for the development of inflammation. CRP concentration increases in situations such as diabetes, obesity, coronary heart diseases, sedentary lifestyle, and smoking. While there is an increase in CRP production from the liver with the release of TNF-α and IL-6, CRP can also be released from mature adipocytes via lipopolysaccharide, resistin, and TNF-α.[3] The cut-off point of 3 mg/L for the CRP level is used to identify high- and low-risk groups.[19] According to an 11-year prospective study; individuals with a CRP value of ≥3 mg/L developed diabetes. Individuals with high serum CRP levels were shown to have a higher risk of developing type 2 diabetes within 5 years.[20] Regarding the CRP level as a cardiovascular risk marker in individuals with diabetes; it is considered that CRP concentrations 0 - <1 mg/L indicate low risk, 1-3 mg/L indicate

moderate risk, >3-10 mg/L indicate high risk, and >10 mg/L indicate an indeterminate increase.[21]

The relationship of pro- and anti-inflammatory factors with diabetes is shown in Table 1.[3,7,10,12,14,16,17,22]

Adipose Tissue and Insulin Resistance

The function of adipose tissue under normal conditions is to store circulating free fatty acids as triglycerides in adipocytes. Adipose tissue suppresses the negative effects of lipids in the insulin pathway. As a result, glucose utilization by cells (especially skeletal muscle cells) increases and lipolysis of stored triglycerides is inhibited. Having enough intracellular glucose in peripheral tissues inhibits glucose output from the liver. In the case of obesity; insulin resistance, chronic inflammation, and dysfunction in adipose tissue occur. Disturbance in adipokine secretion also occurs. As a result, lipolysis and the release of free fatty acids by adipose tissue increase. The function of the insulin pathway also decreases. However, the glucose output from liver is stimulated.[23]

The increased reactive oxygen species (ROS) formation in adipose tissue leads to an increase in oxidative stress in the blood. In the case of increased oxidative stress, an enhancement in nicotinamide adenine dinucleotide phosphate oxidase and a reduction in antioxidant enzymes occur. Consequently, the production of adipokines (in adipose tissue) is impaired. Plasminogen activator inhibitor-1, TNF-α, and monocyte chemotactic protein-1 levels increase, whereas adiponectin levels decrease. Therefore, decrease in insulin sensitivity can occur and insulin resistance can develop.[24]

Mitochondrial dysfunction in white adipose tissue in humans adversely affects insulin sensitivity in the liver and skeletal muscles. Because of this dysfunction, there is a decline in lipogenesis and an enhancement in lipolysis in white adipose tissue. Therefore, depending on the increase in glycerol and fatty acids and the release of IL-1β and TNF-α, glucose uptake in skeletal muscles and liver decreases and ectopic lipid accumulation occurs.[25]

Table 1. The relationship of pro- and anti-inflammatory factors with diabetes[3,7,10,12,14,16,17,22]

Factors	Potential effects
TNF-α	Insulin resistance ↑ Insulin receptor signal ↓ GLUT 4 ↓ Adiponectin ↓
IL-6	Insulin resistance ↑ Insulin action ↓ Adiponectin ↓
Adiponectin	Insulin sensitivity ↑ Glucose production ↓ Gluconeogenic enzymes ↓ TNF-α-mediated NF-κB ↓
Visfatin	Blood glucose ↓ Glucose utilization ↑
Resistin	Insulin resistance ↑
IL-1β	Insulin secretion ↓ Beta cell mass ↓
IL-10	Insulin sensitivity ↑

GLUT 4: Glucose transporter 4, IL-10: Interleukin-10, IL-1β: Interleukin-1β, IL-6: Interleukin-6, NF-κB: Nuclear factor-kappa B, TNF-α: Tumor necrosis factor-alpha.

The Pathogenesis of Diabetes

Hyperglycemia can cause oxidative stress and endoplasmic reticulum stress. Oxidative stress can stimulate the formation of numerous pro-inflammatory mediators that can lead to inflammation in pancreatic islet cells and peripheral tissues. Insulin resistance can develop in peripheral tissues due to inflammation. With inflammation in pancreatic islet cells, the normal function of beta cells is disrupted and diabetes can occur. Some metabolic pathways causing insulin resistance can cause inflammation and affect stress-induced kinases [JUN N-terminal kinase and IKB kinase-β (IKK-β)]. These kinases are involved in diabetes pathogenesis. In particular, IKK-β can stimulate the release of IL-1β and TNF-α in the liver and adipose tissue by activating NF-κB. These cytokines can also lead to insulin resistance.[26]

The disruption of the balance between insulin action and secretion plays a crucial role in the pathophysiology of diabetes. The disruption of the balance results in hyperglycemia. Furthermore, when there is β-cell dysfunction, insulin secretion is decreased. In this case, the capacity to maintain glucose levels in the body is limited. In addition, insulin resistance can lead to increased hepatic glucose production and reduced glucose uptake in muscles, liver, and adipose tissue. Therefore, hyperglycemia (due to insulin resistance and β-cell dysfunction) has a critical place in diabetes progression.[27]

Hyperglycemia, Insulin Resistance and Inflammation

Chronically elevated TNF-α and IL-6 levels are seen in metabolic diseases. TNF-α and IL-6 can change the sensitivity of insulin through activating various steps of the insulin signal pathway. These pro-inflammatory components induce serine phosphorylation instead of tyrosine in IRS-1. Therefore, insulin resistance can occur by inhibiting insulin signal activation.[3]

Various stimuli such as hyperglycemia, increased free fatty acid levels, and cytokines can cause oxidative stress by increasing the formation of ROS. Oxidative stress and ROS activate the serine/threonine kinase signaling cascades. These activated kinases target IRS proteins and IR in the insulin signaling pathway. IRS-1 and IRS-2 enhance phosphorylation of serine and reduce tyrosine phosphorylation. With the decrease in the activity of signal molecules such as phosphatidylinositol-3-kinase, the effect of insulin decreases and insulin resistance can develop. In addition, serine kinase triggers inflammation by affecting the NF-κB pathway and thus the effect of insulin can be inhibited.[28] Furthermore, hyperglycemia is associated with inflammation by stimulating IL-6 production from endothelium and macrophages.[3]

High circulating glucose concentrations (hyperglycemia) activate protein kinase C (PKC) by increasing the formation of diacylglycerol. The increased PKC pathway causes the secretion of pro-inflammatory components through increasing NF-κB.[29] Thus, it was emphasized that there is a close connection between hyperglycemia and inflammation.

In hyperglycemia, the advanced glycation end products (AGEs) production increases.[3] AGEs are heterogeneous compounds resulting from the non-enzymatic reaction between the nitrogenous groups of proteins, lipoproteins, and/or nucleic acids with the carbonyl groups

of reducing sugars. Protein glycation begins when the carbonyl group of the monosaccharides and the free amino group of the amino acids form a Schiff base. While Schiff base is formed in hours, this structure turns into Amadori products within days. Amadori products convert to dicarbonyl compounds and then to AGEs within weeks. One of the mechanisms in AGE formation is the polyol pathway. Hyperglycemia caused by diabetes in the polyol pathway, some of the abundant glucose is first converted to sorbitol and then to 3-deoxy-glucosone, an AGE intermediate and produced in the creation of AGE.[30] The AGE formed bind to relevant receptors, causing pro-inflammatory response. Therefore, increased AGE can cause an increase in plasma CRP and TNF-α concentrations.[3] Furthermore, the interplay between AGEs and specific receptors accelerates oxidative stress, resulting in an increased inflammatory signal. Activation of NF-κB and formation of ROS are effective in increasing this inflammatory signal.[31]

Diabetes, Inflammation and Medical Nutrition Therapy

The most studied nutritional component in relation to diabetes and inflammation is omega-3 fatty acids. Furthermore, there is also evidence for whole grains, foods with low glycemic index, antioxidant vitamins, and polyphenolic compounds.[4,32]

Eicosanoids consisting of n-3 (prostaglandin-3 and leukotriene-5) have a weaker inflammatory effect than those consisting of n-6 (prostaglandin-2, and leukotriene-4). Therefore, fish oil containing n-3 has an inflammation-reducing effect and n-3 can show its anti-inflammatory effect by directly affecting the cytokine production. Fish oil can achieve this effect by suppressing NF-κB activation.[4] Koopmans et al.[33] conducted a study on diabetic pigs and found that CRP concentrations were significantly greater in the group fed rich in saturated fat and cholesterol, while it was importantly lesser in the group fed rich in unsaturated fat. It was concluded that the diet rich in saturated fat and cholesterol stimulated inflammation by showing pro-inflammatory effect. According to a meta-analysis study; type 2 diabetic patients who took omega-3 supplements showed that triglyceride levels significantly declined, while there were no significant differences in hemoglobin A1c (HbA1c), total cholesterol, fasting and postprandial plasma glucose levels. However, high (>1.5) eicosapentaenoic acid/docosahexaenoic acid intake was found to cause a tendency in plasma insulin, HbA1c, total cholesterol and triglyceride levels to decrease.[34]

Consumption of fruits and vegetables has been related to inflammation.[4] A study related to diabetes found that vegetable and fruit consumption was adversely correlated to oxidative stress.[35] According to a meta-analysis study; vegetable and fruit consumption was found to reduce CRP and TNF-α levels. They attributed that consumption of fruits and vegetables can reduce pro-inflammatory markers due to their nutritional components such as antioxidant vitamins (A-C-E), soluble fiber, and flavonoids.[36]

According to 28 randomized controlled studies; no relationship was found among IL-6, TNF-α and CRP levels with the glycemic index or load.[37] However, there is also evidence in the literature showing that there is a relationship between inflammation and glycemic index. It was found that lower serum CRP concentrations in individuals on low-glycemic diet.[38] For this reason, care should be taken to provide that the glycemic index or load is not too high and that the amount of carbohydrates to be taken at meals is balanced. Wolever et al.[39] carried out a study in individuals with diabetes and examined the relationship between glycemic index and inflammation. They reported that CRP levels were significantly lower by 30% in those who followed a low glycemic index nutritional therapy in comparison with those who followed a high glycemic index nutritional therapy. It was stated that hyperglycemia, which is seen as a result of high glycemic index nutritional therapy, stimulates the release of inflammatory cytokines from monocytes.[39]

Dietary AGE proteins can cause inflammation in individuals with diabetes. Animal-based foods such as red meat, cheese, and egg yolk contain high levels of protein and fat. Consuming large amounts of these foods can cause high levels of AGE intake.[4] In an intervention study on diabetics; it was observed that the TNF-α, CRP, and intercellular adhesion molecule-1 levels increased in those fed a diet containing high AGE (16.3 ± 3.7 x10^6 AGE units per day) compared to those fed a diet containing low AGE (3.67 ± 1.2 x10^6 AGE units per day).[40] By preventing the accumulation of AGEs, the progression of diabetes-associated atherosclerosis can be slowed. Methylglyoxal, formed via a non-enzymatic reaction, is the precursor of most AGEs formed in diabetes. It was also shown in mice with diabetes that increased plasma methylglyoxal levels cause endothelial inflammation.[41]

Magnesium is an essential cofactor for more than 300 enzymes in carbohydrate metabolism (including all enzymes of glycolysis).[42,43] Magnesium is involved in the regulation of insulin signaling, in the insulin-mediated glucose utilization and in the phosphorylation of IR kinase.[43] The lack of dietary magnesium can cause impaired IR signaling and insulin resistance. Additionally, there was a reverse relation between magnesium intake and fasting insulin levels. In the study conducted in a Japanese population for the incidence of diabetes; increased magnesium intake was found to be a significant protective element, especially in those with insulin resistance and low-grade inflammation.[42]

Vitamin B_{12} shows potential antioxidant properties because it can trigger the methionine synthase activity. In addition, it directly reacts with reactive oxygen and/or nitrogen species and can reduce oxidative stress by affecting signal molecules. At the same time, vitamin B_{12} shows potential anti-inflammatory properties by inhibiting NF-κB. Vitamin B_{12} is also involved in the use of carbohydrates. Low levels of vitamin B_{12} can cause hyperglycemia.[44] Furthermore, a relationship among vitamin B_{12} deficiency with glucose intolerance and insulin resistance was reported by Madhu.[45] Lee et al.[44] carried out a study in individuals with diabetes and reported that blood glucose and CRP concentrations were significantly greater in individuals with low vitamin B_{12} levels. In addition, it was stated that the risk of vitamin B_{12} deficiency and inflammation was higher in diabetic vegetarians.[44]

The Mediterranean diet is a diet rich-olive oil, whole grains, vegetables, fruits, legumes, and nuts with moderate consumption-poultry and fish, low consumption-whole-fat dairy products and red meat and moderate wine consumption.[46] Esposito et al.[47] reported that the Mediterranean diet is a suitable diet for diabetes management.[47] Maiorino et al.[48] carried out a randomized controlled study and detected that diabetic patients with a higher score (6-9 points) on adherence to the Mediterranean diet were detected to have lower CRP and higher adiponectin levels than those who scored <3.[48] In order to improve glycemic control in diabetic individuals; vegetarian diets, the Dietary Approaches to Stop Hypertension diet, the German Food Pyramid Index, and the Alternative Healthy Eating Index can be used as alternatives besides the Mediterranean diet.[46,49]

In adults with diabetes, the percentages of total energy from macronutrients should be 45-60% for carbohydrates, 15-20% for proteins, 20-35% for fats, and each should be evaluated individually. In addition, the percentage of total daily energy from saturated fats should not exceed 7% and trans-fat intake should be kept to a minimum. To adequately control blood glucose, the percentage of energy from added sucrose or fructose should not exceed 10% of total daily energy.[49] The recommended amount for fiber intake should be a minimum of 14 g/1000 kcal. Furthermore, the average daily protein intake for diabetics (without kidney diseases) should be 1-1.5 g/kg body weight/day. At the same time, it is recommended for individuals with diabetes to consume 1 portion of fish at least 2 times a week for omega-3 fatty acid intake due to its anti-inflammatory properties. In addition, while 5% weight loss is recommended for clinical benefit in individuals with diabetes, 7-10% weight loss should be targeted to inhibit development to type 2 diabetes in people with pre-diabetes.[50]

The importance of nutrition in the reciprocal relationship between inflammation and diabetes is shown in Figure 1. Furthermore, the effects of cytokines and the factors affecting the levels of cytokines are shown in Figure 2.

CONCLUSION

Since diabetes is a disease characterized by chronic hyperglycemia and low-grade inflammation, anti-hyperglycemic and anti-inflammatory strategies in diabetes should be included in national and international dietary guidelines. Therefore, in order to keep blood glucose and inflammatory markers levels within normal ranges, achieving a healthy body weight should be targeted and body weight maintenance should be ensured. Energy, macro- and micronutrient intakes should be taken at recommended levels. Intakes of saturated fats, trans fats, and refined carbohydrates should be reduced. The consumption of fruits and vegetables should be increased, paying attention to the low glycemic index or load. Meal times and the numbers of macronutrients (especially carbohydrates) in the meal should be adjusted in accordance with the medicine or insulin therapy used. It should not be forgotten that medical nutrition therapy should be planned specifically for the individual to provide homeostasis in metabolism. Thus, complications that may occur due to diabetes and inflammation will be prevented.

MAIN POINTS

- Diabetes is a disease characterized by chronic hyperglycemia and low-grade inflammation.

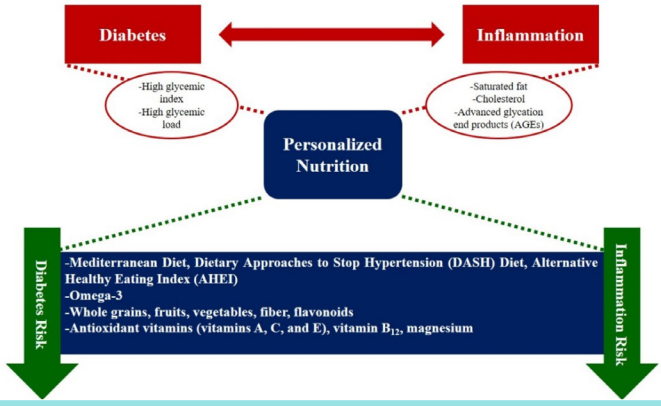

Figure 1. The importance of nutrition in the reciprocal relationship between inflammation and diabetes. Providing adequate and balanced individual nutrition within the scope of anti-hyperglycemic and anti-inflammatory nutritional strategies is effective in reducing the risk of diabetes and inflammation.

AGEs: Advanced glycation end products, AHEI: Alternative Healthy Eating Index, DASH: Dietary Approaches to Stop Hypertension.

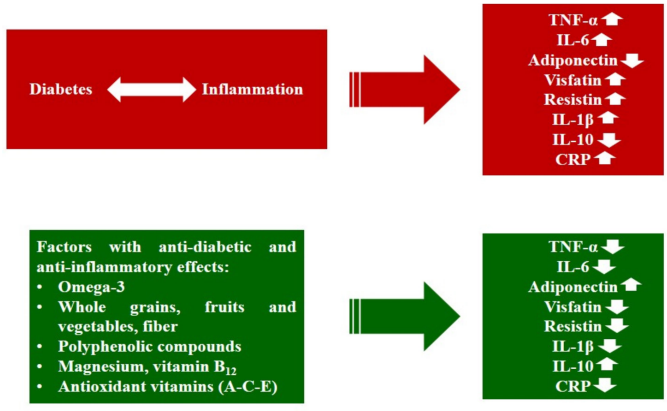

Figure 2. Effects of cytokines and factors affecting the levels of cytokines.

CRP: C-reactive protein, IL-10: Interleukin-10, IL-1β: Interleukin-1β, IL-6: Interleukin-6, TNF-α: Tumor necrosis factor-alpha.

- Inflammation-related mechanisms can cause hyperglycemia, insulin resistance, and diabetes.
- Diabetes-related mechanisms can cause inflammation.
- Anti-hyperglycemic and anti-inflammatory dietary recommendations are important for maintaining homeostasis.
- Medical nutrition therapy should be planned specifically for the person to provide homeostasis in metabolism.

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