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Open Access Journal of Endocrinology
ISSN: 2578-4641

Dietary Modulation of Chronic Inflammation of Diabetes: A Narrative Review

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Review Article
Volume 7 Issue 1
Received Date: March 13, 2023
Published Date: April 19, 2023
DOI: 10.23880/oaje-16000181

Abstract

Diabetes is a prevalent disease that affects millions of people around the world with severe and costly complications, such as neuropathy, retinopathy, nephropathy, peripheral vascular disease, ischemic heart disease, and cerebrovascular disease. It has been determined that prolonged state of hyperglycemia causes oxidative and nitrosamine stress and ischemia to the tissues, which leads to inflammation that the immune system cannot resolve. Because of this, diabetic patients live in a state of chronic inflammation. Current treatment of diabetes primarily revolves around glycemic control and lifestyle modifications; and while modern diabetic drugs continue to improve, nutritional aspects usually lag in the overall management of the disease. However, well optimized nutrition can not only minimize the source of inflammation and decrease the existing chronic inflammation, but it can also help the immune system to transition into the resolution and repair state. Such anti-inflammatory diet should abide by the following rules: 1) caloric restriction; 2) consumption of adequate amount of proteins; 3) decreased consumption of saturated fats; 4) increased consumption of unsaturated fats, especially omega-3 fatty acids; 5) increased intake of fermented fiber; 6) increased intake of polyphenols; 7) decreased consumption of both arachidonic acid and linoleic acid. It is important to mention that it might not be easy for the patient to switch their diet to the new one and maintain it over the long period of time. However, if done correctly, it might be a relatively cheap and effective addition to the standard medical treatment of diabetes.

Keywords: Diabetes mellitus; Hyperglycemia; Chronic inflammation; Inflammation resolution; Nutrition

Abbreviations: CDC: Center for Disease Control and Prevention; NO: Nitric Oxide; ROS: Reactive Oxygen Species; JAK: Janus Kinase; STAT: Signal Transducer and Activator of Transcription; PI3K: Pathway, Phosphoinositide-3-Kinase; PKB: Protein Kinase B; DAMPs: Damage Associated Molecular Patterns; PAMPs: Pattern Associated Molecular Patterns; TLRs: Toll Like Receptors; CLRs: C Type Lectin Receptors; ILs: Interleukins; CSF: Colony Stimulating Factors; IFNs: Interferons; TNFs: Tumor Necrosis Factors; TGFs: Transforming Growth Factor; CSF: Colony Stimulating Factors; IFNs: Interferons; TNFs: Tumor Necrosis Factors; TGFs: Transforming Growth Factor; ECM: Extracellular Matrix; ADA: American Diabetes Association; AACE: The American Association of Clinical Endocrinologists; ACE: The American College of Endocrinology; SCFA: Short-Chain Fatty Acids; LA: Linoleic Acid; AA: Arachidonic Acid; LPS: Liposaccharide.

Introduction

Diabetes in one of the most common chronic diseases that affects 37.3 million people in the United States - 11.3% of its population [1]. This disease has been strongly associated with both microvascular and macrovascular complications, such as neuropathy, retinopathy, nephropathy, peripheral vascular disease, ischemic heart disease, and cerebrovascular disease [2]. About 30 - 50% of patients develop those complications, which result in tissue and organ damage [2]. Additionally, The Center for Disease Control and Prevention (CDC) reported that the total cost of diabetes is $327 billion yearly in medical costs and lost work. It has also been estimated by the CDC that the medical costs for people with diabetes are twice as high as for people without it [3].

Pathophysiology of Vascular Complications of Diabetes

Polyol pathway: Diabetes-associated damage to small (e.g., capillaries) and large (e.g., arteries and veins) blood vessels is caused by chronic hyperglycemia and resulting over activation of the polyol pathway. This pathway is responsible for reducing glucose to sorbitol and then oxidizing it to fructose [4].

Alteration of the redox state: As a result of the polyol pathway, excessive amounts of nicotinamide adenine dinucleotide phosphate (NADPH) and nicotinamide adenine dinucleotide (NAD+) cofactors are consumed for production of NADP+ and NADH cofactors, respectively [4-6]. Altered concentrations of those cofactors lead to a set of metabolic imbalances, such as depletion of glutathione, nitric oxide (NO) and antioxidants, and increased production of reactive oxygen species (ROS) and superoxide anions. As a result of this, tissues suffer from oxidative and nitrosative stress, vasoconstriction and ischemia [4,7-10].

Formation of advanced glycation end products: As concentrations of glucose and fructose rise, those sugars can non-enzymatically bind with proteins, lipids, and nucleic acids, forming advanced glycation end products (AGEs) through the process called Maillard reaction[4,11]. Accumulation of AGEs in different cell types alters their extracellular and intracellular structure and disrupts their functions. AGEs caused microangiopathy, for instance, results from AGEs binding with collagen fibers of the endothelial cells, which causes loss of elasticity and thickening of the capillary basement membrane [4,12,13]. AGEs can also bind with multiple cell-surface-expressed AGE receptors (RAGEs), activating several signaling pathways in the cells: Janus kinase (JAK2)-signal transducer and activator of transcription (STAT1) pathway, phosphoinositide-3-kinase (PI3K)-protein kinase B (PKB, or Akt) pathway, mitogen-activated protein kinase (MAPK)-extracellular signal-regulated kinase (ERK) pathway and NADPH oxidase-ROS pathway. Activation of those pathways leads to production of proinflammatory and profibrotic cytokines, growth factors, and oxidative and nitrosative stress [4,11,14-16], which ultimately leads to cell damage, inflammation, and death.

Inflammatory response to diabetes: As mentioned above, chronic hyperglycemia results in a cascade of reactions that ultimately cause damage to cellular structures and trigger inflammatory response from the body. Inflammation is the immune system's natural defense mechanism against harmful stimuli, such as pathogens, toxic compounds, irradiation, or damaged cells that aims to eliminate injurious stimuli and initiate the healing process [17,18]. In general, inflammatory response goes through the following steps: 1) activation of pattern recognition receptors; 2) activation of inflammatory pathways; 3) release of inflammatory mediators; 4) recruitment of inflammatory cells; 5) resolution of inflammation; 6) restoration of tissue functionality.

Activation of pattern recognition receptors: Damaged or dying cells release their contents into the surrounding extracellular matrix. Those intracellular molecules (e.g., S100 proteins, histones, mitochondrial DNA) as well as some other extracellular compounds (e.g., fibrinogen) are regarded as endogenous danger signals and categorized as damage-associated molecular patterns (DAMPs) [19]. Those DAMPs as well as certain parts of microbial structures named pattern-associated molecular patterns (PAMPs) are recognized by pattern recognition receptors (PRRs). PRRs are a family of germ line-encoded receptors that includes Toll-like receptors (TLRs), C-type lectin receptors (CLRs) and others [20]. PRRs are expressed on both immune and nonimmune cells, and are responsible for stimulation of phagocytosis and activation of inflammatory signaling pathways [19-21].

Activation of inflammatory pathways: PAMPs or DAMPs bind with PRRs, which activates various intracellular signaling pathways. Different PRRs activate different inflammatory pathways, such as nuclear factor kappa-B (NF-kB) pathway, MAPK-ERK pathway, and JAK2-STAT1 pathway, which ultimately results in activation of nuclear transcription factors that initiate synthesis of inflammatory mediators [19-21].

Release of inflammatory mediators: Cytokines modulate the immune response and regulate inflammation itself through various complex pathways and interactions. Cytokines are primarily released from immune cells, such as macrophages, lymphocytes, and monocytes, and are divided into pro- and anti-inflammatory cytokines. Pro-inflammatory cytokines are further subdivided into interleukins (ILs),

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colony stimulating factors (CSF), interferons (IFNs), tumor necrosis factors (TNFs), transforming growth factor (TGFs), and chemokines. Their primary role is to recruit leukocytes to the site of injury or infection [21,22].

Recruitment of inflammatory cells: Chemokines that are produced at the site of injury or infection attract neutrophils, monocytes, lymphocytes (T cells, B cells, natural killer cells), and mast cells [23]. Neutrophils play two major parts during inflammation: 1) they help recruit, activate, and program dendritic cells and macrophages; 2) they phagocytose and destroy invading microorganisms. The latter part however, is also responsible for causing damage to host cells and tissues [24]. When monocytes are recruited into the tissues, they differentiate into macrophages and dendritic cells [25]. Macrophages are responsible for antigen phagocytosis, processing, and presentation as well as immunomodulation through production of various cytokines and growth factors. Those cells are also crucial for inflammation initiation, maintenance, and resolution [26]. Dendritic cells primarily function as antigen-presenting cells [25]. Lymphocytes are comprised of T cells, B cells, and natural killer cells, and are responsible for direct cell-mediated killing of virus-infected and tumor cells, antibody production, and regulation of the immune response [27,28]. Mast cells help initiate inflammatory response, and release a myriad of inflammatory mediators, such as cytokines, chemokines, histamine, proteases, prostaglandins, and leukotrienes [29-31].

Resolution of inflammation: Under normal circumstances, immune cells enter the site of injury by the process of chemotaxis and clear the culprit of inflammation. As concentration of antigen drops, production of pro-inflammatory cytokines decreases, which leads to chemokine gradients becoming more diluted. At certain point of time circulating white blood cells can no longer sense these gradients, and are no longer recruited to the site of injury [21,23]. Neutrophils that have already entered the tissues undergo apoptosis, and, consequently, are phagocytosed by macrophages. Upon phagocytosis of apoptotic neutrophils macrophages transform from M1-type (inflammation-phase macrophages) to M2-type (resolution-phase macrophages) [32,33]. While M1-type macrophages synthesize pro-inflammatory cytokines and proinflammatory lipids, such as prostaglandin E2 and D2, M2-type macrophages produce anti-inflammatory cytokines and pro-resolving lipid mediators, such as lipoxins and omega-3 unsaturated fatty acid derivatives named resolvins and protectins. Those pro-resolving mediators perform the following functions: 1) promote monocyte migration; 2) reduce neutrophil entry to the tissues; 3) decrease neutrophil activity, production of ROS, pro-inflammatory cytokines and chemokines; 4) promote apoptosis of neutrophils by macrophages and monocytes [34].

Restoration of tissue functionality: As inflammatory response subsides, reparation and regeneration are required in order to restore tissue functional homeostasis. Macrophages orchestrate those reparative processes through a set of complex interactions with stem and progenitor cells and stromal cells [35,36]. M2-type macrophages produce anti-inflammatory and reparative mediators that promote proliferation and protein synthesis in neighboring cells [37]. They also release transforming growth factor beta (TGF-beta) that promotes differentiation of fibroblasts into myofibroblasts, stimulates synthesis of collagen by myofibroblasts, and increases expression of tissue inhibitors of metalloproteinases (TIMPs) that regulate extracellular matrix (ECM) remodeling. M2-type macrophages also regulate ECM composition and remodeling by helping to maintain the balance between proteases and their inhibitors as well as directly consuming some parts of ECM [38,39]. Another crucial molecule that is produced by macrophages is vascular endothelial growth factor (VEGF), which promotes new blood vessel growth to supply the tissue with oxygen and nutrients [40]. After performing all their functions of inflammation resolution macrophages depart the tissue through the lymphatic channels to the lymph nodes where they present antigens from the inflamed site [32,34]. In a diabetic patient however, acute inflammatory response mechanisms cannot eliminate the injurious stimuli and repair the tissue injury due to the constant production of oxidative agents and AGEs. Because of this diabetic patients live in a state of chronic inflammation that cannot reach its resolution [41].

Current Treatment

The current approach to treatment of diabetes focuses on two main aspects: glycemic control and lifestyle modifications.

Glycemic Control

Since the defining feature of diabetes is high blood glucose level, tight glycemic control is of paramount importance to the success of the treatment. Glycosylated hemoglobin - also known as hemoglobin A1c (HbA1c) - estimates the average blood glucose level over the past three months, and is currently the standard way to measure patient's glycemic control as well as to calculate the risk for complications [42].

Lifestyle Modifications

The purpose of lifestyle modifications for a diabetic patient is to develop good and healthy habits and to eliminate bad and damaging ones, thus reducing the risk for potential complications as well as helping the body to repair and heal itself. Nutrition, physical activity, weight loss, and cessation

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of damaging substances are main components of lifestyle modifications.

Nutrition

Balanced diet is important for maintaining normal blood glucose level, and thus essential in management of diabetes. Eating more non-starchy vegetables (e.g., green beans, spinach, and broccoli), consuming less added sugars and refined grains (e.g., pasta, white bread, and rice), focusing on whole foods instead of processed ones (e.g., canned fruits and vegetables, luncheon meals and cookies), and having smaller portions at higher frequencies are the principal aspects of a healthy diet [43]. In conclusion, proper nutrition could be summarized in the following statement: consuming the right sugars, proteins, fats, vitamins, minerals and trace elements in the right amounts at the right times.

Physical Activity

Another key component of diabetes management is exercise. Multiple studies have highlighted several beneficial effects of physical activity on the body, such as increased sensitivity to insulin [44-47], induction of antioxidant defense systems [48], reduction in inflammatory markers, and production of anti-inflammatory compounds and interleukins [49].

Weight Loss

The third major aspect of a successful diabetes treatment is weight loss. Obesity has become a worldwide epidemic [50], and excess fat deposition throughout the body has been directly linked with hyperinsulinemia and development of diabetes mellitus type 2 [51]. In particular, it has been shown that visceral fat is metabolically active and produces a range of adipose-specific cytokines as well as pro-inflammatory cytokines that contribute to insulin resistance [52]. This is why strategic use of weight loss in diabetic patients has been recommended by The American Diabetes Association (ADA), The American Association of Clinical Endocrinologists (AACE) and The American College of Endocrinology (ACE) [53,54].

Cessation of Damaging Substances

The final component of lifestyle modifications that assists in the treatment of diabetes and its complications is elimination of substances that are damaging to vascular tissues. It has been confirmed by multiple studies that smoking, for example, causes the development of both macro- and microvascular complications as well as directly damages insulin producing cells of the pancreas by increasing inflammatory and oxidative stress to the tissues [55]. Excessive consumption of alcohol also induces oxidative stress in the vasculature by increasing production of free radicals as well as making the cells more susceptible to other stressors [56]. Illicit drugs, such as cocaine, have also been shown to exhibit vascular toxicity by causing profound vasoconstriction, endothelial damage, blood clot formation, and elevation of pro-inflammatory cytokines [57] As mentioned earlier, prolonged hyperglycemia causes damage to the blood vessels, so cessation of substances that negatively affect the same tissues would make sense for the management of diabetes.

Dietary Modulation of Chronic Inflammation

Prolonged state of high blood sugar causes tissues to suffer oxidative and nitrosative stress and ischemia, which leads to their damage and ultimately results in chronic inflammation that immune system cannot resolve. The current treatment paradigm primarily focuses on glucose management and lifestyle modifications. This review will focus on the dietary aspect of diabetes management and on how it could be used to modulate chronic inflammation to help it reach resolution and healing stage. Such diet should minimize the source of inflammation by reducing hyperglycemia and oxidative stress, diminish existing inflammation by decreasing production of pro-inflammatory cytokines, and facilitate resolution by increasing synthesis of anti-inflammatory mediators.

Minimization of the Source of Inflammation

The most important way to minimize the source of inflammation and reduce patient's hyperglycemia is calorie restriction (about 400-calories per meal) [58]. It has been proven that any reduction of excess calorie intake leads to a system-wide decrease in oxidative stress [59-61]. In order for this diet to be a long-term solution however, the patient has to feel satiated. Consuming adequate amount of proteins with every meal may help achieve this result [62,63]. Daily dietary protein requirements depend on the person's lean body mass and physical activity level. However, for the US population daily protein requirement for the average female would be ~75g and for the average male – about 100g [58]. High dietary protein increases the release of glucagon, glucagon-like peptide (GLP-1), and peptide YY (PYY), which helps stabilize blood glucose level [64] and increase satiety [65]. An additional way for the patient to enhance satiety with every meal is to increase the intake of fermented fiber, which facilitates generation of short-chain fatty acids (SCFA), that enhance the signaling of GLP-1 and PPY [66].

Diminishing of Existing Inflammation

In order to diminish existing inflammation, the diet should slow down synthesis of pro-inflammatory cytokines

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and decrease activation of inflammatory pathways. Some of the pro-inflammatory cytokines, such as prostaglandins and leukotrienes, are synthesized from arachidonic acid (AA). Rate limiting enzymes (delta-6 fatty acid desaturase and delta-5 fatty acid desaturase) of AA synthesis are activated by insulin and inhibited by glucagone [67,68] and omega-3 fatty acids, especially long-chain omega-3 fatty acids [69]. Much of the body's AA is synthesized from linoleic acid (LA) - an essential fatty acid that comes exclusively from diet. Therefore, by maintaining proper balance between insulin and glucagon, by increasing consumption of omega-3 fatty acids, and by decreasing consumption of both AA and LA one could limit the rate of AA production and, consequently, slow down existing inflammation [67]. One of the inflammatory pathways that could be controlled by diet is NF-kB pathway. One of the ways this pathway could be activated is by microbial PAMPs or DAMPs binding with Toll-like receptors [70]. TLR-2 and TLR-4 however, could also be activated by saturated fatty acids (primarily palmitic acid) and deactivated by unsaturated fatty acids, such as docosahexaenoic acid [71,72]. Thus, another way one could diminish existing inflammation is by decreasing consumption of saturated fats (< 50g per day) [58] and increasing consumption of unsaturated ones. The second way TLR-4 could be activated is by binding with liposaccharide (LPS) [73]. Intestinal epithelium, assisted by the gut bacterium *Akkermansia muciniphila*, presents a barrier that prevents absorption of LPS. By increasing the intake of fermentable fiber, omega-3 fatty acids, and polyphenols, the population of this bacterium could be increased, therefore decreasing absorption of LPS into the bloodstream (metabolic endotoxemia) [74,75]. NF-kB pathway can be inhibited by adenosine monophosphate-activated protein kinase (AMPK) [74,76]. AMPK is the body's master switch of metabolism that coordinates a myriad of cellular functions and pathways, including cell growth, polarity, and autophagy. AMPK acts like a cell's energy sensor, which is controlled by the balance of AMP and ATP levels. Once level of intracellular ATP diminishes, this enzyme inhibits anabolic pathways and promotes catabolic pathways to generate additional ATP molecules [77-80]. Activation of AMPK, which happens as a result of calorie restricted diet, plays an important role in extinguishing chronic inflammation in a diabetic patient by decreasing production of inflammatory cytokines through inhibition of NF-KB pathway [76,77].

Facilitation of Inflammation Resolution

Facilitation of resolution of any residual inflammation in the body is purely a function of omega-3 fatty acids in the diet. Omega-3 fatty acids are used to synthesize anti-inflammatory mediators, such as resolvins and protectins [81,82]. As discussed earlier, these anti-inflammatory mediators perform several important functions: 1) preventing additional neutrophils from entering the site of injury; 2) facilitating the transition of pro-inflammatory M1-type macrophages into pro-resolution M2-type macrophages (M2); 3) increasing phagocytosis of apoptotic cells [83].

Building an Anti-inflammatory Diet

The physiology of an anti-inflammatory diet has been thoroughly described above. To build such a diet for a patient however, one should know the correct amount and source of each component.

Macronutrients

As mentioned above, the most important aspect of an anti-inflammatory diet is calorie restriction. Each meal of the day should be less than 400 calories and have the following macronutrient composition: 1g of fat for every 2g of protein and every 3g of carbohydrate [58].

Fats

The total fat content should not exceed 50g per day. Most of this daily fat content should come from monounsaturated and polyunsaturated fatty acids, while the levels of saturated fatty acids should remain low [58]. Olive, peanut, and canola oils, avocados, almonds, hazelnuts, pecans, pumpkin and sesame seeds all contain high concentrations of monounsaturated fatty acids. Polyunsaturated fatty acids, in particular omega-3 fatty acids, are found in sunflower, corn, soybean, flax seed, and canola oils, walnuts, and fish. Saturated fatty acids are primarily found in animal foods, however, several plant foods, such as coconut and palm oils, are also known to have high concentrations of saturated fats [84].

Proteins

Daily dietary protein requirements depend on the person's lean body mass and physical activity. For the US population however, the average female needs to consume about 75g of protein per day, and the average male – about 100g [58]. Both plants and animals are great sources of protein. Lentils, beans (black, fava, garbanzo, etc.), peas (green, snow, snap, etc.), nuts (almonds, walnuts, pecans, etc.), seeds (sunflower, flax, sesame, etc.), and whole grains (quinoa, rice, buckwheat, etc.) are excellent plant-based choices. Great sources of animal protein are poultry (chicken, turkey, duck), eggs, seafood (fish, crustaceans, mollusks), dairy (milk, yogurt, cheese), and unprocessed red meat (beef, pork, lamb, veal, mutton, goat). It must be mentioned though, that consumption of dairy products and unprocessed red meats should be moderate. Processed meats, such as bacon, hot dogs, sausages, and cold cuts should generally be avoided [85].

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Carbohydrates

Glycemic load describes how rapidly the total amount of carbohydrates in a meal raises blood glucose levels [86,87]. Since hyperglycemia is at the root of inflammation in diabetes, a successful anti-inflammatory diet should keep blood glucose at a normal level and avoid spikes in blood sugar. Therefore, foods with low to medium glycemic load, such as non-starchy vegetables (carrots, broccoli, etc.), certain fruits (apples, oranges, etc.), beans (black, kidney, etc.), lentils, nuts (peanuts, cashews, etc.), and brown rice are ideal for an anti-inflammatory diet. High glycemic load foods, such as baked potatoes, French fries, refined breakfast cereals, white bread, white-flour pasta, candies, and sugar-sweetened beverages can rapidly raise blood sugar, and should be avoided [87].

Micronutrients

Vitamins and minerals are essential components of numerous biochemical reactions, and are necessary for the body to perform its functions [88]. A well balanced calorie-restricted anti-inflammatory diet contains plenty of fruits, vegetables, whole grains, healthy proteins and fats and supplies adequate amount of vitamins and minerals [58,89].

Potential Need for Supplementation

In order to completely resolve chronic inflammation and repair damaged tissues, the anti-inflammatory diet described above has to be supplemented with additional omega-3 fatty acids and polyphenols [58].

Omega-3 fatty acids: Even the best anti-inflammatory diets often cannot provide sufficient amount of omega-3 fatty acids, especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), that is needed to achieve proper therapeutic blood concentration [58,90]. According to multiple studies, an initial starting supplemental dose of omega-3 fatty acids should be between 2.5 and 4g per day [91-93].

Polyphenols: Polyphenols is group of over 8,000 compounds with different properties and bioavailability that have been identified in various plant species. Polyphenols of the anthocyanin family, which are found in berries, are most compatible with the human physiology [94]. This class of polyphenols exhibits its anti-inflammatory properties by activating AMPK through activation of sirtuins [95,96], inhibiting inflammasome formation [97,98], and promoting proliferation of the gut bacterium Akkermansia muciniphila [74]. Multiple studies have determined the minimum therapeutic dose of polyphenols to be 150 to 500mg per day depending on the patient's condition and genetics [99,100].

Other considerations: Additional supplements, vitamins, minerals, and trace elements could also be added to the patient's diet based on specific needs and conditions or when nutritional requirements are not met through diet alone. For example, a review and meta-analysis of 18 randomized controlled trials demonstrated that administration of alpha-lipoic acid - an antioxidant - decreased levels of inflammatory markers such as C-reactive protein, interleukin-6, and tumor necrosis factor alpha in patients diagnosed with metabolic syndrome and related disorders [101]. It is important to note however, that no supplement can ever replace a healthy well-balanced diet, but it can only help to fill in nutritional gaps.

Conclusions

Diabetes is a disease that affects millions of people around the world, has devastating complications, and costs both healthcare and patients an enormous amount of money. As discussed earlier, diabetes causes continuous damage to tissues, which results in a chronic inflammation that the body cannot clear. While modern diabetic drugs continue to improve, nutritional aspect of diabetes management is often deemphasized overall management of the disease. Well optimized nutrition can minimize the source of inflammation and decrease the existing chronic inflammation and can help the immune system to transition into the resolution and repair state. It is important to mention that it might be hard for the patient to alter their current diet and maintain a new anti-inflammatory one over the long period of time. Appropriate supplementation and dietary modifications may help with the body transition away from chronic inflammation and is a relatively cheap and side effect free addition to the standard medical treatments of diabetes.

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