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Diabetes & its Complications

Combination of Micronutrient Mixture, Probiotics, Collagen Peptides, Omega 3, Cannabidiol, and Diet May Prevent and Improve Current Treatments of Diabetes

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ABSTRACT

Diabetes mellitus is a progressive chronic disease associated with enhanced levels of fasting glucose and HbA1C. Despite valuable recommendations of adopting healthy diet and lifestyle, and reducing exposure to environmental toxins, the risk of developing diabetes type II continues to increase. Internal stressors which increased the risk of developing diabetes type II include oxidative stress, chronic inflammation, intestinal dysbiosis, dysfunctional omega-, oxidative damage to insulin receptors, and increased activity of DPP-4 enzyme which blocks the secretion of insulin from the pancreas to the blood. Addressing one of these defects at a time may not be effective in reducing the risk of diabetes type II. To prevent the risk of diabetes type II, this review proposes to (a) adopt healthy diet and lifestyle and reduce exposure to environmental toxins, (b) supplement with a micronutrient mixture which would simultaneously reduce oxidative stress and chronic inflammation (c) probiotics with prebiotics which would reverse the harmful effects of intestinal dysbiosis, (d) omega-3 to replace oxidized dysfunctional omega 3 and in patients with insulin resistance would directly activate the insulin receptor-linked signaling protein AKT leading to the entry of glucose inside the cells, and (e) collagen peptides containing inhibitor of DPP4 which would increase the secretion of insulin from the pancreas to the blood. Despite diabetic medications, complications such as retinopathy, nephropathy, peripheral neuropathy, and heart disease continue to develop due to resistance to medications. The proposed prevention plan in combination with current treatments may improve and prolong their effectiveness and reduce the rate of progression of the dieses.

Keywords

Diabetes, Oxidative stress, Chronic inflammation, Intestinal dysbiosis, Collagen peptides, Omega-3.

Introduction

Diabetes mellitus is a progressive chronic disease which exhibits higher levels of fasting glucose and HbA1C than normal levels. Despite prevention recommendations of adopting healthy diet and lifestyle, reducing the exposure to environmental toxins, the incidence of diabetes type II continues to increase in the USA and worldwide. In 2021, The Center for Disease Prevention and Control (CDC) reported that 19 million Americans had diabetes in 2010; this number enhanced to 37.3 million in 2019. In 2018, 88 million Americans had prediabetes, this number increased to 96 million in 2019. In 2022, WHO (world Health Organization) reported that the number of diabetes cases in the world rose from 108 million in 1980 to 463 million in 2019.

Human attitudes with respect to diet and lifestyle are not easy to alter, which could account for the lack of impact on the incidence of diabetes. In 2019, 1.6 million Americans aged 20 years and younger had type I diabetes. Type II diabetes is the 5th leading cause of death globally. The prevalence of diabetes type II in the USA depends upon the ethnicity. In 2019, it was 14.8% among Indian/ Alaska Natives, 12.1 % among blacks, 11.8% among Hispanic, 9.5% among Asian, and 7.5% among Whites [1]. These data suggest that diabetes type II has become a growing health concern in the

USA and world-wide. Current prevention recommendations which include adopting healthy diet and lifestyle, and reducing exposure to environmental toxins have failed to prevent incidence of diabetes type II. Despite current treatments, the diseases continues to progress slowly and diabetic complications do develop in many cases. Therefore, a novel effective plan to prevent and improve treatment of type II is needed to develop. Such a plan would be easily adaptable by most people.

This review proposes a prevention plan which includes reducing the impacts of external stressors such as by adopting healthy diet and lifestyle and reducing exposure to environmental toxins. This plan also includes attenuation of internal stressors such as oxidative stress, chronic inflammation, intestinal dysbiosis, dysfunctional omega-3, enhanced activity of DPP-4, and insulin resistance which contribute to the development and progression of diabetes type II. This review also proposes that combination of prevention plan with current treatments may prolong their effectiveness and reduce the rate of progression of this disease.

Proposed Plan to Prevent the Development and Progression of Diabetes Type II

Diet and lifestyle recommendations: To reduce the effects of external stressors, this prevention plan recommends daily consumption of a low fat and high fiber diet with plenty of fruits and vegetables and reduced of sugar and fat intake and decreased intake of very rich protein diet because it enhances the production of branched amino acids (leucine, isoleucine, and valine) which may increase the risk of diabetes type II [2].

Environmental exposure recommendations: To reduce the impact of external stressor, lifestyle recommendations include daily moderate exercise such as walking for 30 minutes 5 days a week, stopping cigarette smoking and vaping (e-cigarette), reducing stress by yoga or vacation, and limiting intake of caffeine because high doses of caffeine may interfere with the repair of DNA damage. Avoid exposure to air pollution containing tiny particles, because it increases the risk of diabetes type II by elevating oxidative stress and chronic inflammation [3,4]. In addition, reduce exposure to EMF (electromagnetic field) radiation emitted from cell phone, Laptop, and Wi-Fi [5]. In addition, it is essential to decrease the impact of internal stressors

Reducing the impact of internal stressors: In addition to reducing the impacts of external stressors, it is required to reduce the impact of all internal stressors which include elevated oxidative stress [6-16] and chronic inflammation [17-25] that lead to the development and progression of this disease and its associated complications [26-29]. Other internal stressors include intestinal dysbiosis (increase in the number of pathogenic bacteria and decline in the number of beneficial bacteria) which participates in the development and progression of diabetes [30-35], increased activity of DPP-4 (dipeptidyl peptidase-4) which inhibits two gut-generated incretin hormones that facilitate the secretion of insulin from the pancreas to the blood in patients with diabetes type II [36], and development of insulin resistance due to oxidative damage of insulin receptors which allows accumulation of glucose in the blood. Insulin resistance can develop after prolonged treatment of diabetes type I with insulin. These data suggest that resolving one or two internal stressors may not be sufficient to have an optimal beneficial effect in the prevention of diabetes type II.

Role of Oxidative Stress and Chronic Inflammation in type II and type I Diabetes

Role of oxidative stress in the development of diabetes type II: Several investigations have revealed that markers of oxidative stress such as DNA adduct 8-hydroxy-2'-deoxyguanosine (8-OHdG), lipid peroxidation product thiobarbituric acid-reactive substances (TBARS), protein oxidation products nitrotyrosine and carbonyl increased and the levels of antioxidant enzymes decrease in patients with hyperglycemia [16]. An elevated production of reactive oxygen species (ROS) was also confirmed in the culture of beta cells of the pancreas [37]. ROS caused reduction in the expression of insulin genes leading to a decreased production of insulin [38]. In addition, prolonged exposure to ROS could reduce the number of beta cells of the pancreas. Enhanced oxidative stress also leads to hyperglycemia-induced insulin resistance [39] by damaging insulin receptors or its-mediated signaling AKT which prevents the translocation of glucose transporter-4 (GLUT-4) to the cell surface membrane, and thereby, inhibiting the entry of glucose uptake inside the cells for generating energy. Hyperglycemia-induced elevated oxidative stress is due to a non-enzymatic glycosylation which leads to the formation of advanced glycosylation end-products (AGEs). Enhanced accumulation of AGEs contributes to vascular damage leading to diabetic-related complications such as retinopathy, nephropathy, and atherosclerosis [40]. Mitochondrial dysfunctions, which includes a defect in biogenesis, number, morphology, and process of fusion and fission, occurs in individuals who develop insulin insufficiency, insulin resistance, and who are obese [41-42]. Hyperglycemia generates excessive amounts of ROS [33], which can impair oxidative phosphorylation of mitochondria in muscle cells causing insulin resistance [42]. Beta cells of the pancreas exposed to chronic hyperglycemia decrease the synthesis of insulin in an animal models of diabetes type II [38]. A study has shown that increased oxidative stress leads to the development of chronic hyperglycemia-induced insulin resistance [39]. This was further confirmed in an experiment in which incubation of primary adipocyte cells in culture with a high concentration of glucose produced enhanced oxidative stress [43]. In 3T3-Li adipocyte cells in culture, oxidative stress-induced insulin resistance occurs by inhibiting the translocation of GLUT-4 from the cytoplasm to the plasma membrane of the cell [44]. A similar observation was made in the intact rat muscle [45]. Several investigations and reviews also have confirmed the role of enhanced oxidative stress in in the initiation and progression of diabetes [6-15]. The fact that elevated levels of markers of oxidative damage were observed in prediabetic patients may further support the role of enhanced oxidative stress in diabetes type II [9]. Oxidative damage of cells, if not fully healed, leads to chronic inflammation which releases

free radicals, proinflammatory cytokines, complement proteins, adhesion molecules, and prostaglandins all of which are toxic to cells.

Role of oxidative stress in the progression of diabetes type I: Hyperglycemia can cause an increased levels of oxidative stress which enhances the risk of developing microvascular and macrovascular complications in diabetes type I. In non-obese diabetic (NOD) mouse models, oxidative stress-induced damage is more pronounced in the beta-cells of the pancreas and vascular tissue compared to diabetic- resistance NOD mice [46]. The levels of markers of oxidative stress such as malondialdehyde (MDA) and protein carbonyl were progressively higher in the plasma of diabetic children and adolescents than in control subjects. The activity of glutathione peroxidase and the level of glutathione were also progressively declined in the erythrocytes of diabetic children and adolescents. Furthermore, the levels of vitamin E and beta-carotene were low in the plasma of diabetic children. These results show that enhanced oxidative stress also participates in the pathogenesis of type I diabetes [47]. The levels of markers of oxidative damage were increased in parents of children as well as children with diabetes type I [48-50].

Role of chronic inflammation in the development of diabetes type II: Chronic inflammation also participates in the pathogenesis of type II diabetes [51]. The level of C-reactive protein (CRP) in plasma increases in type II diabetes with large size low density lipoprotein (LDL) cholesterol, (LDLc A), or small size LDLc (LDLc B) (small) compared to control subjects. The levels of the proinflammatory cytokine IL-6 enhances in diabetes type II with large size LDLc [52]. The levels of CRP and proinflammatory cytokines IL-6, and TNF-alpha were enhanced in the plasma of patients with metabolic syndrome and diabetes type II [53,54]. In addition, the levels of tumor necrosis factor- alpha (TNF-alpha) [55] and monocyte chemotactic protein 1 (MCP-1) [56,57] were elevated in patients with diabetes type II. Chronic hyperglycemia associated with diabetes type II can cause diabetic complications such as retinopathy, nephropathy, neuropathy, cardiovascular disease, and blood vessel damage [58,59]. Increased level of a proinflammatory cytokine TNF-alpha was associated with obesity as well as with insulin resistance and diabetes type II [60]. Other reviews and investigations have suggested that chronic inflammation also participates in the initiation and progression of diabetes [17-25].

Role of autoimmune and chronic inflammation in the development of diabetes type I: Diabetes type 1 is considered an autoimmune disease in which damage to beta cells of the pancreas occurs leading to the cessation of insulin production. Both CD4+ and CD8+ T cells participate in the development of diabetes type I in an animal models [61]. Both humoral and cellular immunity play a role in the pathogenesis of diabetes type I [62,63]. Activated macrophages release excessive amounts of proinflammatory cytokines such as IL-1beta and TNF-alpha which cause inflammatory damage to beta cells of the pancreas [63]. The combination of three inflammatory molecules INF-gamma, IL-6, and TNF-alpha causes damage to beta cells of the pancreas, upregulates the activity of inducible nitric oxide synthase (iNOS) that produces increased levels of nitric oxide (NO) which together with ROS can cause death of beta cells of the pancreas [64,65]. These results show that attenuation of oxidative stress and chronic inflammation may be useful in reducing the progression of diabetes type I.

Role of Oxidative Stress and Chronic Inflammation in the Development of Diabetic-Related Complications

Retinopathy: Diabetic retinopathy occurs in poorly controlled diabetes. Increased oxidative stress and chronic inflammation participate in the development of diabetic retinopathy by damaging the microvessels. The levels of several inflammatory cytokines and chemokines were enhanced in the serum and ocular samples (vitreous and aqueous humor) from diabetic patients [66-68]. Reactive retinal gliosis produces proinflammatory cytokines which damage retinal cells. The level of vascular endothelial growth factor (VEGF) increases, which contributes to the development of vascular permeability and angiogenesis in severe diabetic retinopathy [69,70]. This eye disease occurs in 50% of diabetic patients 10 years after diagnosis, and in 90 % after 25 years of diagnosis. Retinopathy is the primary cause of blindness [26,27].

Nephropathy: Diabetic nephropathy (DN) occurs because of the damage to microvessels of the kidney by increased oxidative stress and chronic inflammation, causing persistent albuminuria and gradual decline in glomerular filtration rate (GFR). DN is the leading cause of end-stage renal disease (ESRD) which occurs approximately 20 years after the onset of diabetes and accounts for 45% of diabetic cases. The incidence of ESRD was similar in both diabetes type I and diabetes type II [34]. Both oxidative stress and the products of chronic inflammation such as proinflammatory cytokines, adhesion molecules, and chemokines play an important role in the development and progression of DN [28]. Thus, both elevated oxidative stress and chronic inflammation participate in the development and progression of DN and end-stage renal disease [71].

Peripheral neuropathy: Diabetic peripheral neuropathy is one of the vascular complications of diabetes. This peripheral nerve disease is very painful and disabling. Enhanced oxidative stress and chronic inflammation- mediated damage to neurons, glia cells, and microvessels lead to the development and progression of diabetic neuropathy [29]. Hyperglycemia-induced increased oxidative stress and advanced glycation products also play a major role in the development and progression of diabetic neuropathy [72].

Impairment of insulin receptors: Enhanced oxidative stress and chronic inflammation damage the insulin receptor, which prevents the binding of insulin to its receptors and insulin receptor-mediated stimulation of AKT signaling pathways [73], and thereby, inhibits the translocation of glucose transporter protein-4 (GLUT-4) stored

in the vesicles in the cytoplasm to the cell surface membrane [74]. This process prevents the uptake of glucose leading to accumulation of glucose in the blood causing hyperglycemia and eventually diabetes type II. Continued oxidative stress and chronic inflammation also damage ability of the pancreas to produce insulin [16]. These investigations reveal that the simultaneous reduction of oxidative stress and chronic inflammation may be useful for the attenuation of the development and progression of diabetes.

Intestinal Dysbiosis

Even though Dr. Hippocrates, a physician and philosopher stated, "All diseases begin in the gut" some 2500 years ago, the importance of intestinal microorganisms in human health and disease was demonstrated much later. The intestinal dysbiosis occurs due to decline in the number of beneficial bacteria and overgrowth of pathogenic bacteria. The growth of harmful bacteria generates proinflammatory cytokines which are toxic to the cells, and deprive the body from certain B-vitamins, vitamin K, neurotransmitters, and short-chain fatty acids which are essential for maintaining good health. Intestinal dysbiosis is also associated with diabetes Type II and Type I [31]. It also participates in the rapid progression of insulin resistance in diabetes type II [75]. The intestinal dysbiosis also decreases the production of short-chain fatty acids such as butyric acid, propionic acid, and acetic acid [76]. Butyric acid has diverse biological functions which include improving intestinal barrier integrity, pancreatic beta cell proliferation, and insulin sensitivity, and reducing glycemia and body weight [77]. Intestinal dysbiosis can also increase the production of other metabolites such as branched amino acids which causes insulin resistance that can lead to the development of diabetes type II [78,79]. It also causes inflammation and enhances intestinal permeability. Intestinal dysbiosis has been observed in animal models and in patients with diabetes type II and its complications such as retinopathy, nephropathy, peripheral neuropathy, cardiovascular diseases, and coronary artery disease [80]. Severity of intestinal dysbiosis is related to the severity of diabetes type II. Therefore, restoring the number of beneficial bacteria and reducing the number of pathogenic bacteria may be needed to decrease the risk of development and the rate of progression of diabetes.

Dysfunctional Omega-3

Increased oxidative stress may oxidize omega-3-fatty acids which become ineffective or even can produce harmful effects [81]. In a randomized, placebo controlled, double blind clinical trial involving 92 patients with diabetes type II, the effect of omega-3 on glycemic index was investigated. The results showed that daily supplementation with 2,714 mg for a period of two-months reduced HbA1c without affecting the activity of antioxidant enzymes [82]. Another randomized placebo controlled trial involving 51 subjects aged 10-18 years with diabetes type I revealed that supplementation with 600 mg omega-3 (180 mg EPA and 120 mg DHA) for 12 weeks increased the level of flow mediated dilation (FMD) and reduced the level of triglycerides, and thereby, may reduce the risk of cardiovascular dieses in these patients [83].

DHA is more effective than EPA in reducing markers of chronic inflammation [84]. Omega-3 acts as an endocannabinoid ligand such as anandamide and 2-AG which activates endocannabinoid receptors CB1 and CB2(85). DHA/EPA promotes translocation of GLUT-4 from cytoplasmic vesicles to the plasma membrane by causing phosphorylation of insulin receptor-linked serine/thereonine protein kinase (AKT) in both normal and insulin resistance individuals [86]. Translocated GLUT-4 allows the entry of glucose in adipocytes which use glucose for generating energy.

Enhanced Activity of DPP-4 Enzyme

Two gut-generated incretin hormones, which facilitate the secretion of insulin from the pancreas are inhibited by the rise in DPP-4 (dipeptidyl peptidase-4) activity in patients with diabetes type II [36]. Therefore, a non-toxic inhibitor of DPP-4 would be helpful in the prevention.

Role of Antioxidants in Reducing Oxidative Stress and Inflammation

Since increased oxidative stress and chronic inflammation play an important role in the development and progression of diabetes and its complications, the role of antioxidants which reduce them was evaluated in the prevention and progression of diabetes. Most clinical studies have been performed to evaluate the role of individual antioxidants for a short period of time in improving glycemic index. Such studies have yielded an inconsistent beneficial effect in patients with diabetes. Some examples are described here.

Vitamin A: A review has suggested that supplementation with vitamin A may be helpful in patients with diabetes type II who suffer from vitamin A deficiency [87]. Treatment with all-trans-retinoic acid increased insulin sensitivity [88].

Vitamin C: Administration of high doses of vitamin C did not improve endothelial dysfunction and insulin resistance [89]. Analysis of 26 observational studies and 12 randomized controlled trials revealed that supplementation with vitamin C reduced fasting glucose levels but failed to decrease the levels of HbA1**c** [90].

Coenzyme Q10: A review of seven clinical trials showed that supplementation with coenzyme Q10 had no beneficial effects on glycemic control, lipid profiles or blood pressure in patients with diabetes [91].

Alpha-lipoic acid: Supplementation with alpha-lipoic acid alone reduced polyneuropathy associated with diabetes [92].

Resveratrol: Analysis of several clinical studies on supplementation with resveratrol for a period of 4-5 weeks had no impact on the levels of fasting glucose and HbA1c in patients with diabetes type II. No adverse effects were reported [93].

Curcumin: Analysis of clinical investigations revealed that supplementation with curcumin for a period of 7-10 weeks

decreased the levels of lipid peroxidation, fasting glucose, HbA1c, triglycerides, total cholesterol, LDLc and C-reactive protein, systolic blood pressure, and increased the levels of HDLc [94].

Quercetin: Supplementation with quercetin had no effect on the levels of fasting glucose, HbA1c, serum insulin, and lipid profile. Another clinical study showed that quercetin treatment improved glycemic control. Quercetin activates adenosine monophosphate kinase (AMPK) in skeletal muscles which stimulates AKT that causes translocation of GLUT-4 from the cytoplasm to the cell membrane which then allows entry of glucose inside the cells [95,96]. Most clinical studies on the effects of individual antioxidants in diabetes have been performed for a period of 4-12 weeks.

Despite overwhelming evidence, which supports the role of oxidative stress in experimental models of diabetes as well as in human diabetes, large well-designed long-term clinical trials with antioxidants such as vitamin E and alpha-lipoic acid individually failed to yield benefits in the management of diabetes [97]. A review of clinical studies on the effect of vitamin E, vitamin C, coenzyme Q10, alpha-lipoic acid, and L-carnitine concluded that these antioxidants individually produced no significant benefits in the management of diabetic complications [98]. In another clinical study, treatment with vitamin E or vitamin C in combination with metformin for a period of 90 days improved glycemic control [99].

A few potential reasons for the failure of a single antioxidant to yield consistent beneficial effects in patients with diabetes are described here.

a) Diabetic patients have an elevated level of oxidative environment. Supplemented single antioxidant in such an environment would be oxidized which then would act as a pro-oxidant rather than as an antioxidant.
b) Different antioxidants are distributed differently and in different amounts in the subcellular compartments of the cells. Supplemented single antioxidant cannot accumulate in all subcellular parts of the cell in sufficient amounts to provide an adequate protection against oxidative damage.
c) Alpha-tocopherol is a more efficient scavenger of free radicals in reduced oxygen pressure, whereas beta-carotene and vitamin A are more effective in higher oxygen pressure [100]. The pressure of oxygen varies from one organ to another and within the cells in the same organ [101]. A single antioxidant cannot protect against oxidative damage under such a varying oxygen pressure in the body.
d) Elevation of both antioxidant enzymes and dietary and endogenous antioxidant compounds is essential to attenuate simultaneously oxidative stress and chronic inflammation because they act by different mechanisms. Antioxidant compounds neutralize free radicals by donating electrons to those molecules with unpaired electrons, whereas antioxidant enzymes remove hydrogen peroxide (H2O2) by catalysis, converting them to water and oxygen. Supplementation with a single antioxidant alone cannot achieve this goal.
e) Supplementation with a single antioxidant cannot protect molecules against oxidative damage in both the aqueous and lipid environment of the cells.

Requirements of Micronutrient Mixture Which Can Elevate the Levels of Antioxidant Enzymes and Antioxidant Compounds

The failure of individual antioxidant to produce consistent benefits led us to develop a micronutrient mixture which can elevate the levels of antioxidant enzymes and dietary and endogenous antioxidant compounds at the same time. Previously we suggested that the levels of antioxidant enzymes and antioxidant compounds should be simultaneously elevated to decrease oxidative stress and inflammation at the same time [102]. Oral administration of the proposed mixture of micronutrients would enhance the levels of antioxidant compounds; however, it was not certain whether it can elevate the levels of antioxidant enzymes which requires an activation of Nrf2. The process of activation of Nrf2 and its role in enhancing antioxidant enzymes is briefly described here.

ROS-induced Activation of Nrf2: Under normal physiological conditions, ROS (reactive oxygen species) is essential to activate Nrf2. Activated Nrf2 dissociates itself from Keap1-CuI-Rbx1 complex in the cytoplasm and then migrates to the nucleus where it heterodimerizes with a small Maf protein and binds with ARE (antioxidant response element) leading to increased transcription of genes coding for several enzymes including antioxidant enzymes such as glutathione peroxidase, catalase, and superoxide dismutase [103-105].

Presence of ROS-resistant Nrf2 and its activation: Nrf2 becomes resistant to ROS during chronic oxidative stress [106-108]. Elevated oxidative stress is observed in diabetic patients despite the availability of Nrf2, suggesting that ROS has failed to activate Nrf2 in diabetes. The importance of Nrf2 activation was demonstrated in experiments in which the rate of wound healing in streptozotocin-induced diabetic mice lacking Nrf2 (-/-) was slowed down compared to diabetic mice with Nrf2 (+/+). Activation of Nrf2 by pharmacological agents improved the rate of diabetic wound healing [109]. Some antioxidant compounds, such as vitamin E and genistein [110], alpha-lipoic acid [111], curcumin [112], resveratrol [113,114], omega-3-fatty acids [115,116], glutathione [117], NAC [118], and coenzyme Q10 [119] activate ROS-resistant Nrf2. Activation of Nrf2 [120,121] and some antioxidant compounds also decreased chronic inflammation [122-129]. Thus the proposed micronutrient mixture has antioxidants which can elevate both antioxidant enzymes by activating Nrf2 as well as antioxidant compounds.

Ingredients of Proposed Micronutrient Mixture

This micronutrient mixture contains vitamin A (retinyl palmitate), vitamin E (both d- alpha-tocopherol acetate and d-alpha-tocopheryl succinate), natural mixed carotenoids, vitamin C (calcium ascorbate), vitamin D3, all B-vitamins, coenzyme Q10, alpha-lipoic acid, N-acetylcysteine (NAC), resveratrol, curcumin, quercetin, green tea extract, and minerals selenium and zinc. This

micronutrient mixture has no iron, copper, manganese, or heavy metals. This mixture has been tested clinically for its effectiveness in reducing oxidative stress and chronic inflammation. This micronutrient mixture would simultaneously attenuate oxidative stress and chronic inflammation by enhancing the levels of antioxidant enzymes through activation of the Nrf2 pathway as well as the levels of dietary and endogenous antioxidant compounds [130].

Reversal of Intestinal Dysbiosis by Probiotics with Prebiotics

Administration of probiotics with prebiotics may reverse intestinal dysbiosis by enhancing the number of beneficial bacteria and reducing the number of pathogenic bacteria, and thereby, decrease the risk of development and progression of diabetes [131-133]. Addition of prebiotics to probiotics was considered essential because they provide substrate to bacteria for fermentation which is necessary to produce short-chain fatty acids such as butyric acid.

Omega-3 Improves Glucose Metabolism in Patients with Insulin Resistance

In patients with diabetes type II and type I, insulin resistance develops due to damage to the insulin receptor or its linked cell signaling molecule AKT by increased oxidative stress. If the insulin resistance issue is not resolved, it can lead to diabetic-related complications such as nephropathy, retinopathy, and peripheral neuropathy. Supplementation with omega-3 fatty acids can improve glucose metabolism in insulin resistant patients. Omega 3 promotes translocation of GLUT-4 from cytoplasmic vesicles to the plasma membrane by causing phosphorylation of insulin receptor-linked serine/thereonine protein kinase (AKT) in insulin resistance patients with diabetes [86]. Translocated GLUT-4 allows the entry of glucose in the cells which use glucose for generating energy.

Collagen Peptides Contain Inhibitor of DPP-4 Activity

Increased activity of dipeptidyl peptidase-4 (DPP-4) degrades the two gut-generated incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), causing a decline in the secretion of insulin from the pancreas to the blood in patients with diabetes type II [36]. Collagen peptides increase the secretion of insulin by inhibiting the enzyme DPP-4 [134] without toxicity. Collage peptides contain Amla extract and white tea extract that have inhibitors of DPP-4 enzyme

Current Treatments with Oral Diabetic Drugs

All diabetic medications reduce the levels of fasting blood glucose, HbA1c, and enhance insulin sensitivity in patients with diabetes. There are different classes of oral drugs which maintain glycemic control by different mechanisms [135]. They include alpha-glucosidase inhibitors (break down of carbohydrate and sugar in the intestine), biguanides-metformin (increases insulin sensitivity and decreases the production and release of glucose by the liver), dipeptidyl peptidase-4 (DPP-4) inhibitors (enhance secretion of insulin from the pancreas to the blood), agonists of GLP-1 (glucagon-like peptide-1) receptor (stimulate the beta-cell of the pancreas to produce and secrete more insulin), dopamine receptor-2 agonists (decrease insulin resistance and the production of glucose by the liver), meglitinides (stimulate the pancreas to produce more insulin), sodium-glucose transport protein-2 (SGLT2) inhibitors (block the re-absorption of glucose by the kidney), sulfonylureas (stimulate insulin production and release from the beta-cells of the pancreas), thiazolidinediones (TZDs (increase insulin sensitivity, decrease the production of glucose by the liver, accumulation of free fatty acids, inflammatory cytokines, and preserve the function of beta cells of the pancreas). Generally, insulin is administered to patients with diabetes II who become resistance to all oral drugs to improve glycemic index. Although such treatment is effective in attenuating the levels of fasting glucose and HbA1c, the risk of hypoglycemia enhances [136]. When patients with diabetes type I become resistance to insulin, diabetic oral drugs such as metformin [137], SGLT-2 inhibitors [138], and agonists of GLP-1 receptor [139] are added to maintain a good glycemic index.

Limitation of Current Treatments

Although inhibitors of DPP-4 such as sitagliptin and vildagliptin approved by the FDA are commonly used for improving glycemic index, they produce some side effects. Therefore, a non-toxic inhibitor of DPP-4 would be useful in diabetes.

Despite oral drugs and insulin therapy, diabetes continues to progress slowly, and diabetic complications such as retinopathy, nephropathy, peripheral neuropathy, and heart disease develop in many cases. In 2016, 130,000 patients had lower extremities amputated, 438,000 had ischemic heart disease, and 313,000 had stroke [1]. The diabetic medications have improved glycemic index, but after prolong treatment, the patients become resistance to medications. Since these drugs do not attenuate causes, the disease continues to progress leading to diabetic-related complications in many cases.

Proposed Suggestions for Improving Effectiveness Current Treatments of Diabetes

Combination of proposed prevention plan with current therapies may improve effectiveness of therapies and reduce the rate of progression of the disease and thereby, reduce the risk of diabetic-related complications.

Conclusions

Diabetes mellitus is a progressive chronic disease which is associated with enhanced levels of fasting glucose and HbA1C compared to normal subjects. Despite valuable dietary, lifestyle, and environmental recommendations for reducing the risk of diabetes type II, the incidence of this disease continues to increase in the USA and the world-wide. The primary reason for the failure of above recommendations was that they did not attenuate internal stressors which were primary contributors to the development and progression of diabetes type II. These stressors include increased oxidative stress, chronic inflammation, intestinal dysbiosis, loss of collagen, and dysfunctional omega-3. The proposed prevention plan includes adopting healthy diet and lifestyle, and reducing exposure

to environmental toxins together with daily supplementation with a micronutrient mixture which would reduce oxidative stress and chronic inflammation, probiotics with prebiotics which would reverse the harmful effects of intestinal dysbiosis, omega-3 to replace dysfunctional omega-3, and collagen peptides containing inhibitor of DPP-4 enzymes which would increase secretion of insulin from the pancreas to the blood. Despite the use of different classes of diabetic oral drugs and insulin, the disease progresses slowly, and in many cases diabetic complications such as retinopathy, nephropathy, peripheral neuropathy, and heart disease continue to develop. This review also proposes that combination of proposed prevention plan with current treatments may improve their effectiveness and reduce the rate of progression of the disease and thereby decreased the risk of developing diabetes-related complications. The proposed plan for improving the treatment of diabetes type II would be also useful in the management of diabetes type I.

Conflict of Interest

The author is Chief Scientific Officer of Engage Global of Utah. This company sells nutritional products to consumers.

References

1. CDC. National Diabetes Statistics Report. Estimates of diabetes and its burden in the United State. 2020.
2. Cuomo P, Capparelli R, Iannelli A, et al. Role of Branched-Chain Amino Acid Metabolism in Type 2 Diabetes, Obesity Cardiovascular Disease and Non-Alcoholic Fatty Liver Disease. Int J Mol Sci. 2022; 23: 4325.
3. Meo SA, Memon AN, Sheikh SA, et al. Effect of environmental air pollution on type 2 diabetes mellitus. Eur Rev Med Pharmacol Sci. 2015; 19: 123-128.
4. Li Y, Xu L, Shan Z, et al. Association between air pollution and type 2 diabetes: an updated review of the literature. Ther Adv Endocrinol Metab. 2019; 10: 2042018819897046.
5. Meo SA, Alsubaie Y, Almubarak Z, et al. Association of Exposure to Radio-Frequency Electromagnetic Field Radiation RF-EMFR Generated by Mobile Phone Base Stations with Glycated Hemoglobin (HbA1c) and Risk of Type 2 Diabetes Mellitus. Int J Environ Res Public Health. 2015; 12: 14519-14528.
6. Stefano GB, Challenger S, Kream RM. Hyperglycemia-associated alterations in cellular signaling and dysregulated mitochondrial bioenergetics in human metabolic disorders. Eur J Nutr. 2016; 55: 2339-2345.
7. Yamagishi S, Maeda S, Matsui T, et al. Role of advanced glycation end products AGEs and oxidative stress in vascular complications in diabetes. Biochim Biophys Acta. 2012; 1820: 663-671.
8. Giovannini C, Piaggi S, Federico G, et al. High levels of gamma-H2AX foci and cell membrane oxidation in adolescents with type 1 diabetes. Mutat Res. 2014; 770: 128-135.
9. Maschirow L, Khalaf K, Al-Aubaidy HA, et al. Inflammation, coagulation, endothelial dysfunction and oxidative stress in prediabetes-Biomarkers as a possible tool for early disease detection for rural screening. Clin Biochem. 2015; 48: 581-585.
10. Tatsch E, De Carvalho JA, Hausen BS, et al. Oxidative DNA damage is associated with inflammatory response, insulin resistance and microvascular complications in type 2 diabetes. Mutat Res. 2015; 782: 17-22.
11. Saad MI, Abdelkhalek TM, Saleh MM, et al. Insights into the molecular mechanisms of diabetes-induced endothelial dysfunction: focus on oxidative stress and endothelial progenitor cells. Endocrine. 2015; 50: 537-567.
12. Kowluru RA, Kowluru A, Mishra M, et al. Oxidative stress and epigenetic modifications in the pathogenesis of diabetic retinopathy. Prog Retin Eye Res. 2015; 48: 40-61.
13. Waris S, Winklhofer-Roob BM, Roob JM, et al. Increased DNA dicarbonyl glycation and oxidation markers in patients with type 2 diabetes and link to diabetic nephropathy. J Diabetes Res. 2015; 2015: 915486.
14. Unuofin OJ, Sogolo LL. Atioxidant effects and mechanisms of medical plants and their bioactive compounds for the prevention and treatment of type 2 diabetes: An updated review. Oxid Med Cell Longev. 2020; 2020: 1356893.
15. Prasad KN. Micronutrients for the prevention of diabetes and improvement of the standard therapy. CRC Press. 2011.
16. Oguntibeju OO. Type 2 diabetes mellitus, oxidative stress and inflammation: examining the links. Int J Physiol Pathophysiol Pharmacol. 2019; 11: 45-63.
17. Hussain G, Rizvi SA, Singhal S, et al. Serum levels of TNF-alpha in peripheral neuropathy patients and its correlation with nerve conduction velocity in type 2 diabetes mellitus. Diabetes Metab Syndr. 2013; 7: 238-242.
18. Nishimoto S, Fukuda D, Higashikuni Y, et al. Obesity-induced DNA released from adipocytes stimulates chronic adipose tissue inflammation and insulin resistance. Sci Adv. 2016; 2: e1501332.
19. Reinehr T, Karges B, Meissner T, et al. Inflammatory Markers in Obese Adolescents with Type 2 Diabetes and Their Relationship to Hepatokines and Adipokines. J Pediatr. 2016; 173: 131-135.
20. Barry JC, Shakibakho S, Durrer C, et al. Hyporesponsiveness to the anti-inflammatory action of interleukin-10 in type 2 diabetes. Sci Rep. 2016; 6: 21244.
21. Morettini M, Storm F, Sacchetti M, et al. Effects of walking on low-grade inflammation and their implications for Type 2 Diabetes. Prev Med Rep. 2015; 2: 538-547.
22. Karstoft K, Pedersen BK. Exercise and type 2 diabetes: focus on metabolism and inflammation. Immunol Cell Biol. 2016; 94: 146-150.
23. Singh K, Agrawal NK, Gupta SK, et al. Increased expression of TLR9 associated with pro-inflammatory S100A8 and IL-8 in diabetic wounds could lead to unresolved inflammation in type 2 diabetes mellitus (T2DM) cases with impaired wound

healing. J Diabetes Complications. 2016; 30: 99-108.

24. Perlman AS, Chevalier JM, Wilkinson P, et al. Serum Inflammatory and Immune Mediators Are Elevated in Early Stage Diabetic Nephropathy. Ann Clin Lab Sci. 2015; 45: 256-263.
25. Chaudhury A, Duvoor C, Reddy Dendi VS, et al. Clinical Review of Antidiabetic Drugs: Implications for Type 2 Diabetes Mellitus Management. Front Endocrinol Lausanne. 2017; 8: 6.
26. Kowluru RA, Chan PS. Oxidative stress and diabetic retinopathy. Exp Diabetes Res. 2007; 2007: 43603.
27. Kang Q, Yang C. Oxidative stress and diabetic retinopathy: Molecular mechanisms, pathogenetic role and therapeutic implications. Redox Biol. 2020; 37: 101799.
28. Donate-Correa J, Luis-Rodriguez D, Martin-Nunez E, et al. Inflammatory Targets in Diabetic Nephropathy. J Clin Med. 2020; 9: 458.
29. Sandireddy R, Yerra VG, Areti A, et al. Neuroinflammation and oxidative stress in diabetic neuropathy: futuristic strategies based on these targets. Int J Endocrinol. 2014; 2014: 674987.
30. DeGruttola AK, Low D, Mizoguchi A, et al. Current Understanding of Dysbiosis in Disease in Human and Animal Models. Inflamm Bowel Dis. 2016; 22: 1137-1150.
31. DeGruttola AK, Low D, Mizoguchi A, et al. Current Understanding of Dysbiosis in Disease in Human and Animal Models. Inflamm Bowel Dis. 2016; 22: 1137-1150.
32. Sharma S, Tripathi P. Gut microbiome and type 2 diabetes: where we are and where to go. J Nutr Biochem. 2019; 63: 101-108.
33. Sakai K, Matsumoto K, Nishikawa T, et al. Mitochondrial reactive oxygen species reduce insulin secretion by pancreatic beta-cells. Biochem Biophys Res Commun. 2003; 300: 216-222.
34. Sagoo MK, Gnudi L. Diabetic nephropathy: Is there a role for oxidative stress. Free Radic Biol Med. 2018; 116: 50-63.
35. Yehualashet AS, Yikna BB. Microbial Ecosystem in Diabetes Mellitus: Consideration of the Gastrointestinal System. Diabetes Metab Syndr Obes. 2021; 14: 1841-1854.
36. Boer GA, Holst JJ. Incretin Hormones and Type 2 Diabetes-Mechanistic Insights and Therapeutic Approaches. Biology Basel. 2020; 9: 473.
37. Lee YJ, Suh KS, Choi MC, et al. Kaempferol protects HIT-T15 pancreatic beta cells from 2-deoxy-D-ribose-induced oxidative damage. Phytother Res. 2010; 24: 419-423.
38. Kawahito S, Kitahata H, Oshita S. Problems associated with glucose toxicity: role of hyperglycemia-induced oxidative stress. World J Gastroenterol. 2009; 15: 4137-4142.
39. Eriksson JW. Metabolic stress in insulin's target cells leads to ROS accumulation - a hypothetical common pathway causing insulin resistance. FEBS Lett. 2007; 581: 3734-3742.
40. Mengstie MA, Chekol Abebe E, Behaile Teklemariam A, et al. Endogenous advanced glycation end products in the pathogenesis of chronic diabetic complications. Front Mol Biosci. 2022; 9: 1002710.
41. Sivitz WI, Yorek MA. Mitochondrial dysfunction in diabetes: from molecular mechanisms to functional significance and therapeutic opportunities. Antioxid Redox Signal. 2010; 12: 537-577.
42. Sergi D, Naumovski N, Heilbronn LK, et al. Mitochondrial (Dys) function and Insulin Resistance: From Pathophysiological Molecular Mechanisms to the Impact of Diet. Front Physiol. 2019; 10: 532.
43. Lu B, Ennis D, Lai R, et al. Enhanced sensitivity of insulin-resistant adipocytes to vanadate is associated with oxidative stress and decreased reduction of vanadate (+5) to vanadyl (+4). J Biol Chem. 2001; 276: 35589-35598.
44. Rudich A, Tirosh A, Potashnik R, et al. Prolonged oxidative stress impairs insulin-induced GLUT4 translocation in 3T3-L1 adipocytes. Diabetes. 1998; 47: 1562-1569.
45. Dokken BB, Saengsirisuwan V, Kim JS, et al. Oxidative stress-induced insulin resistance in rat skeletal muscle: role of glycogen synthase kinase-3. Am J Physiol Endocrinol Metab. 2008; 294: E615-E621.
46. Haskins K, Bradley B, Powers K, et al. Oxidative stress in type 1 diabetes. Ann N Y Acad Sci. 2003; 1005: 43-54.
47. Dominguez C, Ruiz E, Gussinye M, et al. Oxidative stress at onset and in early stages of type 1 diabetes in children and adolescents. Diabetes Care. 1998; 21: 1736-1742.
48. Matteucci E, Giampietro O. Oxidative stress in families of type 1 diabetic patients. Diabetes Care. 2000; 23: 1182-1186.
49. Varvarovska J, Racek J, Stozicky F, et al. Parameters of oxidative stress in children with Type 1 diabetes mellitus and their relatives. J Diabetes Complications. 2003; 17: 7-10.
50. Matteucci E, Rosada J, Pinelli M, et al. Systolic blood pressure response to exercise in type 1 diabetes families compared with healthy control individuals. J Hypertens. 2006; 24: 1745-1751.
51. Elimam H, Abdulla AM, Taha IM. Inflammatory markers and control of type 2 diabetes mellitus. Diabetes Metab Syndr. 2019; 13: 800-804.
52. Vinagre I, Sanchez-Quesada JL, Sanchez-Hernandez J, et al. Inflammatory biomarkers in type 2 diabetic patients: effect of glycemic control and impact of LDL subfraction phenotype. Cardiovasc Diabetol. 2014; 13: 34.
53. Pickup JC, Chusney GD, Thomas SM, et al. Plasma interleukin-6, tumour necrosis factor alpha and blood cytokine production in type 2 diabetes. Life Sci. 2000; 67: 291-300.
54. Mirza S, Hossain M, Mathews C, et al. Type 2-diabetes is associated with elevated levels of TNF-alpha, IL-6 and adiponectin and low levels of leptin in a population of Mexican Americans: a cross-sectional study. Cytokine. 2012; 57: 136-142.
55. Azar ST, Salti I, Zantout MS, et al. Alterations in plasma transforming growth factor beta in normoalbuminuric type 1

and type 2 diabetic patients. J Clin Endocrinol Metab. 2000; 85: 4680-4682.

56. Piemonti L, Calori G, Mercalli A, et al. Fasting plasma leptin, tumor necrosis factor-alpha receptor 2, and monocyte chemoattracting protein 1 concentration in a population of glucose-tolerant and glucose-intolerant women: impact on cardiovascular mortality. Diabetes Care. 2003; 26: 2883-2889.
57. Sell H, Eckel J. Monocyte chemotactic protein-1 and its role in insulin resistance. Curr Opin Lipidol. 2007; 18: 258-262.
58. Tsalamandris S, Antonopoulos AS, Oikonomou E, et al. The Role of Inflammation in Diabetes: Current Concepts and Future Perspectives. Eur Cardiol. 2019; 14: 50-59.
59. Inzucchi SE. Diagnosis of diabetes. N Engl J Med. 2013; 368: 193.
60. Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. Science. 1993; 259: 87-91.
61. Atkinson MA, Eisenbarth GS, Michels AW. Type 1 diabetes. Lancet. 2014; 383: 69-82.
62. Atkinson MA, Bluestone JA, Eisenbarth GS, et al. How does type 1 diabetes develop: the notion of homicide or beta-cell suicide revisited. Diabetes. 2011; 60: 1370-1379.
63. Willcox A, Richardson SJ, Bone AJ, et al. Analysis of islet inflammation in human type 1 diabetes. Clin Exp Immunol. 2009; 155: 173-181.
64. Thomas HE, Darwiche R, Corbett JA, et al. Interleukin-1 plus gamma-interferon-induced pancreatic beta-cell dysfunction is mediated by beta-cell nitric oxide production. Diabetes. 2002; 51: 311-316.
65. Arif S, Moore F, Marks K, et al. Peripheral and islet interleukin-17 pathway activation characterizes human autoimmune diabetes and promotes cytokine-mediated beta-cell death. Diabetes. 2011; 60: 2112-2119.
66. Rubsam A, Parikh S, Fort PE. Role of Inflammation in Diabetic Retinopathy. Int J Mol Sci. 2018; 19: 942.
67. Kern TS. Contributions of inflammatory processes to the development of the early stages of diabetic retinopathy. Exp Diabetes Res. 2007; 2007: 95103.
68. Adamis AP. Is diabetic retinopathy an inflammatory disease. Br J Opththalmol. 2002; 86: 363-365.
69. Miller JW, Adamis AP, Shima DT, et al. Vascular endothelial growth factor/vascular permeability factor is temporally and spatially correlated with ocular angiogenesis in a primate model. Am J Pathol. 1994; 145: 574-584.
70. Funatsu H, Noma H, Mimura T, et al. Association of vitrious inflammatory factors with diabetic macular edema. Opthalmology. 2009; 116: 73-79.
71. Xu G, Luo K, Liu H, et al. The progress of inflammation and oxidative stress in patients with chronic kidney disease. Ren Fail. 2015; 37: 45-49.
72. Hosseini A, Abdollahi M. Diabetic neuropathy and oxidative stress: therapeutic perspectives. Oxid Med Cell Longev. 2013; 2013: 168039.
73. Rains JL, Jain SK. Oxidative stress, insulin signaling, and diabetes. Free Radic Biol Med. 2011; 50: 567-575.
74. Hurrle S, Hsu WH. The etiology of oxidative stress in insulin resistance. Biomed J. 2017; 40: 257-262.
75. Chen Z, Radjabzadeh D, Chen L, et al. Association of Insulin Resistance and Type 2 Diabetes With Gut Microbial Diversity: A Microbiome-Wide Analysis From Population Studies. JAMA Netw Open. 2021; 4: e2118811.
76. Mayorga-Ramos A, Barba-Ostria C, Simancas-Racines D, et al. Protective role of butyrate in obesity and diabetes: New insights. Front Nutr. 2022; 9: 1067647.
77. Arora T, Tremaroli V. Therapeutic Potential of Butyrate for Treatment of Type 2 Diabetes. Front Endocrinol Lausanne. 2021; 12: 761834.
78. Gojda J, Cahova M. Gut Microbiota as the Link between Elevated BCAA Serum Levels and Insulin Resistance. Biomolecules. 2021; 11: 1414.
79. Newgard CB, An J, Bain JR, et al. A branched-chain amino acid-related metabolic signature that differentiates obese and lean humans and contributes to insulin resistance. Cell Metab. 2009; 9: 311-326.
80. Iatcu CO, Steen A, Covasa M. Gut Microbiota and Complications of Type-2 Diabetes. Nutrients. 2021; 14: 166.
81. Albert BB, Cameron-Smith D, Hofman PL, et al. Oxidation of marine omega-3 supplements and human health. Biomed Res Int. 2013; 2013: 464921.
82. Toorang F, Djazayery A, Djalali M. Effects of Omega-3 Fatty Acids Supplement on Antioxidant Enzymes Activity in Type 2 Diabetic Patients. Iran J Public Health. 2016; 45: 340-345.
83. Khorshidi M, Sayyari A, Aryaeian N, et al. Effects of omega-3 supplementation on endothelial function, vascular structure, and metabolic parameters in adolescents with type 1 diabetes mellitus: A randomized clinical trial. Front Nutr. 2022; 9: 962773.
84. Allaire J, Couture P, Leclerc M, et al. A randomized, crossover, head-to-head comparison of eicosapentaenoic acid and docosahexaenoic acid supplementation to reduce inflammation markers in men and women: the Comparing EPA to DHA (ComparED) Study. Am J Clin Nutr. 2016; 104: 280-287.
85. Caramia G. Essential fatty acids and lipid mediators. Endocannabinoids. Pediatr Med Chir. 2012; 34: 65-72.
86. Zhang Y, He L, Chen X, et al. Omega-3 polyunsaturated fatty acids promote SNAREs mediated GLUT4 vesicle docking and fusion. J Nutr Biochem. 2022; 101: 108912.
87. Iqbal S, Naseem I. Role of vitamin A in type 2 diabetes mellitus biology: effects of intervention therapy in a deficient state. Nutrition. 2015; 31: 901-907.
88. Dakshinamurti K. Vitamins and their derivatives in the

prevention and treatment of metabolic syndrome diseases diabetes. Can J Physiol Pharmacol. 2015; 93: 355-362.

89. Chen H, Karne RJ, Hall G, et al. High-dose oral vitamin C partially replenishes vitamin C levels in patients with Type 2 diabetes and low vitamin C levels but does not improve endothelial dysfunction or insulin resistance. Am J Physiol Heart Circ Physiol. 2006; 290: H137-H145.
90. Tabatabaei-Malazy O, Nikfar S, Larijani B, et al. Influence of ascorbic acid supplementation on type 2 diabetes mellitus in observational and randomized controlled trials; a systematic review with meta-analysis. J Pharm Pharm Sci. 2014; 17: 554-582.
91. Suksomboon N, Poolsup N, Juanak N. Effects of coenzyme Q10 supplementation on metabolic profile in diabetes: a systematic review and meta-analysis. J Clin Pharm Ther. 2015; 40: 413-418.
92. Golbidi S, Badran M, Laher I. Diabetes and alpha lipoic Acid. Front Pharmacol. 2011; 2: 69.
93. Jeyaraman MM, Al-Yousif NSH, Singh Mann A, et al. Resveratrol for adults with type 2 diabetes mellitus. Cochrane Database Syst Rev. 2020; 1: CD011919.
94. Marton LT, Pescinini-e-Salzedas LM, Camargo MEC, et al. The Effects of Curcumin on Diabetes Mellitus: A Systematic Review. Fron Endocrinol. 2021; 12: 669448.
95. Dhanya RA. A Quercetin for managing type 2 diabetes and its complications, an insight into multitarget therapy. Biomed Pharmacother. 2022; 146: 112560.
96. Dhanya R, Arya AD, Nisha P, et al. Quercetin, a Lead Compound against Type 2 Diabetes Ameliorates Glucose Uptake via AMPK Pathway in Skeletal Muscle Cell Line. Front Pharmacol. 2017; 8: 336.
97. Johansen JS, Harris AK, Rychly DJ, et al. Oxidative stress and the use of antioxidants in diabetes: linking basic science to clinical practice. Cardiovasc Diabetol. 2005; 4: 5.
98. Golbidi S, Ebadi SA, Laher I. Antioxidants in the treatment of diabetes. Curr Diabetes Rev. 2011; 7: 106-125.
99. El-Aal AA, El-Ghffar EAA, Ghali AA, et al. The effect of vitamin C and/or E supplementations on type 2 diabetic adult males under metformin treatment: A single-blinded randomized controlled clinical trial. Diabetes Metab Syndr. 2018; 12: 483-489.
100. Vile GF, Winterbourn CC. Inhibition of adriamycin-promoted microsomal lipid peroxidation by beta-carotene, alpha-tocopherol and retinol at high and low oxygen partial pressures. FEBS Lett. 1988; 238: 353-356.
101. Ortiz-Prado E, Dunn JF, Vasconez J, et al. Partial pressure of oxygen in the human body: a general review. Am J Blood Res. 2019; 9: 1-14.
102. Prasad KN. Simultaneous activation of Nrf2 and elevation of antioxidant compounds for reducing oxidative stress and chronic inflammation in human Alzheimer's disease. Mech Ageing Dev. 2016; 153: 41-47.
103. Hashimoto M, Yoshimoto M, Sisk A, et al. NACP, a synaptic protein involved in Alzheimer's disease, is differentially regulated during megakaryocyte differentiation. Biochem Biophys Res Commun. 1997; 237: 611-616.
104. Kirsh VA, Hayes RB, Mayne ST, et al. Supplemental and dietary vitamin E, beta-carotene, and vitamin C intakes and prostate cancer risk. J Natl Cancer Inst. 2006; 98: 245-254.
105. Azad MAK, Sarker M, Wan D. Immunomodulatory Effects of Probiotics on Cytokine Profiles. Biomed Res Int. 2018; 2018: 8063647.
106. Ramsey CP, Glass CA, Montgomery MB, et al. Expression of Nrf2 in neurodegenerative diseases. J Neuropathol Exp Neurol. 2007; 66: 75-85.
107. Bayir H, Adelson PD, Wisniewski SR, et al. Therapeutic hypothermia preserves antioxidant defenses after severe traumatic brain injury in infants and children. Crit Care Med. 2009; 37: 689-695.
108. Lastres-Becker I, Ulusoy A, Innamorato NG, et al. alpha-Synuclein expression and Nrf2 deficiency cooperate to aggravate protein aggregation, neuronal death and inflammation in early-stage Parkinson's disease. Hum Mol Genet. 2012; 21: 3173-3192.
109. Long M, Rojo de la Vega M, Wen Q, et al. An Essential Role of NRF2 in Diabetic Wound Healing. Diabetes. 2016; 65: 780-793.
110. Andero R, Daviu N, Escorihuela RM, et al. 7,8-dihydroxyflavone, a TrkB receptor agonist, blocks long-term spatial memory impairment caused by immobilization stress in rats. Hippocampus. 2012; 22: 399-408.
111. Suh JH, Shenvi SV, Dixon BM, et al. Decline in transcriptional activity of Nrf2 causes age-related loss of glutathione synthesis, which is reversible with lipoic acid. Proc Natl Acad Sci USA. 2004; 101: 3381-3386.
112. Trujillo J, Chirino YI, Molina-Jijon E, et al. Renoprotective effect of the antioxidant curcumin: Recent findings. Redox biology. 2013; 1: 448-456.
113. Steele ML, Fuller S, Patel M, et al. Effect of Nrf2 activators on release of glutathione, cysteinylglycine and homocysteine by human U373 astroglial cells. Redox biology. 2013; 1: 441-445.
114. Kode A, Rajendrasozhan S, Caito S, et al. Resveratrol induces glutathione synthesis by activation of Nrf2 and protects against cigarette smoke-mediated oxidative stress in human lung epithelial cells. Am J Physiol Lung Cell Mol Physiol. 2008; 294: L478-L488.
115. Gao L, Wang J, Sekhar KR, et al. Novel n-3 fatty acid oxidation products activate Nrf2 by destabilizing the association between Keap1 and Cullin3. J Biol Chem. 2007; 282: 2529-2537.
116. Saw CL, Yang AY, Guo Y, et al. Astaxanthin and omega-3 fatty acids individually and in combination protect against oxidative stress via the Nrf2-ARE pathway. Food Chem

Toxicol. 2013; 62: 869-875.

117. Albanes D, Till C, Klein EA, et al. Plasma tocopherols and risk of prostate cancer in the Selenium and Vitamin E Cancer Prevention Trial SELECT. Cancer Prev Res Phila. 2014; 7: 886-895.

118. Bai XY, Ma Y, Ding R, et al. miR-335 and miR-34a Promote renal senescence by suppressing mitochondrial antioxidative enzymes. J Am Soc Nephrol. 2011; 22: 1252-1261.

119. Beriat GK, Ezerarslan H, Akmansu SH, et al. Comparison of efficacy of different treatment methods in the treatment of idiopathic tinnitus. Kulak Burun Bogaz Ihtis Derg. 2011; 21: 145-153.

120. Li W, Khor TO, Xu C, et al. Activation of Nrf2-antioxidant signaling attenuates NFkappaB-inflammatory response and elicits apoptosis. Biochem Pharmacol. 2008; 76: 1485-1489.

121. Kim J, Cha YN, Surh YJ. A protective role of nuclear factor-erythroid 2-related factor-2 Nrf2 in inflammatory disorders. Mutat Res. 2010; 690: 12-23.

122. Abate A, Yang G, Dennery PA, et al. Synergistic inhibition of cyclooxygenase-2 expression by vitamin E and aspirin. Free Radic Biol Med. 2000; 29: 1135-1142.

123. Devaraj S, Tang R, Adams-Huet B, et al. Effect of high-dose alpha-tocopherol supplementation on biomarkers of oxidative stress and inflammation and carotid atherosclerosis in patients with coronary artery disease. Am J Clin Nutr. 2007; 86: 1392-1398.

124. Fu Y, Zheng S, Lin J, et al. Curcumin protects the rat liver from CCl4-caused injury and fibrogenesis by attenuating oxidative stress and suppressing inflammation. Mol Pharmacol. 2008; 73: 399-409.

125. Lee HS, Jung KK, Cho JY, et al. Neuroprotective effect of curcumin is mainly mediated by blockade of microglial cell activation. Pharmazie. 2007; 62: 937-942.

126. Peairs AT, Rankin JW. Inflammatory Response to a High-fat, Low-carbohydrate Weight Loss Diet: Effect of Antioxidants. Obesity Silver Spring. 2008; 16: 1573-1578.

127. Rahman S, Bhatia K, Khan AQ, et al. Topically applied vitamin E prevents massive cutaneous inflammatory and oxidative stress responses induced by double application of 12-O-tetradecanoylphorbol-13-acetate TPA in mice. Chem Biol Interact. 2008; 172: 195-205.

128. Reznick AZ, Cross CE, Hu ML, et al. Modification of plasma proteins by cigarette smoke as measured by protein carbonyl formation. Biochem J. 1992; 286: 607-611.

129. Zhu J, Yong W, Wu X, et al. Anti-inflammatory effect of resveratrol on TNF-alpha-induced MCP-1 expression in adipocytes. Biochem Biophys Res Commun. 2008; 369: 471-477.

130. Prasad KN. The Simultaneous Activation of Nrf2 and Antioxidant Compounds may reduce the Risk, Progression, and Improve the Management of Diabetes by Reducing Oxidative and Inflammatory Damages. J Nutr Health Sci. 2022; 101: 1-6.

131. Huda MN, Kim M, Bennett BJ. Modulating the Microbiota as a Therapeutic Intervention for Type 2 Diabetes. Front Endocrinol Lausanne. 2021; 12: 632335.

132. Mishra SP, Wang S, Nagpal R, et al. Probiotics and Prebiotics for the Amelioration of Type 1 Diabetes: Present and Future Perspectives. Microorganisms. 2019; 7: 67.

133. Gradisteanu Pircalabioru G, Corcionivoschi N, Gundogdu O, et al. Dysbiosis in the Development of Type I Diabetes and Associated Complications: From Mechanisms to Targeted Gut Microbes Manipulation Therapies. Int J Mol Sci. 2021; 22: 2763.

134. Wang B, Yu Z, Yokoyama W, et al. Collagen peptides with DPP-IV inhibitory activity from sheep skin and their stability to in vitro gastrointestinal digestion. Food Biosci. 2021; 42: 101161.

135. Association AD. What are my optionsfor type II diabetes medicatios. Oral and other injectable medicine. Merrifield, Verginia: American Diabetes Association. 2022.

136. Heller SR, Geybels MS, Iqbal A, et al. A higher non-severe hypoglycaemia rate is associated with an increased risk of subsequent severe hypoglycaemia and major adverse cardiovascular events in individuals with type 2 diabetes in the LEADER study. Diabetologia. 2022; 65: 55-64.

137. Livingstone R, Boyle JG, Petrie JR, et al. A new perspective on metformin therapy in type 1 diabetes. Diabetologia. 2017; 60: 1594-1600.

138. Rao L, Ren C, Luo S, et al. Sodium-glucose cotransporter 2 inhibitors as an add-on therapy to insulin for type 1 diabetes mellitus: Meta-analysis of randomized controlled trials. Acta Diabetol. 2021; 58: 869-880.

139. Janzen KM, Steuber TD, Nisly SA. GLP-1 Agonists in Type 1 Diabetes Mellitus. Ann Pharmacother. 2016; 50: 656-665.