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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

Prasad KN*

PhD, 245 El Faisan Drive, San Rafael, CA 94903, USA

***Corresponding author:** Prasad KN, Ph.D. Retired Professor (University of Colorado Medical School), Engage Global, Inc., 245 El Faisan Drive, San Rafael, CA, 94903, USA, Tel: 415-686-6251, E-mail: knprasad@comcast.net

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Abstract

Despite extensive research, the incidence of diabetes continues to increase, and the management of diabetes needs improvement, because in 2016, more than 100,000 patients had lower extremity amputated, suffered ischemic heart disease and stroke. Analysis of investigations indicates that increased oxidative stress and chronic inflammation enhance the risk, progression, diabetic–related complications, and reduce effectiveness of drug therapy. Therefore, simultaneously attenuation of these cellular abnormalities may help in reducing the risk of development, progression, and prolonging the effectiveness of drug therapy. Although supplementation with a single micronutrient produced it yielded impressive beneficial effects in animal models of diabetes, inconsistent beneficial effects were observed in patients with diabetes. Simultaneous increase in the levels of antioxidant enzymes through the activation of Nrf2 (nuclear transcriptional factor-2), and dietary and endogenous antioxidant compounds through supplementation may be necessary to decrease oxidative and inflammatory damages at the same time in patients with diabetes. This review proposes a comprehensive mixture of micronutrients which would increase the levels of antioxidant enzymes thorough the activate Nrf2, and endogenous antioxidant compounds through supplementation, and thereby, simultaneously reduce oxidative stress and inflammation. This mixture is likely to reduce the risk of development, progression, and improve the efficacy of drug therapy in the management of diabetes.

Teaching points

- Prevalence of diabetes varies among ethnic groups in the USA.
- Enhanced oxidative stress and chronic inflammation are major contributors to the development and progression of diabetes and diabetic-related complications.
- Reasons for inconsistent benefits with the use of a single antioxidants in diabetes
- Proposed micronutrient mixture may simultaneously reduce oxidative stress and chronic inflammation in diabetes

This micronutrient mixture may reduce the incidence, progression, and improve the efficacy of drug therapy in diabetes

Keywords: Nuclear Transcriptional Factor Nrf2; Antioxidant Enzymes, MicroRNAs, Diabetes, Antioxidants Compounds, Prevention, Oxidative Stress, Chronic Inflammation

Introduction

Diabetes mellitus is characterized by hyperglycemia that results from insufficient or lack of production of insulin by the pancreas and is referred to as type 1 diabetes. Hyperglycemia may also occur due to insulin resistance which is caused by a defect in the glucose transporter proteins, insulin receptors or both, and is referred to as type 2 diabetes. The incidence of primarily diabetes type 2 has reached epidemic proportions throughout the world including the USA. In the USA, about 19 million people had diabetes in 2010; this number increased to 21 million in 2012 and 34.2 million (10.5%) in 2018. There were 88 million Americans with pre-diabetic condition in 2018. The numbers of undiagnosed cases were 7 million in 2010, 8 million in 2012, and 7.3 million in 2018. The prevalence of diabetes increases with age. In 2018, 26.8% of people 65 years or older had diabetes. It also depends upon the ethnicity. Age-adjusted prevalence of diabetes among 18 years and older in the USA was 14.8% among American Indian/Alaska Natives. The prevalence was 12.5% among Hispanic, 11.7% among non-Hispanic Black, 9.2% among Non-Hispanic Asian, and 7.5% among Non-Hispanic White [1]. There are 422 million diabetic cases world-wide.

Despite extensive studies, the numbers of diabetes cases continue to increase in the USA. One of the reasons could be that the current recommendations, such as losing weight, doing daily moderate exercise, eating a balanced diet, and stopping of tobacco smoking are not being followed. The current drug therapy utilizes initially one drug but later requires multiple drugs to control glucose levels in the blood. Despite these treatments, diabetic relations complications such as retinopathy, nephropathy, peripheral neuropathy, and heart diseases develop. In 2016, 130,000 patients had lower extremities amputated, 438,000 had ischemic heart disease, and 313,000 had stroke [1]. One of the reasons could be that the current drug treatments do not significantly affect the levels of oxidative stress and chronic inflammation at the same time. Therefore, it is essential to develop an additional guideline which is based on cellular damages that contribute to the development and progression of type 2 diabetes. A review has proposed that increased oxidative stress and chronic inflammation are primarily contributors to the development and progression of type 2 diabetes as well as to all diabetes-related complications [2]. Additional investigations on the role of oxidative stress in the initiation and progression of diabetes have been reported [3-11]. Enhanced oxidative damage, if not repaired, causes the development of chronic inflammation, which releases free radicals, pro-inflammatory cytokines, complement proteins, adhesion molecules, and prostaglandins, all of which are toxic. This issue has been discussed in a previous review [2]. Since then, additional investigations on the role of chronic inflammation in diabetes have been reported [12-20]. Strongest evidence for the role of oxidative stress in diabetes comes from the investigation that showed that the levels of markers of oxidative damage were increased in pre-diabetic patients [6]. In addition, the levels of markers of oxidative damage were elevated in the parents of type 1 diabetes as well as in the children with type 1 diabetes [21-23]. Oxidative and inflammatory damages can impair function of glucose transporter proteins and insulin receptors that lead to hyperglycemia in type 2 diabetes. Continued oxidative stress and chronic inflammation eventually impair the ability of pancreas to produce insulin. These studies suggest that simultaneous attenuation of oxidative stress and chronic inflammation may be one of the rational strategies for reducing the risk of initiation and progression of diabetes as well as for improving the efficacy of drug therapy. To address this issue, previous studies have utilized a single antioxidant primarily in animal models of diabetes. These antioxidants include vitamin A, vitamin C, vitamin D, vitamin E, alpha-lipoid acid, n-acetylcysteine, L-carnitine, coenzyme Q10, folic acid and thymine, omega-3-fatty acids, and metal chromium. The studies on the effects of these individual antioxidants in diabetes have been previously reviewed [2]. Treatment with a single antioxidant produced beneficial effects ranging from some improvement to none in animal models and in patients with diabetes [24-26]. Other antioxidants, such as sulphoraphane, riboflavin, curcumin, resveratrol, alpha-lipoic acid, vitamin C, omega-3-fatty acids, and coenzyme Q10, when used individually, produced similar results in animal models of diabetes and human diabetes [27-34]. Some studies suggested that supplementation with resveratrol alone had no effect on glycemic control [35], selenium had no effect on insulin resistance [36], and chromium compound had no effect on glycated hemoglobin (A1C) in patients with type 2 diabetes [37]. One of the reasons for the above inconsistent results is that a single antioxidant is not sufficient to reduce oxidative stress and chronic inflammation at the same time in all sub-cellular compartments of the cell Other reasons could be that a single antioxidant in a highly oxidative environment of diabetic patients is oxidized and then acts as a pro-oxidant rather than as an antioxidant.

Antioxidants compounds decrease oxidative damage by scavenging free radicals, but they also reduce chronic inflammation [38-45]. The antioxidant enzymes reduce oxidative stress in part by a mechanism that is different from that of antioxidant compounds; they destroy free radicals by catalysis, whereas antioxidant compounds remove them by scavenging.

It has been proposed that simultaneous enhancement of the levels of antioxidant enzymes through the activation of Nrf2 (nuclear transcriptional factor-2), and in the levels of dietary and endogenous antioxidant compounds by supplementation may be necessary to optimally reduce oxidative stress and chronic inflammation at the same time (Prasad, 2015). The levels of antioxidant compounds can easily be enhanced by an oral supplementation; however, increasing the levels of antioxidant enzymes require an activation of a nuclear transcriptional factor-2 Nrf2.

This review briefly describes the activation and regulation of Nrf2 levels. It also proposes a mixture of micronutrients that can reduce the risk of development, progression of diabetes, and improve the effectiveness of drug treatment. This micronutrient mixture may achieve the above goal by simultaneously reducing oxidative stress and chronic inflammation by enhancing the levels of antioxidant enzymes through activating the Nrf2 pathway, and dietary and endogenous antioxidant compounds at the same time.

Characteristics of Nrf2

The nuclear transcriptional factor, Nrf2 (nuclear factor-erythroid-2- related factor 2) belongs to the Cap "N" Collar (CNC) family that contains a conserved basic leucine zipper (bZIP) transcriptional factor [46]. Under physiological condition, Nrf2 is associated with Kelch-like ECH associated protein 1 (Keap1) that acts as an inhibitor of Nrf2 [47]. Keap1 protein serves as an adaptor to link Nrf2 to the ubiquitin ligase CuI-Rbx1 complex for degradation by proteasomes and maintains the steady levels of Nrf2 in the cytoplasm. Nrf2-keap1 complex is primarily located in the cytoplasm. Keap1 acts as a sensor for ROS/electrophilic stress.

Activation of Nrf2 requires ROS: Under 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 cytoprotective enzymes including antioxidant enzymes and phase-2-detoxifying enzymes [48-50]. ROS-activated Nrf2 reduces oxidative damage only under acute oxidative stress.

Activation of ROS-resistant Nrf2: It seems that Nrf2 becomes resistant to ROS during chronic oxidative stress [51-53]. This is supported by the observation that increased oxidative damage occurs in diabetic patients despite the presence of Nrf2. The question arises as to how to activate ROS-resistant Nrf2 in these patients.

Requirement of Binding of Nrf2 with ARE for Increasing the Levels of Antioxidant Enzymes

An activation of Nrf2 alone is not enough to enhance the levels of antioxidant enzymes and phase-2-detoxifying enzymes. Activated Nrf2 must bind with ARE in the nucleus for increasing the transcription of genes coding the cytoprotective enzymes including antioxidant enzymes. Older individuals or patients with diabetes have chronic oxidative stress, which can impair the binding ability of Nrf2 with ARE. This was further confirmed in experiment which showed that the binding ability of Nrf2 with ARE was impaired in older rats; however, treatment with antioxidant such as alpha-lipoic acid restored this binding abnormality of Nrf2 [54].

Regulation of the Levels and Activity of Nrf2

Keap1 regulates the levels of Nrf2 by controlling its rate of degradation by the proteasome, whereas Nrf2 regulates Keap1 levels by controlling its transcription [55]. Immediate early response-3 (IER-3) gene, a multifunctional stress response gene, also regulates Nrf2 activity. Deletion of IER-3 gene increases Nrf2 activity, whereas overexpression of IER-3 decreases it [56].

The levels of Nrf2 are also regulated epigenetically by methylation of CpG (cytosine-phosphate-guanosine) and acetylation of histone3. Hypermethylation of CpG [57] and hyperacetylation of histone3 increase the transcription of Nrf2, whereas hypomethylation of CpG and hypoacetylation of histone3 decrease it [58].

Regulation of Activation of Nrf2 by MicroRNAs

MicroRNAs are evolutionary conserved small non-coding endogenous single-stranded RNAs of approximately 22 nucleotides in length, and are present in all living organisms including humans [59-62]. Each miRNA binds with 3'-UTR of the specific mRNA causing its degradation, and thereby, reducing the formation of its target protein [61]. Deregulation of the levels of miRNAs is involved in the pathogenesis of diabetes; however, the role of microRNAs in regulating the activation of Nrf2 is briefly described here.

Diabetic mice with nephropathy had reduced expression of miR-200a and increased expression of miR-21 [63]. Treatment of mice with curcumin analog C66 that exhibits antioxidant and anti-inflammation activities increased the expression of renal miR-200a which inhibited its target protein Keap1, an inhibitor of Nrf2, that allows activation of Nrf2. Treatment of mice with C66 reduced the expression of miR21 that increases the activation of Nrf2. MiR-21 binds with the 3'-UTR mRNA of Nrf2; and therefore, decreased expression of miR-21that would allow enhanced levels of Nrf2 that would migrate to the nucleus where it binds with ARE to enhance the transcription of antioxidant enzymes. Thus, miR-200a enhances Nrf2 activation by inhibiting Keap1 levels, whereas miR-21 increases the levels of Nrf2 by binding to the Nrf2 mRNA. Thus antioxidant can activate Nrf2 by increasing the expression of miR200a and decreasing the expression of miR21.

Deregulation of Nrf2 in Diabetes

Enhanced oxidative stress and chronic inflammation are present in diabetic patients despite the availability of Nrf2. This indicates that an activation of Nrf2 becomes resistant to ROS in this disease. The expression of Nrf2 mRNA and Nrf2 protein were decreased in the skin of patients with diabetes compared to the skin of normal individuals [64]. Expression of Nrf2 was reduced, and the levels of 3-nitrityrosine (a marker of oxidative damage) and phosphorylation of extracellular signal-related kinase (ERK) were elevated in the heart tissue of streptozotocin-induced diabetic mice and diabetic patients [65]. The same investigation revealed that treatment with insulin increased the transcription of Nrf2 in these mice. Treatment with H2O2 (hydrogen peroxide) induced insulin resistance and increased phosphorylation of ERK in cultured cardiomyocytes. Induction of increased expression of Nrf2 restored insulin sensitivity and reduced ERK phosphorylation in H2O2 treated cardiomyocytes. Treatment of streptozotocin-induced diabetic Nrf2 (+/+) mice with sulforaphane, an activator of Nrf2, reduced oxidative stress and pathological changes in the kidney, and improved renal function in Nrf2 (+/+). However, no such effect was observed in diabetic Nrf2 (-/-) mice [66]. The rate of wound healing in streptozotocin-induced diabetic mice lacking Nrf2 (-/-) was slowed compared to diabetic mice with Nrf2 (+/+). Activation of Nrf2 by pharmacological agents improved diabetic wound healing [67]. These studies showed that Nrf2 would be a useful target for developing new drugs that would be useful for the treatment of diabetes and diabetic-related complications [68; 69]. However, activation of Nrf2 alone may not be adequate to optimally reduce oxidative stress and chronic inflammation. This is due to the fact that the levels of antioxidant compounds are also reduced in diabetic patients; therefore, their levels must also be simultaneously increased. Some antioxidant compounds that activate ROS-resistant Nrf2 by a ROS have been identified. These studies are described here.

Antioxidant Compounds Activate ROS-Resistant Nrf2

Some antioxidant compounds, such as vitamin E and genistein [70], alpha-lipoic acid [54], curcumin [71], resveratrol [72,73], omega-3-fatty acids [74,75], glutathione [76], NAC [77], and coenzyme Q10 [78] activate ROS-resistant Nrf2. Antioxidants activate ROS-resistant Nrf2 by altering the expression of microRNAs [63].

Proposed Micronutrient Mixture may Simultaneously Reduce Oxidative Stress and Chronic Inflammation

Failure of individual antioxidant to produce consistent significant benefits in prevention or treatment of diabetic patients led us to propose a micronutrient mixture containing vitamin A, natural mixed carotenoids, vitamin C , vitamin E, curcumin, resveratrol, alpha-lipoic acid, coenzyme Q10, a synthetic antioxidant N-acetylcysteine (NAC), vitamin D3, all B-vitamins, and minerals selenium and zinc. This micronutrient mixture may optimally reduce oxidative stress by simultaneously enhancing the levels of antioxidant enzymes through activation of the Nrf2/ARE pathway and antioxidant compounds. Activation of Nrf2 [79,80] and some antioxidant compounds also decrease chronic inflammation [38-45]. Therefore, the proposed micronutrient mixture may simultaneously reduce oxidative stress and chronic inflammation in patients with diabetes.

Proposed Micronutrient Mixture may reduce the Risk of Development and Progression of type 2 Diabetes

Except the recommendations of modifying the diet and lifestyle, there a no pharmacological approaches to reduce the risk of initiation and progression of type 2 diabetes. Although these recommendations are valuable, they have had no significant impact in reducing the incidence of diabetes. The proposed mixture of micronutrients may be effective in decreasing the incidence of type 2 diabetes. Individuals who are obese with no pre-diabetic conditions are suitable for testing the efficacy of proposed micronutrient mixture together with modifications in diet and lifestyle in reducing the risk of developing diabetes.

Individuals who are pre-diabetic or those who have a family history of diabetes but have not developed symptoms of the disease are suitable for determining the efficacy of proposed micronutrient together with modifications in diet and lifestyle in reducing the progression of diabetes.

Proposed Mixture of Micronutrients May Delay the Onset and Progression of Type 1 Diabetes

At present, there are no strategies to delay the onset and progression of symptoms in children with a family history of type 1 diabetes. Because of attenuation of oxidative and inflammatory damages by daily consumption of the proposed mixture of micronutrients before the onset of hyperglycemia, the onset and progression of symptoms of type 1 diabetes may be delayed. Such a micronutrient mixture for the same reasons may also reduce insulin doses for maintaining the levels of glucose within normal range.

Proposed Mixture of Micronutrients in Combination with Drug Therapy

Despite the use of medications, diabetes and diabetic-related complications continue to progress due to the fact that oxidative stress and chronic inflammations are not simultaneously and optimally attenuated by these treatments. The proposed micronutrient in combination with drug therapy may decrease the progression and the risk of diabetic –related complications by reducing oxidative stress and chronic inflammation, and by improving glucose transport and its utilization. Because of reduction of oxidative and inflammatory damages by this micronutrient mixture, the doses and number of drugs needed to maintain the levels of glucose within normal range may be reduced.

Conclusions

Several investigations have suggested that increased oxidative stress and chronic inflammation contribute to the initiation and progression of type 2 diabetes. Certain antioxidants may activate ROS- resistant Nrf2, which may enhance the levels of antioxidant enzymes. However, this may not be sufficient to optimally reduce oxidative stress and chronic inflammation, because the levels of dietary and endogenous antioxidant compounds are also depleted under the high oxidative environment of patients with type 2 diabetes. Therefore, their levels must also be enhanced by supplementation. The proposed micronutrient mixture may simultaneously decrease oxidative stress and chronic inflammation by enhancing the levels of antioxidant enzymes through activating the Nrf2/

ARE pathway, as well as dietary and endogenous antioxidant compounds by supplementation. Such a micronutrient mixture may reduce the risk of developing and progressing type 2 diabetes, and may improve the efficacy of drug therapy by slowly reducing the need for multiple drugs for maintaining the glucose levels within the normal range. This micronutrient mixture may also reduce the rate of progression of Type1 diabetes and may also reduce the dose of insulin needed to control glucose levels in the blood.

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Conflicts of Interest

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

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