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The research and development on the antioxidants in prevention of diabetic complications

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ABSTRACT

Diabetes mellitus can damage the eyes, kidneys, nerves and heart. Microvascular and macrovascular disorders are the leading causes of morbidity and mortality in diabetic patients. Hyperglycemia can increase the indicators of lipid peroxidation and oxidative stress in which free radicals have the main role in the pathogenesis of these complications. Therefore, antioxidants which combat oxidative stress should be able to prevent and repair free radicals induced damages. Although free radicals contribute to kidney damage, atherosclerosis, diabetes, heart disease, nephrotoxicity and hepatotoxicity; however, clinical trials do not uniquely confirm a substantial impact on diabetic damage. It seems that antioxidants in vegetables, fruits and grains help preventing diabetes complications; however, there is little evidence that taking single antioxidants such as vitamin E or vitamin C protect these complications. The findings about combination antioxidants are also complicated and not entirely clear. In this review paper we tried to present the role of oxidative stress on micro-vascular complications of type 2 diabetes mellitus. Other objective of this paper is to review the new findings about the role of various antioxidants on prevention and treatment of diabetes mellitus as well as its complications including retinopathy, nephropathy and neuropathy.

1. Introduction

The prevalence of diabetes among adults has been increased significantly worldwide. It has been predicted that the number of adults with diabetes will increase from 135 million in 1995 to 30 million in 2025. The age range of diabetic patients in developing and developed countries is between 45–64 and 63–65 years, respectively. Diabetes is the fourth leading cause of death globally and every 1 min 6 persons die from the complications of diabetes [1].

Diabetic causes arterial diseases in conjunction with neuropathy which accounts for more than 60% of all non-traumatic amputations in the United States. Diabetes mellitus and impaired glucose tolerance increase cardiovascular disease risk up to 8-fold [2]. Furthermore, new blood vessel growth is impaired in response to ischemia in diabetic patients, resulting in decreased collateral vessel formation in ischemic hearts and in non-healing foot ulcers [3].

A high-fat diet has also been shown to release free radicals and contribute to impairment of β-cell function and also damage to mitochondrial DNA. Interesting studies have shown that hyperglycemia even in non-diabetic rats can increase muscle protein carbonyl content and increase the levels of malondialdehyde and 4-hydroxynonenal, indicators of lipid peroxidation and oxidative stress. These biomarkers of insulin resistance and oxidative stress suggest that free radicals have significant role in the pathogenesis of insulin resistance and impaired insulin signaling [4]. Therefore, antioxidants which combat oxidative stress should be able to prevent and repair free radical induced damages.

Free radicals are mainly reactive oxygen species (ROS) consisting of superoxide free radicals, hydrogen peroxide, singlet oxygen, nitric oxide (NO) and proxy nitrite. While on the one hand hyperglycemia increases free radical production, on the other hand it impairs the endogenous antioxidant defense system [5,6]. Antioxidant defense mechanisms include both enzymatic and nonenzymatic strategies. Common antioxidants

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include vitamins A, C and E, glutathione, and the enzymes superoxide dismutase, catalase, glutathione reductase and also α-lipoic acid, coenzyme Q10, several bioflavonoids, cofactors (folic acid, vitamins B1, B2, B6, B12), and antioxidant minerals (copper, zinc, selenium, and manganese) [7]. Medicinal plants are the most important source of antioxidants which seem to act on various diseases better than the above mentioned ones [8–10]. So, the aim of this study was to present the effect of oxidative stress on micro-vascular complications of type 2 diabetes. Better knowledge in this field can facilitate designing interventional studies for preventing or averting micro-vascular complications in diabetic patients. Other objective of this paper is to review the available data about the impacts of these two kinds of antioxidants on vascular complications of diabetes mellitus including retinopathy, nephropathy and neuropathy.

2. The mechanisms of diabetes induced tissue damage

Hyperglycemia, and in diabetic microvasculature, intracellular hyperglycemia, have been shown to cause tissue damage through 5 major mechanisms:

1. Increase in expression of the receptor for advanced glycation end products (AGEs) and its activating ligands;
2. Increase in intracellular formation AGEs;
3. Increase in flux of glucose and other sugars through the polyol pathway;
4. Activation of protein kinase C isoforms;
5. Overactivity of the hexosamine pathway.

All five mechanisms have been shown to be activated by mitochondrial overproduction of reactive oxygen species (ROS). In contrast, diabetic macrovascular and heart damage, are resulted from increased oxidation of fatty acids, resulting from pathway-specific insulin resistance [11].

Many cellular pathways that cause insulin resistance and diabetic complications have linked to the production of free radicals and oxidative stress. Early effects of elevated glucose may increase the presence of potentially protective pathways but prolonged exposure of elevated glucose can cause formation of ROS and can be detrimental even after glucose control. Excessive levels of free radicals cause damage to cell lipid membranes, cell proteins and nucleic acids, which finally may cause cell death [12,13]. Besides, elevation of ceruloplasmin during hyperglycemia is suggestive of elevated ROS. Oxidative stress can trigger the onset of diabetes mellitus by decreasing insulin sensitivity and damaging the β-cells of pancreas ROS can penetrate through β-cell membranes and destroy those cells [12].

Hyperglycemia can cause increased production of ROS in different cell types. For example with increase in age in type 2 DM in rat models, elevated levels of 8-hydroxydeoxy guanosine (8-OHdG) and hydroxynonenal (HNE)-modified proteins in pancreatic β-cells have been reported. Studies have shown that acute glucose surge in addition to chronic hyperglycemia can promote oxidative stress mechanisms during type 2 DM [12].

Oxidative stress and apoptotic cell death during disorders such as diabetes mellitus are significantly associated with impairment in cellular energy maintenance and mitochondrial function. ROS exposure can lead to the opening of the mitochondrial membrane permeability transition pore, reduction of mitochondrial β-nicotinamide adenine dinucleotide (NAD^+) stores, and thereby apoptotic cell injury. Free fatty acids also can lead to ROS release, mitochondrial DNA damage, and impaired pancreatic β-cell function [14].

ROS can oxidize the DNA, protein and lipid and have an important role of chronic diseases like diabetes [15]. Elevated oxidative stress in diabetics is claimed to promote the development of myocardial injury, retinopathy, nephropathy, and neuropathy. The possible mechanisms of oxidative stress in developing these complications include glucose autoxidation, decreased tissue concentration of low molecular weight antioxidants like glutathione and vitamin E, and deteriorated activation of antioxidant defense enzymes such as catalase and superoxide dismutase (SOD) [1]. Experimental and clinical studies indicate that increase in oxidative stress may be responsible for progressing risk of cardiovascular diseases in diabetic or insulin-resistant states because of elevated levels of glucose [16–18]. Common risk factors for cardiovascular diseases amongst non-diabetic, insulin-resistant, and diabetic patients are reasonable because pathologies for cardiovascular diseases amongst these three groups of patients are very similar, although the progression and severity of the pathologies are not the same. However, it is not clear whether oxidative stress is causing micro-vascular pathologies because micro-vascular pathologies are noticed only in the diabetic state and are freely associated with hyperglycemia. In contrast, microvascular pathologies such as predicate loss and meningeal expansion, which contribute to diabetic retinopathy and nephropathy, respectively, are not reported in the aging populations or insulin-resistant state in spite of the fact that they experience oxidative stress to a similar level as diabetes [19].

Thus, an increase in oxidative stress induced by free fatty acids, lipids, or other processes is not sufficient to cause micro-vascular complications of diabetes. It is still possible that oxidative stress may promote the micro-vascular pathologies although it is unlikely that micro-vessel pathologies of diabetes are initiated by oxidative stress [15].

Lastly, the damage caused by oxidative stress is likely to be tissue specific because hyperglycemia appears to increase oxidant production in many cell types and tissues that do not manifest significant pathologies [19].

3. Oxidative stress and diabetic retinopathy

Diabetic retinopathy is one of the most important causes of blindness in adults. The reasons of this complication are micro-vascular damage, swelling of blood vessels and fluid leak. If diabetic retinopathy not prevented, new vessels grow and finally retinal detachment will be occurred [20]. The occurrence of this disease depends on the duration of diabetes and rarely develops in first few years of diabetes but the incidence increases to 50% by 10 years and 90% by 25 years of diabetes. The increase in survival of diabetic patients has been lead to increase in prevalence of diabetic retinopathy. The retina has high content of polysaturated fatty acids and has the highest uptake of oxygen and also highest oxidation of glucose. As a result retina is more prone to oxidative stress. The correlation between hyperglycemia, oxidative stress and changes in the redox homeostasis is the main phenomenon in the pathogenesis of diabetic retinopathy. It has been suggested that oxidative stress contributes not only to the development of diabetic retinopathy but also in the resistance of it even

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