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Major review

Implication of oxidative stress in progression of diabetic retinopathy

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ABSTRACT

Diabetic retinopathy, a severe sight-threatening complication of diabetes mellitus, accounts for a large number of cases of acquired, yet potentially avoidable, blindness. The principal mechanism of its pathogenesis appears to be alterations in the microvasculature of retina as the result of hyperglycemia. The elevated concentration of blood glucose is a harbinger of numerous molecular changes. These lead to various responses that result in microangiopathy. Oxidative stress, one such response, is attributed to disruption in the homeostasis of free radical production during the various vital processes such as the electron transport chain reaction and the scavenging mechanisms designed to neutralize these damaging molecules. This imbalance has been linked to the pathophysiology of diabetic retinopathy. Excessive formation of free radicals influences almost all pathways involved in normal human physiology. Thus, hyperglycemia-induced oxidative stress is one of the factors associated with biochemical changes. These changes are further responsible for the various structural and functional abnormalities seen in diabetic retinopathy.

1. Introduction

Diabetes mellitus is one of the most common disorders, accounting for up to 26 million cases in the United States alone. Another 79 million people are considered prediabetic. Thus, almost one-third of America's population is already enmeshed in this disorder.[11] Diabetes mellitus results in persistently elevated levels of blood glucose—hyperglycemia. This is caused either by insufficient secretion of insulin from pancreatic beta-cells or by the unresponsiveness of various receptor cells to insulin. The former condition represents type 1 (or insulin-dependent) diabetes mellitus, whereas the latter corresponds to type 2 (or insulin-independent) diabetes mellitus. The hyperglycemia subsequently leads to various abnormalities in the microvasculature in different regions of the body. Such microvascular abnormalities in the retina lead to certain characteristic events such as neovascularization, macular edema, and retinal detachment. These events are the markers of retinal damage caused during hyperglycemia and indicate the progression of diabetic retinopathy. Diabetic retinopathy is one of the most common complications of diabetes mellitus. According to a survey, diabetic retinopathy accounted for almost 28.5% (4.2 million) of the total cases of blindness in those ages more than 40 years during 2005-2008 in the US.[63] Oxidative stress is considered as one of the critical factors involved in the etiology of diabetic retinopathy. This

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involvement is because of its capability to induce numerous alterations in the biochemical pathways essential for normal physiology. These alterations are responsible for progression of microangiopathy in the capillaries of the retina and, hence, affect both anatomy and function.[29]

2. Oxidative stress

2.1. *What are free radicals?*

Oxidative stress is a pathologic condition in which there is an imbalance between the formation and destruction of free radicals. Free radicals can be defined as the chemical species that contain a single unpaired electron in their outermost valence shell and have the capability of independent existence. Because of the presence of this unpaired electron, these species can easily undergo chemical reactions that involve donation or acceptance of an electron from other chemical compounds. Various types of free radicals are formed regularly in the cells as a result of the electron transport chain reaction in the mitochondria, various metabolic processes, and some other means, such as exposure to certain exogenous substances like x-rays, ozone gas, cigarette smoking, various types of atmospheric pollutants, and numerous industrial chemicals, but are kept in check by the free radical-scavenging mechanisms and antioxidants. The most potent free radicals are those that contain an oxygen atom, such as superoxide radical, hydroxyl radical, and hydrogen peroxide radical. These are commonly termed as reactive oxygen species (ROS) and are regarded as extremely toxic.[31,44] The condition of oxidative stress arises when either the free radicals are formed in large excess or the antioxidants (such as vitamin A, C and E, glutathione, alpha-lipoic acid, carotenoids, numerous bioflavonoids), antioxidant minerals (such as copper, zinc, manganese, and selenium), or various other radical-degrading mechanisms (e.g., enzymatic scavenging of free radicals, which involves certain enzymes such as superoxide dismutase, glutathione peroxidase, and glutathione reductase) fail to destroy the number of free radicals being formed. In short, any situation that disrupts the homeostasis of the rate of formation and destruction of the free radicals gives rise to oxidative stress and eventually damages the cells.[21,29,31]

2.2. *How do free radicals affect our body?*

The free radicals (particularly superoxide radical) formed in the body, although in a limited number, are utilized by our immune system to destroy the microorganisms that invade cells. This destructive nature is due to the reactive temperament of free radicals; however, as the effective number of free radicals increases, their toxicity becomes lethal to cells.[37] Exposure to free radicals causes cell damage in several forms, including severe destruction of vital structural units via lipid peroxidation (thus, ruining cellular membranes), mitochondrial damage (disrupting the formation of ATP molecules), damage to protein structures (impairing the physiology of various enzymes and receptors, resulting in abnormal functioning of concerned biomolecules and their related biochemical pathways), and structural damage to DNA (accounting for abrupt changes in the genetic order). The aforementioned damages interfere with various normal physiologic processes required for supporting and maintaining vital life-sustaining pathways.[6,15,16,48]

2.3. *How does hyperglycemia lead to oxidative stress?*

Before describing how oxidative stress leads to the progression of diabetic retinopathy, let us first discuss how hyperglycemia originates oxidative stress. Glucose metabolism prominently takes place via 2 pathways: glycolysis and citric acid cycle. In both these pathways, carbon dioxide and reduced forms of nicotinamide adenine dinucleotide (NAD^+) and flavin adenine dinucleotide (FADH), such as NADH and $FADH_2$, respectively, are formed as metabolic by-products. These reduced forms (NADH and $FADH_2$) play a vital electron-donating role in the electron transport chain reaction, resulting in the generation of adenosine triphosphate, along with the reduction of oxygen to superoxide radical. The formation of free radicals during this reduction reaction occurs physiologically, every day. Nevertheless, they are produced in quite low amounts and are efficiently removed via various radical-scavenging mechanisms and antioxidants. With increasing glucose concentration, a hallmark of diabetes mellitus, excess amounts of NADH and $FADH_2$ are produced that, upon entering the electron transport chain, generate a surfeit of superoxide radicals, hence unbalancing the free radical homeostasis, ultimately resulting in oxidative stress.[49] Moreover, during hyperglycemia, glucose auto-oxidation increases. This event sets up a voltage gradient across the mitochondrial membrane. Subsequently, after achieving a threshold voltage value, transfer of electrons inside complex III in the electron transport chain is blocked. This interruption in electron transfer leads to their accumulation at coenzyme Q, which donates these accumulated electrons to molecular oxygen present in the cells, hence leading to superoxide radical formation. Thus, the events described previously make mitochondria the main site of production of superoxide radicals during hyperglycemia, leading to oxidative stress.[61]

Of interest, obesity is typically involved in the etiology of type 2 diabetes mellitus. Obesity is one of the greatest risk factors for insulin resistance. The molecular mechanism behind it is best explained by obesity-induced inflammation. The adipose tissue primarily comprises of fat cells called adipocytes. These are responsible for releasing macrophage chemoattractant protein-1 (MCP-1), the function of which is to recruit macrophages, leading to their accumulation in adipocytes. The recruited macrophages release a variety of inflammatory mediators, such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and IL-1β. These further cause the induction of inducible nitric oxide synthase, resulting in secretion of excess amount of nitric oxide. Nitric oxide reacts with superoxide radicals (produced by mitochondria during electron transport chain reaction) to generate peroxynitrite, one of the most highly reactive species. Peroxynitrite increases oxidative stress and leads to nitrosylation and other post-translational modifications, such as tyrosine nitration, of various proteins. Insulin is one such protein whose signaling alters after the previously described post-translational modifications, leading to insulin resistance. Moreover, insulin