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OXIDATIVE STRESS AND DIABETES MELLITUS - A REVIEW

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Abstracts

Humans are exposed to a wide variety of substances, resulting in the production of reactive species called free radicals (ROS). Free radicals are formed as a by-product of normal cell metabolism. However, several factors are known to disrupt the balance between ROS production and cellular defense mechanisms. This imbalance leads to cellular dysfunction and destruction, leading to tissue damage. Aggravated ROS production can directly lead to structural and functional changes in proteins, lipids, and nucleic acids. It also regulates several intracellular signaling pathways that lead to insulin resistance and impaired β-cell function. Additionally, ROS generation due to hyperglycemia is contributing complication of diabetes mellitus. The antioxidant system is developed in the human body to play a vital role in the biological system to protect against free radicals. The aim of this review is to elaborate on the basics of oxidative stress and Diabetes Mellitus.

Keywords: Oxidative Stress, Antioxidant, Free Radical, Diabetes Mellitus.

1. Introduction

Diabetes mellitus**"** is derived from the Greek words dia (=through), bainein (=togo), diabetes translates to "pass-through" and mellitus means sweet. It is a metabolic disorder that affects nearly 17 million people worldwide. It is considered one of the leading causes of death globally [1]. The disease causes weight loss just as body mass passes through the urine. Although it has been known for centuries that the urine of diabetics is pleasant, a doctor named Willis coined the term diabetes mellitus [2]. It is characterized by hyperglycemia caused by a deficiency in insulin secretion, insulin function, or both. Several factors such as hyperlipidemia and enhanced oxidative stress play an important role in the pathogenesis of diabetes mellitus [3]. The disease is progressive and has been linked to an increased risk of consequences [4].

2. Classification of Diabetes Mellitus

Different forms of Diabetes Mellitus are

General: Type 1 diabetes mellitus (formerly called insulin-dependent diabetes mellitus).

- Auto-immune type 1 diabetes mellitus (type 1A)
- Non-autoimmune or idiopathic type 1 diabetes mellitus (type 1B)

Type 2 diabetes (also known as non-insulin dependent diabetes)

Specific: defined gene mutations: Maturity-onset diabetes of youth (MODY)

3. Pathophysiology

Carbohydrates and glucose specifically are a significant wellspring of energy for most living organisms. The majority of the blood glucose during a fast is provided by the liver and utilized by the brain without the help of insulin. After a meal, the rise in blood glucose level rapidly stimulates insulin secretion, resulting in increased glucose transport, metabolism, and storage by muscle and adipocytes within minutes. In addition, insulin inhibits glucagon secretion and lowers serum free acid concentrations, contributing to the sharp decline in hepatic glucose production. Ina normal person about half the glucose ingested is converted into energy through the glycolytic pathway and about half is stored as fat and glycogen with the help of insulin and other enzymes. Insulin production is more or less constant within the beta cells, regardless of blood glucose levels, insulin production within beta cells remains almost unchanged. It is stored inside vacuoles and excreted through exocytosis, which is primarily stimulated by food, mainly a diet containing absorbent glucose. The main stimulus is an increase in blood glucose levels after eating.

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Pathogenesis of Type I Diabetes Mellitus

Three interconnected mechanisms are responsible for the destruction of islets cells:
1. Genetic susceptibility 2. Auto Immunity 3. environment

a) Pathogenesis of Type-2 Diabetes Mellitus

The two metabolic defects that characterize type-2 diabetes are as follows:
1. A disruption of insulin β cell secretion
2. Reduced response of peripheral tissues to respond to insulin (insulin resistance)

4. Complications of Diabetes

Diabetes patients are more likely to develop the macrovascular disease, such as cerebrovascular disease, coronary artery disease, and peripheral vascular disease, due to atherosclerosis of large vessels and microvascular diseases such as nephropathy and retinopathy, peripheral and autonomic neuropathies and lower extremity disease.

Both types of diabetes can develop complications that are divided into 2 main groups [5].

1. **Acute metabolic complications**: Diabetic ketoacidosis, Hyperosmolar nonketotic coma, and hypoglycemia are examples of acute metabolic complications.
2. **Late systemic complications**: arteriosclerosis, diabetic microangiopathy, diabetic nephropathy, diabetic retinopathy, diabetic neuropathy, and infections. Diabetes is also associated with a significant increase in large vessel atherosclerosis, including heart, brain, and peripheral vascular disease (cardiovascular disease).

5. Oxidative Stress and Diabetes

Oxidative stress and tissue damage are common endpoints in chronic diseases such as atherosclerosis, diabetes, and rheumatoid arthritis [6]. Oxidative stress is now proposed as an underlying mechanism of diabetes and diabetic complications [7]. In diabetes, sustained hyperglycemia increases free radical production, especially reactive oxygen species (ROS), in all tissues due to glucose autooxidation and protein glycosylation (Fig.1). Increased ROS levels in diabetes are due to increased production and/or decreased destruction by nonenzymatic and enzymatic catalase (CAT), reduced glutathione (GSH), and superoxide dismutase (SOD) antioxidants. The levels of these antioxidant enzymes significantly impact the susceptibility of various tissues to oxidative stress and are involved in the development of diabetic complications [8]. Oxidants are produced as a result of normal intracellular metabolism in mitochondria and peroxisomes and from various cytosolic enzymatic systems. Additionally, many external agents can trigger ROS generation. Advanced enzymatic and non-enzymatic antioxidant defense systems, including catalase (CAT), superoxide dismutase (SOD), and reduced glutathione (GSH), counteract total ROS levels to maintain physiological homeostasis.

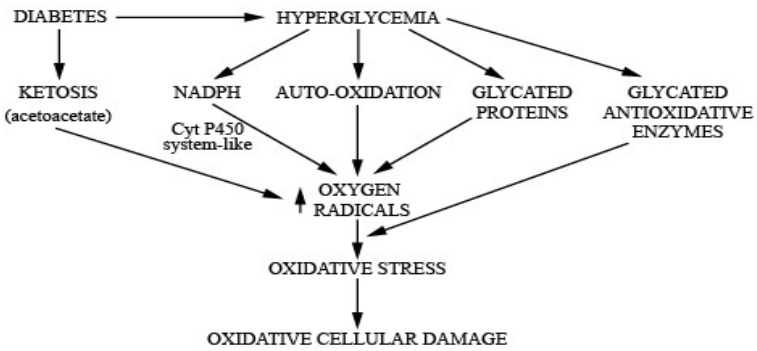

Figure. 1: Features of Hyperglycemia induced Oxidative cell damage

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Reduced Reactive oxygen species levels below the homeostatic set point may disturb the normal function of oxidants in cell proliferation and host defense. Similarly, elevated ROS is also detrimental, causing cell death and accelerating aging and age-related diseases. Traditionally, damage from increased ROS was thought to result from random damage to proteins, lipids, and DNA. In addition to these effects, increased ROS levels may also act as a stress signal activating specific redox-sensitive signaling pathways. Once activated, these different signaling pathways can have potentially harmful or protective functions. (9)

Oxidative stress can result from the overproduction of ROS, an impaired antioxidant system, or a combination of these factors. The main ROS produced during oxygen metabolism is superoxide, which is a highly reactive cytotoxic ROS. Superoxide is balanced against a much less reactive product, hydrogen peroxide (H2O2), by a family of metalloenzymes known as superoxide dismutase (SOD) [10]. The ubiquitous superoxide dismutase (SODs) catalyze the distribution of superoxide to molecular oxygen and peroxide and are therefore essential in the defense of cells against the toxic products of respiration.

Superoxide radicals are commonly produced in aerobic biological systems, and superoxide dismutase (SOD) provides important protection against them (Fig.2). Therefore, SOD is the first line of defense against ROS-mediated damage. In mammalian cells, GSH is one of the most important antioxidants which is a tripeptide containing γ-Glu-Cys-Gly, which plays many cellular functions. In particular, thiol-containing moieties are strong reducing agents [11]. Intracellular GSH is converted to GSSG by the selenium-containing GSH peroxidase, which catalyzes the reduction of H_20_2 in the presence of GSH and GSH peroxidase along with the oxidation of glucose-6-phosphate and 6-phosphogluconate, providing NADPH for reduction of GSSG by GSSG reductase. This is the major pathway of H_2O_2 metabolism in many cells. Therefore, it is important for protecting membrane lipids from oxidation. Intermediates such as O_2 and H_2O_2 are widely formed in biological systems, generating reactive oxygen species and forming organic peroxides. GSH is the major function of destroying reactive oxygen intermediates and free radicals constantly produced in metabolism. [12]

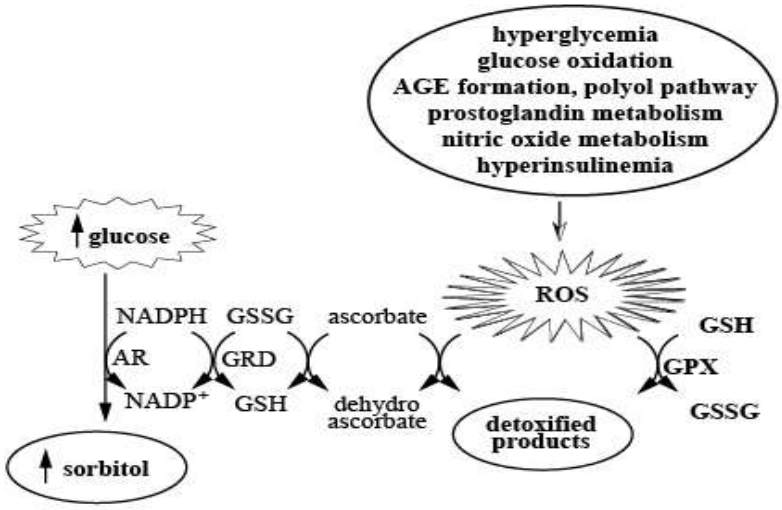

Figure.2: Impact of ROS and causes Cellular oxidative damage

Catalase (CAT, H_2O_2; H_2O_2 oxidoreductase) is an enzyme that breaks down hydrogen peroxide (H_2O_2) into molecular oxygen (O_2) and water (H_2O). This action of catalase is known as catalytic activity (13). It also exhibits peroxidase activity and catalyzes the oxidation of various hydrogen donors in the presence of relatively low concentrations of hydrogen peroxide. When lipids react with free radicals, they undergo peroxidation to form lipid peroxides. Lipid peroxide decomposes to form many products including malondialdehyde [14]. The toxicity of oxygen, or its radical derivatives, is often associated with lipid peroxidation. Lipid peroxidation induced by low-level exposure to nitrogen dioxide seems to occur by splitting the hydrogen atoms or by adding nitrogen

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dioxide to the olefin. The progression of the reaction is largely influenced by the presence of radical scavenging species, especially oxygen (15).

The most common way to measure lipid peroxide is to estimate the malondialdehyde (MDA) content. MDA is produced during lipid peroxidation after breaking the carbon chain of unsaturated fatty acids. The amount of malondialdehyde was then determined by the colorimetric method following a reaction with thiobarbituric acid [16].

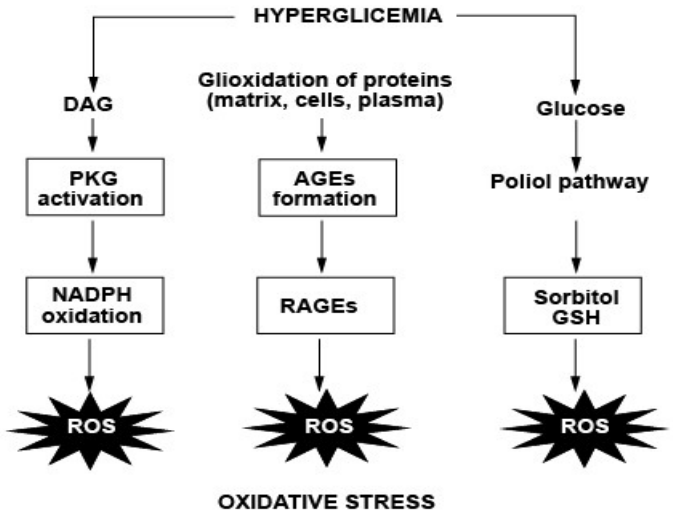

Figure. 3: Hyperglycemic alterations in diabetes

Oxidative stress results from an imbalance between radical-producing and radical-scavenging systems. Increased free radical production, decreased antioxidant defense activity, or both. In humans, oxidative stress is known to play an important role in the development of many diseases and the aging process or may intensify their symptoms (17). The impact of oxidative stress in the pathogenesis of diabetes involves not only the generation of free oxygen radicals, but also non-enzymatic protein glycosylation, impaired glucose auto-oxidation, altered antioxidant enzymes, lipid peroxidation, and decreased levels of ascorbic acid. ROS generation is increased by hyperglycemia, which reduces insulin secretion and action (18). The hallmark of diabetes is insulin deficiency which is connected with hyperstimulation of β-due to chronic hyperglycemia.

Previous studies suggested that increased concentration of glucose and free fatty acids associated with ROS and RNS accumulation may easily impair β-cell function due to abnormal antioxidants in beta cells of the pancreas (19). Additionally, Long-chain acyl-CoAs are produced during the process of increased fatty acid metabolism in β-cells and can keep ATP-sensitive K+ channels in β-cells open to a decline in ATP production and insulin secretion (20). It also affects the insulin gene transcription process. Oxidative stress primarily affects β-cell function in two ways: It reduces insulin secretion and promotes β-cell apoptosis. However, increased ROS production due to hyperglycemia and increased FFAs can lead to insulin resistance by altering insulin signaling and activating proinflammatory signaling proteins (21;22 23.).

Antioxidant defense mechanisms have developed in humans to guard against free radicals. These systems include antioxidants produced by the body (endogenous) and antioxidants obtained from food (exogenous). The first is enzymatic defenses such as glutathione peroxidase, catalase, and superoxide dismutase (which metabolize superoxide, hydrogen peroxide, and lipid peroxides and prevent most of the formation of the toxic radical), and non-enzymatic defense mechanism (24)

The important non-enzymatic antioxidants are Vitamins and minerals. water-soluble types such as vitamin C and fat-soluble vitamins including vitamin A, and E are antioxidants vitamins. Vitamin E is a major scavenger with significant activity in protecting the biomolecules of the biomembrane which is attacked by free radicals (25). The supplementation of antioxidants such as selenium,

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alpha lipoic acid, and vitamins is positively associated with the reduction of diabetes-related complications and improved insulin sensitivity (26). Therefore, antioxidants play a vital role in counteracting free radicals and protecting against various diseases.

6. Conclusion

The pathogenesis and progression of diabetes mellitus are correlated with reactive oxygen species production and oxidative stress which develops the complication of diabetes mellitus by activating major signaling pathways. Numerous studies have reported the link between oxidative stress and diabetes mellitus. Antioxidant therapies are very effective against oxidative stress-induced diabetes complications and it has shown great promise in the management of both type 1 and type 2 diabetes.

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