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An Overview on Oxidative Stress in Diabetes Mellitus

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ABSTRACT

Diabetes mellitus is a complicated metabolic disorder of carbohydrate metabolism that has gravely affected the human health and quality of life. It is a global health crisis, which has been persistently affecting the humanity, irrespective of the socioeconomic profile and geographic location of the population. According to an estimate, every five seconds one person is detected with diabetes somewhere in the world, while someone dies of it every ten seconds. Oxidative stress plays a major role in the onset and progression of diabetes. Many of the common risk factors, such as increased age, unhealthy eating habits and obesity, all contribute to an oxidative environment that may change insulin sensitivity either by increasing insulin resistance or impairing glucose tolerance. The mechanisms by which alteration in insulin sensitivity occurs are often multifactorial and quite complex, involving multiple cell signaling pathways. A common outcome of diabetes is hyperglycemia, which in turn contributes to the progression and disturbance of an overall cellular oxidative status. Oxidative stress seems to be a significant causative agent both in onset as well as progression of diseases.

Keywords : Diabetes Mellitus, Oxidative Stress, Biomarkers

I. INTRODUCTION

Diabetes mellitus, is a chronic metabolic disorder characterized by a high blood glucose concentration-hyperglycemia (fasting plasma glucose > 7.0 mmol/l or plasma glucose > 11.1 mmol/l 2 hours after a meal) – caused by insulin deficiency, often combined with insulin resistance [1]. Diabetes mellitus is a complicated metabolic disorder that has gravely troubled the human health and quality of life. It is a global health crisis, which has been persistently affecting the humanity, irrespective of the socioeconomic profile and geographic location of the population. According to an estimate, every five seconds one person is detected with diabetes somewhere in the world, while someone dies of it every ten seconds [2].

Oxidative stress plays a major role in the onset and progression of diabetes. The development of oxidative stress in the body leads to the generation of free radicals which in turn causes major damage to the body [3]. Further the onset of diabetes is promoted by the oxidative stress as it causes damage to the β-cells and reduces insulin sensitivity [4]. Most common risk factors includes as increased age, unhealthy life style and obesity, all contribute to an oxidative environment that may increase insulin resistance or impairing glucose tolerance. The process by which alteration in insulin sensitivity occurs is often multifactorial and quite complex, involving multiple cell signaling pathways. A common outcome of diabetes is hyperglycemia, which in turn contributes to the progression and disturbance of an overall cellular oxidative status [5]. This review discusses the role of oxidative stress in the diabetes process.

II. Oxidative Stress And Diabetes

The human body is incessantly exposed to free radicals from inside the body (endogenous) and outside the body (exogenous). For production of energy cells need continuous supply of oxygen. During the process of metabolic respiration, the cells take in oxygen, burn it, and release energy [6]. Throughout these metabolic processes, free radicals species are generated; however these free radicals are scavenged by the body's internal

enzymatic and non-enzymatic antioxidant army. Oxidative stress occurs when there is an imbalance occurs between free radical production and scavenging by the anti-oxidants. This imbalance happens for one of two reasons: a) when the body's antioxidant status is decreased, or b) when excessive free radical species are generated [6]. For instance in diabetes, due to hyperglycemia there is an increased speed of endogenous free radical generation and reduction in antioxidant status, which leads to diabetic oxidative stress. It is this oxidative stress which plays pivotal role in the progression and the development of diabetes and its complications [6]. Ha et al (2000), reported that oxidative stress is one of the prominent factor for vascular complications in diabetes including nephropathy [6].

Several mechanisms, including autoxidative glycosylation, formation of AGEs (advanced glycation end products), and increased polyol pathway activity contribute to increased oxidative stress as shown in Figure 1. In hyperglycemic condition auto-oxidation of glucose can generate tremendous reactive oxygen species, which is believed to be the main source of free radicals. During hyperglycemic condition glucose in presence of transition metals gets oxidized to an enediol radical anion that is converted into superoxide radical species and ketoaldehydes. The superoxide anion radicals gets dismutated into hydrogen peroxide, which in the presence of transitional metals can lead to production of extremely reactive hydroxyl radicals [7]. Superoxide anion radicals can also react with nitric oxide to form reactive peroxynitrite radicals. During hyperglycemia, lipid peroxidation of low density lipoprotein (LDL) can be promote by a superoxide-dependent pathway to produce free radical species [8].

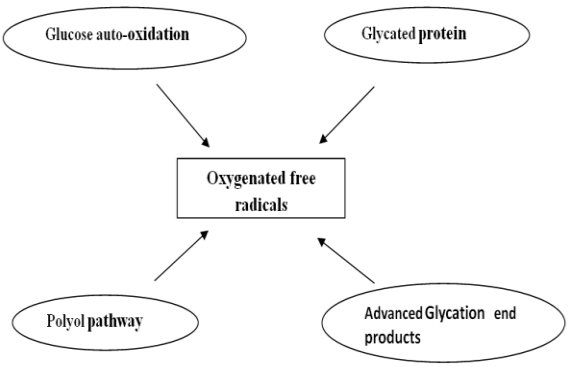

Figure 1: Mechanisms involved in glucose-induced oxidative stress

Another important free radical generating source in diabetes is protein glycation. In glycation condensation of glucose with the ε-amino group of lysine, the α-amino group of an N-terminal amino acid or the amines of nucleic acids occurs, which leads to the formation of advanced glycation end products (AGEs). Glycation has been the major source of increased generation of ROS in diabetes patients [9]. AGEs are supposed to be responsible in the genesis of most of the irreversible complications of diabetes, including vascular complication expanded extracellular matrix, hyperplasia, and cellular hypertrophy [10]. In addition to glucose-induced oxidative stress by glycol-oxidation product formation, fructose which is elevated as a result of polyol pathway activation also leads to the formation of AGE precursor's like glyoxyl, methylglyoxal and 3-deoxyglucosone [11]. These AGEs, via their receptors (RAGEs), inactivate enzymes by altering their structures, increases free radicals formation, and suppress the activity of nitric oxide. Elevation in intracellular oxidative stress results in activation of the transcription factor NF-κB, which promotes up-regulation of various NF-κB controlled target genes [12]. NF-κB promotes generation of nitric oxide, which is supposed to be a mediator of pancreatic β-cell damage. In addition, prolonged hyperglycemia promotes glycation of antioxidant enzymes, which could alter their structure and function such that they are unable to scavenge free radicals, exacerbating oxidative stress in diabetes [12]. Therefore, the process of glucose oxidation promotes not only increased ROS products but also for decrease bioavailability of cellular antioxidant status.

Biomarkers of Diabetic oxidative stress

Antioxidant defense system in the cell includes glutathione (GSH), as well as antioxidant enzymes such as catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione S-transferase (GST), and glutathione reductase (GRx). Because of their ability to scavenge for and attenuate the effects of ROS, these enzymes serve as biomarkers of oxidative stress.

Lipid peroxidation

Induction of diabetes in rats with diabetogens like alloxan and streptozotocin uniformly promotes an increase in thiobarbituric acid reactive substances (TBARS), an indirect confirmation of intensified free-radical production. MDA has been considered as a

potential primary biomarker of free radical mediated lipid damage and oxidative stress [13]. Elevation in lipid peroxidation is also a confirmation of decline in defense mechanisms of cellular antioxidant currency [14]. Lipid peroxidation of cellular structures promotes atherosclerosis in diabetic patients. In diabetic patients, TBARS in the red blood cells as well as in serum are significantly higher while as reduction in erythrocyte antioxidant status [15, 16]. Thus preventing/reducing the formation of reactive oxygen species would be an efficient means to reduce free radical induced cellular damage, and several antioxidant compounds have been tested in diabetic animal models with varying success.

Glutathione Levels

Reduced glutathione is an important cellular redox buffer having concentrations up to 10 mM [17]. Glutathione may act as a direct free-radical scavenger, as a cofactor for many enzymes, and as a co-substrate for glutathione peroxidase activity [18]. In chemically induced diabetic animals glutathione concentration is found to be decreased in the kidney [19], liver [16] pancreas [20].

Glutathione Peroxidase and Glutathione Reductase Glutathione peroxidase (GPx) converts harmful hydrogen peroxide to water in presence of reduced glutathione as a co-substrate [21]. Glutathione reductase converts oxidized glutathione back to glutathione using the NADPH as a cofactor. In chemically induced diabetic animals glutathione peroxidase and glutathione reductase concentration is found to be decreased in liver [22] and pancreatic [20] tissue.

Superoxide Dismutase

Superoxide dismutase (SOD) is one of the important antioxidant enzyme that neutralize the highly reactive oxygen species superoxide anion (O2−) by dismutation into hydrogen peroxide and molecular oxygen [23]. SOD protects against cellular and histological damages that are produced by ROS which in turn reduces diabetic complications [24]. During development of diabetic nephropathy, superoxide dismutase acts as a major defender in its progression. Down regulation of renal SOD promotes the progression of diabetic nephropathy [25].

Catalase

Nearly every living organism is bestowed by catalase due its potential antioxidant activity. It has been reported that catalase plays a vital role in attenuating oxidative stress-generated diabetic complications [26]. During oxidative stress pancreatic □-cells are protected by catalase from destructive hydrogen peroxide reactive species [27].

III. CONCLUSION

In diabetes mellitus, oxidative stress seems to be a significant causative agent both in onset as well as progression of diseases. Stressful oxidative environment created by hyperglycemic promotes the development of β-cell dysfunction, insulin resistance, impaired glucose tolerance, and mitochondrial dysfunction, which can ultimately lead to the development of diabetic complications. Due to the high prevalence of diabetes at the population level, it imposes great financial problems both on healthcare system and the individuals living with this metabolic disorder. It is important that each country in the world should implement preventive and curative measures [28]. Oxidative stress induced by prolonged hyperglycemia promotes activation of series of stress pathways diabetic complications. Thus there is a need to monitor daily life style in order to avoid hyperglycemia, so that redox state of diabetic patient remain balanced.

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