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Medical Biochemistry

"CORRELATION BETWEEN OXIDATIVE STRESS MARKERS AND DIABETIC CATARACT"

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ABSTRACT Reactive oxygen species causes oxidation that interferes with the physiological processes of the cell. Oxidative stress is defined as an "imbalance between reactive oxygen species production and breakdown by endogenous antioxidants. It causes hazardous events such as lipid peroxidation and oxidative DNA damage. The reactive oxygen species (ROS), which consist principally of molecules like the superoxide anion (O2 −), hydrogen peroxide (H2O2), and hydroxyl radicals, are detoxified by enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px). Different factors such as aging, drug actions and toxicity, inflammation and chronic metabolic disorders like diabetes the production of ROS far exceed the capacity of antioxidants to neutralize. Due to oxidative stress, pancreatic β cell function may be affected, which, given the impaired expression of antioxidant enzymes, is outstandingly sensitive to reactive oxygen species. Oxidative stress in diabetes causes the over production of superoxide radicals in endothelial cells of large and small vessels, as well as in the myocardium and leads to many micro and macro vascular complications. The use of antioxidants, especially those with multiple antioxidant biomolecules like vegetables, fruits and seeds can be effective in preventing complications of diabetes.

KEYWORDS :

Diabetes Mellitus:

Diabetes mellitus (DM) is a complex metabolic disease. It is a major health problem all over the world. As per WHO estimates, it's expected that by 2030 the number of patients with diabetes are going to be nearly double. It is characterized by decrease insulin secretion or insulin action related to chronic hyperglycemia and disturbances of carbohydrate, lipid, and protein metabolism. As a consequence of the metabolic derangements in diabetes, various complications develop including both Macro vascular and micro vascular dysfunctions **[1].** In diabetic patients, long term damage, dysfunction and failure of different organs, especially the eyes (diabetic retinopathy and cataract), kidneys (diabetic nephropathy), nerves (diabetic neuropathy), heart (myocardial infarction) and blood vessels (atherosclerosis) are related to uncontrolled hyperglycemia.

Oxidative Stress

Exceptionally under some circumstances, oxygen could also be a killer of cells when it generates reactive species that causes necrosis and ultimately the necrobiosis. By certain mechanism reactive oxygen species causes oxidation that interferes with the physiological processes of the cell **[2]**. Oxidative stress, defined as an imbalance between reactive oxygen species production and breakdown by endogenous antioxidants, later due to different factors such as aging, drug actions and toxicity, inflammation and chronic metabolic disorders like diabetes the production of ROS far exceed the capacity of antioxidants to neutralize. The reactive oxygen species (ROS), which consist principally of molecules like the superoxide anion (O2−), hydrogen peroxide (H2O2), and hydroxyl radicals, are detoxified by enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-Px) and Xanthine oxidase (XOD). Free radical-induced damage in oxidative stress has been confirmed as a contributor to the pathogenesis and Patho-physiology of the many chronic health problems like neurodegenerative conditions (Parkinson, Alzheimer, Huntington's disease and amyotrophic lateral sclerosis) emphysema, cardiovascular and inflammatory diseases, cataracts and cancer **[3]**. A free radical is any atom or molecule that contains one or more unpaired electrons in its outer orbital. This reactive oxygen species modify the function of all classes of biomolecules, targeting most substrates within the cell. Lipids are the most vulnerable to undergo oxidation: polyunsaturated fatty acids, especially arachidonic acid and omega-3 fatty acid , which form malondialdehyde and 4-hydroxynonenal, recognized markers of lipid oxidative decay.

Relation Of Oxidative Stress And Diabetes:

Oxidative stress has been implicated in the pathogenesis of type 2 diabetes and its complications. The imbalance between reactive oxygen species production and breakdown by endogenous antioxidants like catalase (CAT—enzymatic/non-enzymatic), superoxide dismutase (SOD) and glutathione peroxidase (GSH–Px), xanthine oxidase (XOD), malondialdehyde (MDA) makes the tissues susceptible to oxidative stress leading to the development of diabetic complications **[4]**. According to epidemiological studies, diabetic mortalities can be explained notably by an increase in vascular diseases apart from hyperglycemia **[5]**.

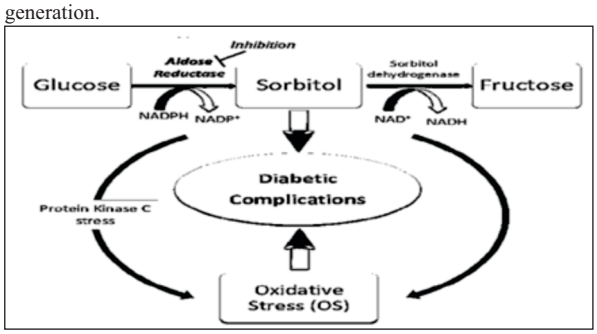
Due to oxidative stress, pancreatic β cell function may be affected, which, given the impaired expression of antioxidant enzymes, is outstandingly sensitive to reactive oxygen species. The ROS interact with the substrates which are involved within the insulin intracellular signaling **[6]**. It causes an elevated sugar (glucose) amounts and enhances the flow of reduced coenzymes (NADH and FADH2) within the mitochondrial membrane. Due to voltage gradient, the mitochondrial membrane attains a critical threshold blocking complex III, which enables ubiquinone reduction by electrons. CoQH2 can subsequently reduce molecular oxygen and finally generating superoxide radical anion **[7]**. During development and progression of diabetes, several mechanisms for the pathogenesis of diabetic complications had been proposed. They include the polyol pathway **[8]**, non-enzymatic glycation **[3, 9]**, protein kinase C (PKC) **[10]**, hexosamine **[11]**, and overproduction of superoxide by the mitochondrial electron transport chain **[12].**

Mechanisms Involved In The Pathogenesis Of Oxidative Stress In Diabetes Mellitus:

1. Contribution Of Polyol Pathway In Diabetes: (13)

The polyol pathway is a glucose-shunt that channels excess glucose to

form fructose. The polyol pathway consists of 2 reactions catalyzed by 2 respective enzymes; the first reaction is reduction of glucose to sorbitol, which is catalyzed by aldose reductase (AR). This reaction is the rate-limiting reaction of this pathway and also converts NADPH to NADP+. The second reaction converts sorbitol to fructose and this reaction is catalyzed by sorbitol dehydrogenase, which makes NADH from NAD+. NADH is a substrate for NADH oxidase leading to production of superoxide anions **[14]**. When fructose is metabolized into fructose-3-phosphate and 3-deoxyglucosone so it is more potent non-enzymatic glycation agent than glucose **[15].** Thus, the influx of glucose through the polyol pathway would increase advanced glycation end products (AGEs) formation, ultimately leading to ROS generation.



2. Advanced Glycation End Products (AGEs):

High glucose produces ROS as a result of glucose auto-oxidation, metabolism and the development of AGEs. The term 'autoxidative glycosylation' describes the suggested role of reducing sugars as catalysts of oxidative chemical modification and cross-linking of proteins. Autoxidative glycosylation is initiated by the oxidation of an aldose or ketose to a more reactive dicarbonyl sugar, which would then react with a protein. AGEs can propagate oxidative stress in the cells and fluids in which it is produced. AGEs play an important role in the development of diabetic complications. The reduced oxygen products formed in the autoxidation reaction include superoxide, the hydrogen radical and hydrogen peroxide which, in the presence of metal ions, would cause oxidative damage to neighboring molecules. The molecules, such as aminoguanidine and pyridoxamine, work to trap glycoxidation intermediates and impede crosslink formation **[16]**. It causes hardening of the vessel walls with loss of their elasticity and increased vascular permeability **[17]**. AGEs combine with the receptors called RAGE and activate signal transduction pathways, which in turn activate NADPH oxidase that produces ROS and NFkB, a nuclear transcription factor. An imbalance between ROS (ROS) production and antioxidant scavenging has been implicated in Type 2 diabetes **[18]**. ROS are a byproduct in Type 2 diabetes, generated during protein glycation and as a consequence of RAGE binding; they impair insulin signaling pathways and induce cytotoxicity in pancreatic β cells **[19].**

3. Lipid Peroxidation:

Lipid peroxidation is a free radical chain reaction formed by removal of a hydrogen atom from a molecule and leaves an unpaired electron due to the attack of reactive oxygen species, namely superoxide radical, hydroxyl radical, nitric oxide radical etc. **[20]**. Polyunsaturated fatty acids are particularly prone to free radical attack because the presence of double bond weakens the carbon hydrogen bond at the adjacent carbon atom. The remaining carbon centered around the radical undergoes molecular rearrangement resulting in the conjugate diene. An increase in malondialdehyde an end product of the oxidation of polyunsaturated fatty acids and reduced glutathione levels are found in erythrocytes from diabetic subjects. Oxidative destruction of polyunsaturated fatty acids by lipid peroxidation is causes damage as it may alter the integrity of cell membranes **[21]**. Diabetes is linked with a high blood glucose level and the high lipid content of the adipose tissues during obesity. This leads to increase in the size of adipocytes and thus leading to the generation of phospholipase A2. This activation of phospholipase A2 finally leads to the process of lipid peroxidation **[22]**.

Diabetic Cataract:

Cataract is a leading cause of visual disability and blindness throughout the world **[23].** Clouding of lens or lens opacity which results in a poor visual outcome is termed as cataract. Epidemiologic studies have indicated that half of the general population older than 50 has cataract **[24]**. In developing countries, 50–90% of all blindness is caused by cataract **[25]**. Over 50 million people worldwide suffer from cataracts and the number will increase as individuals in the current generation grow older **[26]**. Currently, there is no effective medical treatment for cataract except surgery. For these reasons, there is much interest within the prevention of cataract as an alternative to surgery. Cataract formation is influenced by various factors which include aging, diabetes mellitus, malnutrition, hypertension, drugs, trauma, toxins, genetics and other ocular diseases. Cataract formation occurs in both diabetic (osmotic cataract) and non-diabetic (senile cataract) subjects **[27]**.

Among the varied causes, oxidative stress is taken into account to play a key role within the molecular mechanism of cataract formation. There are various mechanisms that have been implicated in the development of cataract formation such as excessive tissue sorbitol concentrations, abnormal glycosylation of lens proteins, and increased free-radical production in the intraocular region. They may result in an increasing clouding of the lens until the whole lens loses its normal transparency and becomes white and opaque **[28]**.

It is a universal truth that life is not possible without oxygen but free radicals and reactive oxygen intermediates (ROI) have been implicated in a wide variety of degenerative diseases including cataractogenesis **[29]**. Systemic diseases, long term complications of diabetes such as non-enzymatic glycation and autoxidation of glucose may have significant effects on the antioxidant status of diabetic subjects. However, chronic oxidative stress generated by the polyol pathway is likely to be an important contributory factor in the slow and progressive development of diabetic cataract.

Mechanism Of Action Of Antioxidants:

Antioxidants counter the action of free radicals by several mechanisms. These mechanisms include:

1) Enzymes that degrade free radicals,
2) Proteins such as transferrin that can bind metals which stimulate the production of free radicals.
3) Antioxidants such as vitamins C and E that act as free radical scavengers **[30]**.

Antioxidant functions by lowering oxidative stress, DNA mutations, malignant transformations, as well as other parameters of cell damage. In a study, the total antioxidant capacity in plasma of type1 diabetics was shown to be 16% lower than that of normal subjects **[31]**. In another study total antioxidant power was reported to be higher in plasma and saliva of diabetic patients suggesting existence of increased free radical production **[32]**. Oxidative reactions play an important role in human life, they can also be harmful; hence, plants and animals preserves the diverse systems of various antioxidants, such as glutathione, lycopene, beta-carotene, carotenoids, selenium, flavonoids and natural vitamins together with vitamin C, vitamin A, and vitamin E, antioxidant enzymes including glutathione S. transferase, superoxide dismutase, catalase and peroxidase. Antioxidant phytochemicals reduce the complications of chronic diseases such as diabetes, heart disease and obesity **[33].** Phytochemicals regulate the activity of α-glucosidase and lipase due to their antioxidant properties, and reduce glycemic levels, improve pancreatic function, and have synergistic action with hypoglycemic drugs and thus are effective in improving diabetes. Various enzymatic and non- enzymatic antioxidant defense mechanisms play an essential role in eliminating reactive oxygen species. In enzymatic antioxidant system, SOD directly converts superoxide to hydrogen peroxide, followed by detoxification to water either through catalase in the lysosomes or through glutathione peroxidase within the mitochondria. Glutathione reductase is another essential enzyme, which regenerates glutathione which can be used as a hydrogen donor by glutathione peroxidase throughout the elimination of hydrogen peroxide.

CONCLUSION:

In this paper we reviewed the role of oxidative stress in the complications of diabetes. The results suggest that oxidant products including ROS and RNS are increased by glucose metabolism and FFA via multiple pathways resulting in oxidation of major bio-macromolecules like lipids, nucleic acids and proteins, leading to development of conditions like nephropathy, neuropathy, retinopathy, cataract and other disorders. In fact, oxidative stress plays a key role within the onset and progression of the complications of diabetes. Free radical production in body may be a continuous process as a part of normal function, but excess free radical production resulting from various endogenous or exogenous causes might play a key role in onset of diabetes mellitus and its complications. Oxidative stress in diabetes causes the over production of superoxide radicals in endothelial cells

of large and small vessels, as well as in the myocardium and leads to many micro and macro vascular complications. The use of antioxidants, especially those with multiple antioxidant biomolecules like vegetables, fruits and seeds can be effective in preventing complications of diabetes. Despite the potential advantages of antioxidant pharmacotherapy, additional systematic randomized trials are required to explore and assess the efficacy and safety scores of the current therapeutic strategy.

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