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Review Article

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Antioxidants and Oxidative Stress in Diabetes

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Abstract Oxidative stress occurs when there is a disturbance in the balance between production of reactive oxygen species and antioxidant defense system. Reactive oxygen species are radicals such as superoxide and hydroxyl while non radical reactive oxygen species are hydrogen peroxide, hypochlorite and singlet oxygen. Auto oxidation of glucose in diabetes, glycation of anti oxidative enzymes and leakage of reactive oxygen species from mitochondria cause increase in oxidative stress in diabetes. Impaired activities of antioxidant defense enzymes such as super oxide dismutase and catalase enhance oxidative cellular stress which can lead to vascular complications in diabetes. However, enzymatic antioxidants such as glutathione peroxide, glutathione reductase and catalase protect the body against the activities of free radicals by catalyzing components of superoxide to molecular oxygen and peroxide. Antioxidants such as Glutathione act as a scavenger as well as a substrate for glutathione peroxides. Non enzymatic antioxidants such as selenium, copper, zinc, ascorbic acid, carotenoids and vitamins also play a role in oxidative stress in diabetes by preventing lipid peroxidation, lowering insulin resistance and improving glucose uptake.

Keywords Oxidative Stress, Antioxidant, Diabetes, Free Radicals

Introduction

Progressive development of type 2 diabetes has been suggested by different research to increase faster with the generation of highly reaction free radicals which are the cause of oxidative stress in diabetes. World wide, it has been considered that diseases such as diabetes are common and becoming prevalent. Oxidative stress has been linked to the pathogenesis of several diseases including diabetes. Oxidative stress is a disturbance that occurs when there is an in balance of antioxidants and reaction oxygen species also called free radicals [1]. This disturbance causes biological damage to bio molecules such as protein, DNA and lipids. Generation of reactive free radicals during hyperglycemia can cause oxidative stress. This generation of free radicals increases the development and progression of diabetes and its complications. Hyperglycemia induces free radicals and impairs the endogenous antioxidant defence system in patients with diabetes. Endogenous antioxidant defense mechanism involves the enzymatic and non-enzymatic pathways. Endogenous antioxidant defense mechanism function in human system to counter balance toxic reactive oxygen species (ROS). Such antioxidants include vitamin A,C, and E, glutathione and the enzymes superoxide dismutase, catalase, glutathione reductase and glutathione peroxidase. The mechanism through which oxidative stress contribute to the development of complications in diabetes is becoming a scientific interest. Experimental and clinical reports show that oxidative stress plays a major role in the pathogenesis and development of complications in diabetes mellitus [1].

Oxidative Stress

Oxidative stress is defined as a disturbance in the balance between the production of reaction oxygen species called free radicals and the body's antioxidants defense system [1]. Oxidative stress occurs when the production of free radicals in the body is greater than the ability of the anti oxidant system to detoxify the free radicals leading to biological damage. Oxidative stress is linked with increased production of oxidizing species and decreases in the effectiveness of antioxidant defenses [2]. Severe oxidative stress can result in cell death and necrosis while moderate oxidation can cause apoptosis [3]. Reactive oxygen species such as superoxide are converted by the oxidoreduction reactions with transition metals into more active radical species which cause massive cellular damage.

Free Radicals

Free radicals are unstable reactive chemicals entities that are short lived species containing one or more unpaired electrons [4]. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are collectively used to describe free radicals and other non- radical reactive derivatives known as oxidants. Biological free radicals are products of normal cellular metabolism. They are unstable and have electrons available to react actively with organic substances such as lipids, proteins and deoxyribonucleic acid (DNA). Over production of free radicals affects biomolecoles such as lipids, proteins and DNA, and eventually lead to the progression of many diseases such as atherosclerosis, diabetics cancer, rheumatoid arthritis, post- ischemic infarction and stroke [1].

Antioxidants

Antioxidants are produced by the body to counteract oxidative stress. They help to 'mop up' free radicals which can harm the human body. Antioxidants are substances whose availability inhibit or delay the oxidation of a substrate. These antioxidants reduce damage due to reactive oxygen species. An antioxidant is a substance that inhibit oxidation of other substances [5].T here are two categories of antioxidant in the human body. These are enzymatic antioxidants and non- enzymatic antioxidants. Enzymatic antioxidants include superoxide dismutase, catalase, glutathione peroxidase and glutathione reductase.

Non enzymatic antioxidants these include low molecular weight compounds like vitamin C, E, B carotene, uric acid and Glutathione. Vitamin C is a water soluble vitamins that provides intracellular and extracellular aqueous phase antioxidant capacity by removing oxygen free radicals [6]. Vitamin E is a lipid soluble antioxidant which is concentrated in the hydrophobic interior site of cell membrane and it is an important antioxidant against oxidant-induced membrane injury. It supplies electron to peroxyl radical during lipid peroxidation and inhibits free radical formation. Glutathione is an antioxidant that is abundant in cell compartments, it detoxifies hydrogen peroxide and lipid peroxide [7]. Glutathione when reduced, donates protons to membrane lipids and prevents them from being attacked by oxidants [8].

Glutathione protects cells by its interaction with pro apoptotic and antiapoptotic signaling pathways [7]. Carotenoids are antioxidants that are in pigments found in plants. It reacts with peroxyl (ROO.) hydroxyl (.OH) and superoxide ($O-_2$) radicals. Carotenoids show antioxidant effects in low oxygen concentrations but exhibit pro-oxidant effects at higher oxygen concentrations.

Sources of Reactive Oxygen Species

Reactive oxygen specie can occur from endogenous source and exogenous source.

Reactive oxygen species occur as a result of normal cellular metabolism. They can occur as free radicals or non radicals. Physiogically occurring free radicals are superoxide anion, hydroxyl radical and hydrogen peroxide.

Hydroxyl radical takes part in lipid peroxidation when it collects electron from polyunsaturated fatty acids. It is a very reactive oxygen species that can cause protein, lipids and DNA damage.

Free radicals trigger lipid peroxidation chain reaction when they remove hydrogen atom. The lipid radicals react with oxygen to produce peroxyl radicals which initiates a chain reaction and transform poly unsaturated fatty acid into lipid hydroperoxides.

Exogenouse sources of oxidants such as Cigarette smoke contains superoxide and nitric oxide [9]. Ozone exposure is another exogenouse source of oxidants which cause lipid peroxidation and induce influx of neutrophils into the epithelium. Other sources are hyperoxia [10], ionizing radiation and heavy metals/lead. Ionizing radiation acts as a source of oxidant when oxygen converts hydroxyl radicals, superoxide and organic radicals into hydrogen peroxides which react with redox active metal ions such as iron and copper through Fenton reactions [11].
Heavy metal ions/ lead induce the generation of reactive radicals which deplet enzyme activities through lipid peroxidation and reaction with proteins and DNA [12].

Oxidative Stress and Diseases

Oxidative stress is implicated in the development of cancer, Parkinson's disease, Alzheimer's disease, atherosclerosis, heart failure, myocardial infarction, fragile X syndrome, Sickle Cell Disease, vitiligo, autism, infection, Chronic fatigue syndrome, Aging, chronic fatigue syndrome and depression. Reactive oxygen species shows some advantages as they can be use by the immune system to attack and kill some pathogens. Oxidative stress is connected to certain cardiovascular disease because oxidation of Low Density Lipoproteins occurs in vascular endothelium and this is a precursor to plaque formation. Oxidative stress is important in ischemic cascade due to oxygen reperfusion injury after hypoxia. This ischemic cascade includes strokes and heart attacks. Oxidative stress is likely to be involved in age-related development of cancer. The reactive species can cause damage to the DNA and are involved in mutagenic. The reactive species can result in apoptosis, promote proliferation, invasiveness and metastasis.

Diabetes

Diabetes is a group of metabolic diseases characterized by high levels of blood sugar (hyperglycemia). It results from defects in insulin production and/or insulin action, and impaired function in the metabolism of carbohydrates, lipids and proteins which leads to long term health complications [13]. There are four main types of diabetes namely type I diabetes, idiopathic diabetes, type ll diabetes and Gestational diabetes mellitus.
Type I diabetes (Insulin dependent) is due to immune mediated beta-cells destruction, leading to insulin deficiency. *Idiopathic diabetes* is the diabetes with no known etiologies and is strongly inherited. *Type II diabetes* (Non-Insulin dependent) is due to insulin secretory defect and insulin resistance. *Gestational diabetes mellitus* is any form of intolerance to glucose with onset or first recognition of pregnancy.
However diabetes is mostly classified basically into TWO major types: Type I Diabetes (IDDM) and Type II Diabetes (NIDDM) [13]. Insufficient insulin or resistance to insulin in the body results in reduced tissue uptake of glucose that results in intracellular hypoglycemia and extracellular hyperglycemia. The intracellular hypoglycemia causes glucogenesis and gluconeogenesis that leads to fats breakdown (causing diabetic ketoacidosis) and decreases protein synthesis and gamma globulins, while the extracellular hyperglycemia leads to hyperglycemic coma. Complications of diabetes from metabolic source such as infection, diabetic ketoacidosis, polydipsia, polyuria, and fatique enhance the progress of diabetes. Macrovascular complication such as stroke, heart disease, foot problem and hypertension enhance the generation of free radicals. In Insulin dependent diabetes mellitus, deficiency of insulin secretion due to the autoimmune destruction of beta pancreatic cells occurs. β-cell destruction represents the onset of clinical disease leading to type 1 diabetes mellitus . Autoimmunity, genetic makeup and environmental factors are causes of islets cell destruction.
In Non-Insulin dependent diabetes mellitus there are mechanisms that keep regulation between tissue sensitivity to insulin which consequently leads to impaired insulin secretion by the pancreatic beta cells and impaired insulin action through insulin resistance. This type of diabetes is caused by multiple genetic defects, and certain environmental factors especially obesity which is responsible for beta cell defects and peripheral tissue insulin resistance.

Oxidative Stress and Diabetes

Oxidative cellular stress in diabetes occurs when there is increase radical generation and decrease radical elimination, impaired activities of anti-oxidant defence enzymes such as superoxides dismutase and catalase

increases oxidation stress. During auto oxidation of glucose, oxidative cellular stress occurs. In diabetes, glycation of antioxidative enzymes can occur leading to limited ability to remove free radicals. Decrease tissues concentration of low molecule weight anti oxidants such as reduced glutathione can also cause oxidative cellular stress. In type I diabetes, leakage of reactive oxygen species from mitochondria occurs.

Oxidative stress in diabetes occurs as a result of alteration in enzymatic systems. When there is impaired glutathione metabolism and decreased level of vitamin C, oxidative stress occurs in diabetes. Lipid peroxidation is also an important inference of oxidative stress in diabetes.

Complications induced by oxidative stress in diabetes are stroke, retinopathy, neuropathy and nephropathy.

Due to abnormalities in diabetes, superoxides are produced in the mitochondrial and this leads to the activation of five major pathways which involve increased formation of advanced glycation end products (AGE), increased expression of the receptors of AGE activation of protein kinase (PKC) isoforms over activity of hexosamine pathway and polyol pathway influx. Signaling path ways involve in oxidative stress in diabetes involve

Superoxide production induced by hyperglycemia in the mitochondria activities damage path ways .These activities occurs when inhibition of glycerol dehyde-3 phosphate dehydrogenase occurs reactive oxygen species inhibit glyceraldehydes 3 phosphate dehydrogenase through a mechanism involving the activation of enzyme poly-ADP-ribose polymerase-1. Oxidative stress that results from hyperglycemia in diabetes may impair insulin resistance. Reactive oxygen species increases the stress signaling pathways in the beta cells which leads to beta cells apoptosis.

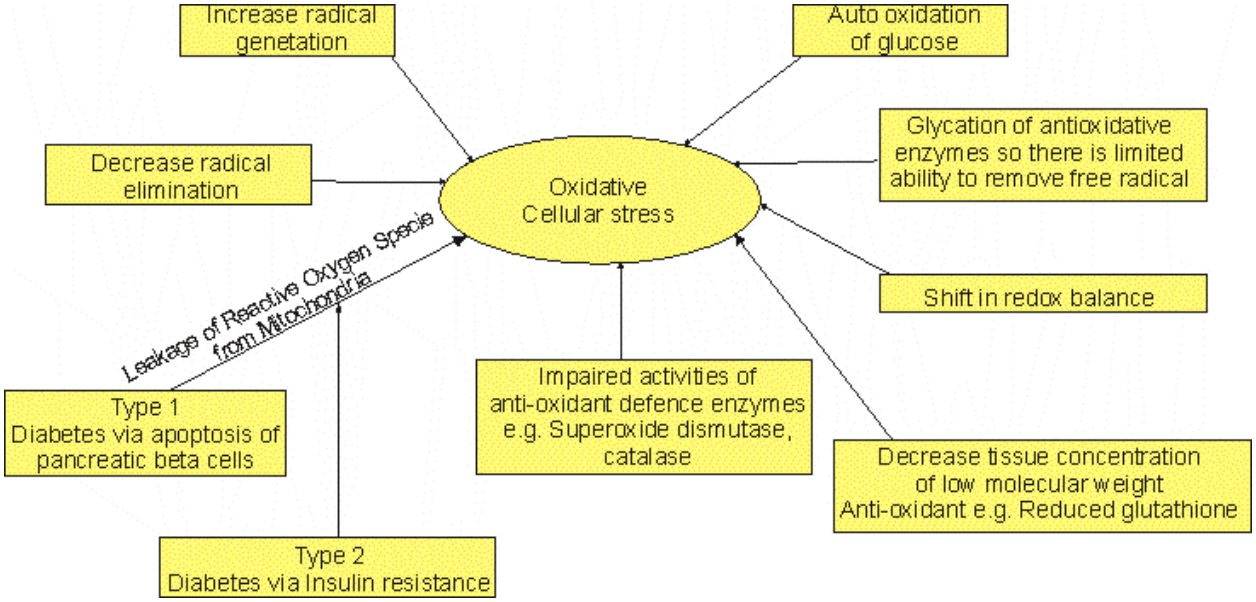

Figure 1: Oxidative Stress and Diabetes

Role of Antioxidants in Oxidative Stress in Diabetes

The body naturally produces anti oxidants like superoxide dismutase, catalase and some peroxidase enzymes to defend it's self against free radicals. They do so by donating hydrogen atoms. Antioxidants have a chelating effect on free radical production that is catalysed by heavy metals that prevent the action of free radicals

Flavenoid antioxidant attach to the DNA forming a barrier of protection against free radical attack. Astaxanthin a powerful antioxidant absorbs excess energy from singlet oxygen, release heat and return the oxygen and it's self back to original state [5] . Non enzymatic antioxidants such as vitamin C plays a role in scavenging reactive oxygen species by undergoing oxidation Glutathione, NADH and NADPH regenerate oxidized products of vitamin C, ascorbic radical and dehydroascorbic radicals. Vitamin E a fat soluble vitamin interacts with lipid hydro peroxides by scavenging them. It plays a combined role with vitamin C in glutathione regeneration when it interacts with lipoic acid. Vitamin A acts as an antioxidant increasing antioxidant non enzymatic defenses has been shown to

ameliorate oxidative stress during the process of diabetes and its complications. The effects of antioxidants on oxidative stress are measured through certain observable biomarkers. These biomarkers are catalases, superoxide dismutase and glutathione reductase as well as thiobarbituric acid reacting substances levels.

Antioxidant defense mechanisms involve both enzymatic and nonenzymatic strategies. There are various non-enzymatic and enzymatic mechanisms for removal of reactive oxygen species. In non-enzymatic antioxidant system includes ascorbic acid, retinol, carotenoids, tocopherols, and trace elements like selenium, copper, zinc, coenzyme Q10, uric acid, factors of folic acid, riboflavin and thiamine. Vitamin E is responsible for prevention of lipid peroxidation.

Glutathione acts as a scavenger as well as a substrate for glutathione peroxidase.

In chronic cardiac complications of diabetes the major organs such heart, kidneys are directly affected by diabetes .In the enzymatic antioxidant defence mechanism, superoxide dismutase and Glutathione reductase are important. Glutathione reductase regenerates glutathione, which can be used as hydrogen donor by glutathione peroxidase through elimination of hydrogen peroxide. SOD converts superoxide to hydrogen peroxide [14]. Enzymatic antioxidants include superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase.

Through normal physiological processes, antioxidants affect signal transduction and regulation of proliferation and the immune response. Vitamin C supplementation is effective in reducing sorbitol accumulation in the red blood cells of diabetics [14].

The use of antioxidant from food or from supplement is an area of study that is increasing in research related to diabetes. Antioxidants prevent and reverse damage due to oxidative stress by minimizing damage to the endothelium. Sources of anti oxidants from food are vitamins A, C, E and beta carotenoids. Some minerals such as manganese, zinc and selenium are good sources of antioxidant. Enzymatic antioxidants, remove the reactive oxygen species directly while non enzymatic antioxidant system have scavenging molecules that are produced endogenously such as uric acid are taken from diet such as vitamin C. Ubiquinone reduce superoxide production by recoupling mitochondrial oxidative phosphorylation. Antioxidants have been developed to treat diabetic complications due to oxidative stress though the use of supplements from plants and vitamins [15]. This is an increasing area of interest in research studies.

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