TARGETING OXIDATIVE STRESS IN DIABETIC COMPLICATIONS: NEW INSIGHTS

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ABSTRACT

This review summarizes the fundamental role of reactive oxygen species in diabetes mellitus pathophysiology. In diabetes mellitus, hyperglycemia is the main causative element of oxidative stress. Hyperglycemia is not only responsible to generate ROS but it also attenuates mechanism of antioxidants via scavenging of substances and enzymes. Diabetes complications caused by oxidative stress includes nephropathy, neuropathy and retinopathy. Free radicals developed are neutralized through exogenous and endogenous antioxidants, in order to protect the cells from their harmful toxic effects. Although, antioxidant therapeutic approach is useful, still it's necessary to assess and investigate the efficacy of this cure strategy.

Keywords: ROS, oxidative stress, diabetic, Hyperglycemia.

INTRODUCTION

Diabetes mellitus, a group of multiple disorders that is caused by defect in action and secretion of insulin. High level of blood glucose termed as hyperglycemia is due to deficiency of insulin which also disturbs metabolism of proteins, fats and carbohydrates (Bastaki, 2005). Diabetes mellitus is subdivided into two types viz Type 1 is insulin dependent (IDDM) and Type 2 is non-insulin dependent (NIDDM). Insulin dependent diabetes mellitus is characterized through breakdown of pancreatic β cells mostly linked to immune-mediated damage (Zhao, 2011). Non-insulin dependent diabetes mellitus alter glucose homeostasis due to resistance or decreased secretion of insulin (Ruhe and McDonald, 2001).

Prolonged hyperglycemia develops micro and macrovascular complication that leads to mortality and morbidity between the affected (Resnick and Howard, 2002). Though efforts have been made to reverse back complications of diabetes for long by glycemic control still, hypoglycemic incidence and high mortality intimate an alternative therapy to resolve this problem (Ismail-Beigi *et al*., 2010).

Now-a-days oxidative stress induced by hyperglycemia has been discerned as the driving force to develop diabetic complications (Kawahito *et al*., 2009). In diabetes, oxidative stress leads to stimulate polyol pathway, activates protein kinase C (PKC), forms AGEs (advanced glycation end products) and ROS (reactive oxygen radicals) (Ceriello, 2003). Hyperglycemia is not only responsible to generate ROS but it also attenuates mechanism of antioxidants via scavenging of substances and enzymes (Ferdinando and Michael, 2010). The basics of oxidative stress in diabetes mellitus discussed by Ullah *et al.* (2016). This review summarized the fundamental role of reactive oxygen species in diabetes.

DIABETES PATHOPHYSIOLOGY

With the intake of meal, level of blood glucose rises which induces secretion of insulin as a result biotransformation, storages and transportation in fat and muscle tissues increases. During fasting, liver is responsible for blood glucose which brain uses, without depending on insulin. Likewise glucose storage, insulin inhibits glucagon secretion and also turns down serum carboxylic acid concentration that leads to decrease production within liver glucose (Kangralkar *et al*., 2010). Extracellular hyperglycemia and intracellular hypoglycemia occurs when glucose consumption reduces due to insulin resistance or deficient insulin in the body. Gluconeogenesis and glucogenesis is caused by intracellular hypoglycemia due to which synthesis of proteins and gamma globulins decreases and breakdown of fats occurs, while the other extracellular hyperglycemia contributes to osmotic dieresis and hyperglycemic coma (Ozougwu *et al*., 2013).

PATHOLOGY OF TYPE-I DIABETES MELLITUS

In Type 1 diabetes mellitus known as insulin dependent diabetes mellitus (IDDM) secretion of insulin is deficient due to destruction of autoimmune pancreatic beta cells which is responsible for disturbances in metabolic process (Ozougwu *et al*., 2013). This Insulin dependent diabetes mellitus (IDDM), a clinical disease is the end stage

destruction of β-cells, which have penetrating lymphocytes, leukocytes and pseudotrophic islets mixture along with cells that secrets glycogen, pancreatic polypeptide and somatostatin, that causes the disease by insusceptible process (Gill and Haskins, 1993). Destruction of islet cell is due to genetic constitute, pathology and environmental components (Michael *et al*., 2000).

DIABETES MELLITUS COMPLICATIONS

The deleterious results of hyperglycemia are divided into two types of complications i.e. macrovascular and microvascular. As small vessels like capillaries are involved in microvascular so it includes complications like diabetic neuropathy, retinopathy and nephropathy while macrovascular comprise of large vessels like veins and arteries so stoke, peripheral arterial and coronary artery disease is due to macrovascular complications (Loghmani, 2005).Nephropathy diabetes universally is the last stage of renal disease. Diabetic nephropathy is a progressive turn down in the rate of glomerular filtration that is induced by hypertrophy of glomerular and tubular epithelial, glomerular hyperfiltration, high excretion of urinary albumin, high thickness of membrane basement and expansion of mesangial along aggregation of extracellular matrix proteins (ECM) (Jain and Vaishall, 2012).

Retinopathy diabetes is due to damage of small vasculature retina, light sensitive and multicellular tissue at endorse of eye. Universally, it is responsible to cause visual damage (Marshall and Allan, 2006). The capillaries of retina are drew by endothelial cells which are responsible for maintenance of blood retinal barrier and cells of smooth muscle surrounds them along pericytes that modulate the vessels (Santos *et al*., 2011).

Diabetic neuropathy is due to loss in function of nerve fiber. The most consented definition of neuropathies is "the presence of signs and symptoms of dysfunctioning of peripheral nerves in people affected of diabetes after excluding other induces" (American Diabetes Association, 2004). Diabetes, in peripheral nervous system induces liberal impairment of sensory nerves and also damages motor nerves (Pazdro and Burgess, 2010). The cause of lower extremity impairment is finally neuropathies (Obrosova, 2009).

OXIDATIVE STRESS IN COMPLICATION OF DIABETES MELLITUS

Free radicals are short lived reactive chemicals which are classified into reactive nitrogen species (RNS) and reactive oxygen species (ROS) while oxidants are the non-radical reactive derivatives. Biological free radicals are the normal cellular metabolic products and are extremely unstable. Electrons are available in them which react with many other substrates like DNA, lipids and proteins. Free radicals are substantially distinguished as they play dual function both by harming and also beneficially helping living system (Valko *et al*., 2007). Free radicals at moderate or lower level beneficially effects like mitogenic reaction induction, defensive action against infective agents and cellular structure developmental process (Pacher *et al*., 2007). Reactive oxygen species have hydroxyl ($^{\cdot}OH$), hypochlorous acid (HOCL), superoxide anion ($O_2^{\cdot-}$) and hydrogen peroxide (H_2O_2) while reactive nitrogen species have peroxynitrite ($OONO^-$), nitrogen dioxide ($NO_2^{\cdot}$) and nitric oxide ($^{\cdot}NO$) (Halliwell and Guttereridge, 2007). Free radicals damages structures of cell at higher concentration because of oxidative stress (Bahorun *et al*., 2006).

Free radicals are developed beneath physiological terms and are neutralized through exogenous and endogenous antioxidants, in order to protect the cells from their harmful toxic effects. Free radicals can also be neutralized through non-enzymatic reactions with oxygen or via ionizing radiotherapy (Pham-Huy *et al*., 2008). In mitochondria, this process may takes place through oxidative phosphorylation. Oxygen is believed to be one of the most important factors of life but sometimes it may become enemy of cells and kill them by generating reactive species (Weseler and Bast, 2010). However, oxidative stress may be defined as imbalance between prooxidants and antioxidants because of various factors like toxicity, aging, inflammation and drug addiction [Sies, 1985]. In general, formation exceeds or/and highly reactive substances like ROS and RNS removal is insufficient, it leads to oxidative stress (Johansen, 2005). Oxygen is the most responsive specie which can become the component of damage and harmful molecules.

As shown in table 1a, the endogenous antioxidants constitute enzymatic antioxidants like glutathione reductase (GR), superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) while non-enzymatic antioxidants are vitamin C, vitamin E, α lipoic acid and glutathione (GSH) (Lubos *et al*., 2011). However, exogenous antioxidants includes trace metals, falvonoids etc (Halliwell, 2011).

Various experimental efforts have mentioned the association within diabetes mellitus and oxidative stress by measurement of biomarkers of oxidative stress in both diabetic rodents and patients. As mentioned in table 1b, hyperglycemia is responsible for high level of oxidative DNA damaging markers like 8-dihydro-2-deoxyguanosine (8-oxodG), 8-oxo-7 and 8-hydro-2-deoxyguanosine (8-OHdG); products of lipid-peroxidation assessed as thiobarbituric acid-reactive substances (TBARS); products of oxidative protein likeS, level of carbonyl and nitrotyrosine and also leads to decreased action of antioxidant enzymes. Various studies of cell culturing have proved that in diabetes mellitus production of reactive oxygen species increases (Inoguchi *et al*., 1992).

As free radicals are able to instantly oxidize or/and damages proteins, lipids and DNA, they also function in the advancement and onset of diabetes complications (Rosen *et al*., 2000). When defensive network of antioxidant gets absent, oxidative stress increases due to which stress-sensitive intracellular pathway activates and products of gen are formed that induce cellular impairment and leads to late diabetes mellitus complications (Nourooz-Zadeh *et al*., 1997).

OXUDATIVE STRESS BIOMARKERS IN DIABETES MELLITUS

LIPIDS

Diabetes mellitus disturbs the body lipid profile and thus cells become susceptible for peroxidation of lipids (Patricia, 2009). Various The research proved that free radicals attack polyunsaturated fatty acids more frequently as multiple binding is present in them (Butterfiel, 1998). Fatty acids are produced through radical reaction of lipid hyperperoxides (LHP) which give rise to extremely toxic and reactive radicals of lipid for the formation of new lipid hyperperoxides (Matough *et al*., 2012). While studying reactive oxygen species, lipid peroxidation is considered the most vital oxidative stress biomarker (Hatice 2004). Through peroxidation of lipids, formation of malondialdehyde (MDA) takes place, which is being reacted with thiobarbituric acid inorder to evaluate lipid peroxides (Esterbauer *et al*., 1991).

PROTEINS

In vitro, reactive oxygen species reacts with amino acid thus producing non-functioning and denatured proteins which inturn responsible towards oxidative stress (Nishigaki *et al*., 1981). Oxidative degeneration and glycation of protein is induced by diabetic hyperglycemia through the production of free radicals. Level of glycated protein is estimated with the use of biomarkers like fructosamine and hemoglobin glycation. In antioxidant enzymes, structure and function changes occur because of non-enzymatic glycation, thus in diabetes, oxidative stress is enhanced when free radicals get detoxified (Maritim *et al*., 2003).

SUPEROXIDE DISMUTASE

Superoxide dismutase acts as a catalyst. Superoxide dismutase, in metabolism of oxygen, catalysis the main reactive oxygen species, that is superoxide into peroxide and molecular oxygen. The first line of defense against cell injury mediated by reactive oxygen species is provided by superoxide dismutase (Tiwari *et al*., 2013).

CATALASE

Catalase regulates metabolism of hydrogen peroxide which in excess damages DNA, RNA and lipids. Catalase as a catalyst converts hydrogen peroxide into oxygen and water along neutralizing it. Due to deficiency of catalase, pancreatic β-cell undergo oxidative stress as excess amount of reactive oxygen species are produced which dysfunction the beta cells and thus diabetes mellitus is caused (Jamieson Dana, 1986). Studies show that hyperglycemia is responsible for increased production of hydrogen peroxide and also gene expression of catalase is down-regulated (Patel *et al*., 2013).

GLUTATHIONE

Diabetes mellitus causes changes in glutathione reductase and peroxidase enzymes. In cell theses enzymes are present, by which peroxide metabolizes into water and also responsible for conversion of glutathione disulfide into glutathione. As there is changed cells get injured due to oxidative stress (Maritim *et al*., 2003).

VITAMINS

Vitamins are vital part of biological system and play important role in biochemical processes. Vitamins are of various types but vitamin A, C and E play role as antioxidant through detoxification of free radicals. Change in the levels of vitamins is substantial oxidative stress biomarker. In different conditions, through pro-oxidants production toxicity is promoted due vitamin A, C and E. Diabetes mellitus is made responsible for increase or decrease vitamin E level in the body (Maritim *et al*., 2003).

In diabetes mellitus, antioxidants as defensive mechanism are impaired with hyper-oxidative stress (Bajaj and Khan, 2012). Moreover, due to diabetes mellitus, antioxidant enzyme activity is altered in different tissues (Ojiako *et al*., 2015). Theoretically, activity changes in enzymes antioxidant leads to oxidative stress in diabetes mellitus (Yuan *et al*., 2010).

CONCLUSION AND FUTURE VIEW

The vital roles of reactive oxygen species (ROS), in the pathophysiology of diabetes mellitus have been incontrovertibly proved. Intuitively, to prevent diabetes mellitus complications and to improve oxidative stress, therapeutic strategy is provided through free radicals formation inhibition. Hence, integrating preparation of antioxidants into therapeutic treatment conventionally, both by supplementation in diet or via ingesting antioxidants naturally, ought to be recommended as holistic approach to prevent and manage diabetes mellitus and its related complications. Although, antioxidant therapeutic approach is useful, still it's necessary to assess and investigate the efficacy of this cure strategy.

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(*Accepted for publication October 2020*)