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Diabetes mellitus and oxidative stress a Co relative and therapeutic approach

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Abstract

Oxidative stress is one of the factors of the lead to type 2 Diabetes Mellitus (T2DM) a serious and fast growing health problem worldwide. Numerous studies report that the pancreatic β - cells pay an important role in T2DM progression but the underlying molecular mechanism has not been fully deciphered. The biochemical changes in diabetes mellitus lead to disturbance in oxidative milieu which turn lads to several macro and micro vascular complication in patients. Diabetes mellitus represents an ideal disease to study the adverse effects to oxidative stress and oxidative stress and its treatment. The literature search performed using the terms: diabetes mellitus, the effect of oxidative stress on β -cell, role of oxidative stress in diabetes mellitus and antioxidant characteristics of oxidative stress in diabetes and proposes their probable clarifications.

Keywords: Antioxidant therapy, β -cell, diabetic complications

Introduction

Diabetes is a metabolic disorder characterized by elevated blood sugar that results from defects in insulin production and/or insulin action, and impaired function in the metabolism of carbohydrates, lipids and proteins which leads to macro and micro vascular complications. There are emerging evidences that oxidative stress makes significant contribution to the progression of diabetes and its associated complications. Type 1 diabetes is a chronic illness, usually caused by an autoimmune destruction of insulin-producing β -cells in the islets of the pancreas. As a consequence, the body produces none to very little insulin resulting in a relative or absolute deficiency of insulin. T2DM also referred as Non-Insulin Dependent Diabetes Mellitus (NIDDM) or adult-onset diabetes, includes patients who have insulin resistance and usually have relative insulin deficiency [2]. However, these patients do not need insulin administration for their treatment and survival of the patient. Majority of the patients with T2DM are obese, and obesity itself further contributes to insulin resistance to some extent. The non-obese individuals with T2DM may have an increased percentage of body fat distributed predominantly in the abdominal region. According to American Diabetes Association (ADA), T2DM accounts for ~90-95% of all diabetes mellitus patients worldwide. T2DM goes undiagnosed for many years because hyperglycemia related complications develop slowly. The risk of developing T2DM increases with age, obesity, and physical inactivity, family history of diabetes, ethnicity and hyperglycemia during pregnancy. It is often related with stronger genetic predisposition as compared to the autoimmune form of type 1 diabetes.

Diabetes mellitus in Indian population

Until recently, India had more diabetics than any other country in the world, according to the International Diabetes Foundation although the country has now been surpassed in the top spot by China. Diabetes currently affects more than 62 million Indians, which is more than 7.2% of the adult population. The average age on onset is 42.5 years Nearly 1 million Indians die due to diabetes every year

According to the Indian, India is projected to be home to 109 million individuals with diabetes by 2035. A study by the American Diabetes Association reports that India will see the greatest increase in people diagnosed with diabetes by 2030. The high incidence is attributed to a combination of genetic susceptibility plus adoption of a high-calorie, low-activity lifestyle by India's growing middle class. Human body is continuously exposed to different types of agents that results in the production of reactive species called as free radicals (ROS/RNS) which by

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the transfer of their free unpaired electron causes the oxidation of cellular machinery. In order to encounter the deleterious effects of such diet that neutralizes such species and keeps the homeostasis of body. Any imbalance between the RS and antioxidants leads to produce a condition known as "oxidative stress" that results in the development of pathological condition among which one is diabetes. Most of the studies reveal the inference of oxidative stress in diabetes pathogenesis by the alteration in enzymatic systems, lipid peroxidation, impaired Glutathione metabolism and decreased Vitamin C levels. Lipids, proteins DNA damage, Glutathione, catalane and superoxide dismutase are various biomarkers of oxidative stress in diabetes mellitus. Oxidative stress induced complications of diabetes may include stroke, neuropathy, retinopathy and nephropathy. The basic aim of this review was to summarize the basics of oxidative stress in diabetes mellitus. Blood Pressure (SBP), cholesterol, HOMA-IR, fat intake and comparatively low physical activity. Diabetes and its complications pose a significant economic burden on countries, healthcare systems, society, individuals and their families. International Diabetes Federation (IDF) estimated that in year 2017 the total healthcare expenditure on diabetes would have been USD 727 billion (20-79 years), which represents an 8% increase compared to the 2015 estimates.

Genetics and Molecular

Mechanism of t2dm the genetics of T2DM is complex and not clearly defined. Insulin resistance is an important factor in T2DM that develops at several levels, with decreased receptor concentration and kinase activity, defect in phosphorylation of insulin receptor substrate-1 & 2 (IRS-1 & 2), Phosphatidylinositide Kinase (PI-3-k) activity, translocation of Glucose Transporter-4 (GLUT 4) and the activity of intracellular enzymes [8]. Insulin binds to its receptors on adipocytes and skeletal muscle cells and increases the uptake of glucose from blood by stimulating the translocation of the cytosolic GLUT 4 to plasma membrane.

Oxidative stress in diabetes mellitus

It is believed that oxidative stress plays important role in the development of vascular complications in diabetes particularly type 2 diabetes (Pham-Huy, 2008) [10]. ROS level elevation in diabetes may be due to decrease in destruction or/and increase in the production by catalase (CAT-enzymatic/non-enzymatic), superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) antioxidants. The variation in the levels of these enzymes makes the tissues susceptible to oxidative stress leading to the development of diabetic complications (Lipinski, 2001). According to epidemiological studies, diabetic mortalities can be explained notably by an increase in vascular diseases other than hyperglycemia (Pham-Huy, 2008) [10]. Path physiology of oxidative stress in diabetes nowadays, evidences have been reported that support the role of oxidative stress in the pathogenesis of both type 1 and type 2 diabetes. Free radical formation in diabetes by non-enzymatic glycation of proteins, glucose oxidation and increased lipid peroxidation leads to damage of enzymes, cellular machinery and also increased insulin resistance due to oxidative stress (Maritim *et al.*, 2003) [13]. According to latest research, lipid is not only but also the polipo protein component of LDL that forms insoluble aggregates oxidative due to hydroxyl radical-induced cross-linkage between apo-B monomers that is responsible for oxidative damage in diabetic complications (Pham-Huy, 2008) [10]. In diabetes mellitus,

main sources of oxidative stress are mitochondria. During oxidative metabolism in mitochondria, a component of the utilized oxygen is reduced to water, and the remaining oxygen is transformed to oxygen free radical (O) which is an important ROS that is converted to other RS such as ONOO-, OH and H2O2 (Moussa, 2008). Insulin signaling is modulated by ROS/RNS by two ways. On one side, in response to insulin, the ROS/RNS are produced to exert its full physiological function and on the other side, the ROS and RNS have got negative regulation on insulin signaling, interpreting them to develop insulin resistance which is a risk factor for diabetes type 2 (Erejuwa, 2012).

Oxidative stress and diabetic complications

Many evidences from experiments have given link between diabetes and oxidative stress by measuring various biomarkers that include DNA damage biomarkers and lipid peroxidation products. It is believed that in the onset and progression of late diabetic complication, free radicals have got a major role due to their ability to damage lipids, proteins and DNA (Ayepola, 2014) [16]. A variety of pathological conditions are induced by oxidative stress such as Rheumatoid arthritis, Diabetes mellitus and cancer (El Faramawy and Rizk, 2011). Free radical and oxidative stress induced complications from DM include coronary artery disease, Neuropathy, nephropathy, retinopathy (Phillips *et al.*, 2004) and stroke (Asfandiyarova *et al.*, 2007). *In-vivo* studies support the role of hyperglycemia in the generation of oxidative stress leading to endothelial dysfunction in blood vessels of diabetic patients (Ceriello, 2006). Increase in the levels of glucose and insulin along with dyslipidemia in patients suffering from diabetes develops macroangiopathies that cause oxidative stress leading to atherosclerosis (Giugliano *et al.*, 1995).

Biomarkers of oxidative stress in diabetes mellitus

- **Proteins:** ROS reacts with some amino acid in vitro, producing anything from modified, denatured and non-functioning proteins that in further may be responsible for oxidative stress (Nishigaki *et al.*, 1981) Diabetic hyperglycemia, by the process of free radical production, causes protein glycation and oxidative degeneration. The degree of such protein glycation is estimated by using some biomarkers such as glycated hemoglobin and fructosamine levels. Alteration in function and structure of antioxidant protein enzymes may also be due to nonenzymatic glycation such that detoxification of free radicals is effected enhancing oxidative stress in diabetes (Maritim *et al.*, 2003) [13] According to in vitro studies myeloperoxidase catalyzes the conversion of L-tyrosine to 3,3- dityrosine which serves as a crosslink between polypeptide chains of the same or different proteins making it a convenient biomarker for protein oxidation (Ylä-Herttuala, 1999).
- **Lipids:** Diabetes mellitus produces disturbances in the lipid profile of body making the cells more susceptible to lipid peroxidation (Patricia, 2009). Experimental studies show that polyunsaturated fatty acids in cell membrane are extremely prone to attack by free radicals due to the presence of multiple bonds (Butterfiel *et al.*, 1998). Lipid hyperperoxides (LHP) through intermediate radical reactions produce such fatty acids that generate highly reactive and toxic lipid radicals that form new LHP (Matough *et al.*, 2012). A critical biomarker of oxidative

stress is Lipid peroxidation which is the most explored area of research when it comes to ROS (Hatice *et al.*, 2004). Malondialdehyde (MDA) is formed as a result of lipid peroxidation that can be used to measure lipid peroxides after reacting it with thiobarbituric acid (Esterbauer *et al.*, 1991).

- **Vitamins:** Vitamins are very important part of biological system as they play important role in different biochemical processes. Among such vitamins, Vitamin A, C and E act as antioxidants by detoxifying the free radicals. Any alteration in their levels is significant biomarkers of oxidative stress. These vitamins also promote toxicity by producing pro-oxidants in certain conditions. Body levels of vitamin E have been reported to be either increased or decreased by diabetes. However conflicting reports present the deleterious effects of vitamin E on diabetes induced vascular changes (Maritim *et al.*, 2003) [13].
- **Glutathione:** Diabetes induces alterations in activity of enzymes glutathione peroxidase and glutathione reductase. These enzymes are found in cell that metabolizes peroxide to water and converting glutathione disulfide back into glutathione (Maritim *et al.*, 2003) [13]. Any alteration in their levels will make the cells prone to oxidative stress and hence cell injury.

Effect of oxidative stress on β -cells death and dysfunction:

The β -cells are essential for glucose homeostasis due to their ability to secrete insulin in response to nutrient uptake. These are among the most metabolically active tissues of the body that rely on oxidative phosphorylation for the generation of ATP and therefore plays an important role in insulin synthesis and secretion. ATP is synthesised by ATP synthases in mitochondria through coupling of the electrochemical H^+ gradient to the oxidative phosphorylation of fuel (glucose or fatty acids). Glucose metabolism in β -cells leads to an elevated intracellular ATP:ADP ratio, which closes the ATP-sensitive K^+ (K_{ATP}) channels, resulting in depolarization of the cell membrane that activates voltage- dependent Ca^{2+} channels, leading to Ca^{2+} entry and insulin release from the β -cells through exocytosis. Aerobic cells produce ROS such as superoxide (O_2^-) and H_2O_2 during oxidative phosphorylation in mitochondria as by-products [24]. When ATP levels are appropriate in the cells, an uncoupling process dissipates the electrochemical H^+ gradient, which plays an important role in reducing the level of ROS. Uncoupling Proteins (UCP) play a physiological role in thermoregulation of the body. Activation of uncoupling proteins leads to inhibition of ATP synthesis and ATP mediated release of insulin from the β -cells of the pancreas. There are five UCP homologues present in mammals namely, UCP1, UCP2, UCP3, UCP4 and UCP5. UCP1 is expressed in brown adipose tissue. UCP2 is found in tissues including heart, kidney, liver, brain, pancreas and white adipose tissue while UCP3 is expressed in skeletal muscles and brown fat cells. However, the function and regulation of these UCPs remain unclear. Specifically, UCP2 appears to play a role in the regulation of ROS production, inflammation, cell proliferation and death of β - cells of the pancreas. Moreover, common causes of ROS generation in β -cells are hyperglycemia, hyperlipidaemias, hypoxia and endoplasmic stress. Besides, β -cells contain only 50% of the SOD and 5% of H_2O_2 scavenging enzymes as compared to liver cells. Thus, β -cells are highly susceptible to oxidative damage. UCP2 expression negatively regulates the insulin

secretion due to its uncoupling activity which reduces mitochondrial ATP synthesis. Acute exposure of β -cells to high concentrations of glucose and free fatty acids stimulates insulin secretion, whereas chronic exposure results in desensitization and suppression of insulin secretion.

Effect of oxidative stress on β -cell proliferation: The number of β -cells in pancreas is usually constant after birth but some evidences indicate that under certain physiological or pathological conditions such as pregnancy, obesity or diabetes, these can regenerate. Some studies suggest that ROS, to some extent could stimulate β -cell regeneration. Forkhead box class O family member proteins (FOXOs) are transcription factors that regulate the β -cell proliferation and differentiation. Due to the increased production of ROS in β -cell, FoxO1 forms a complex with transcription factor along with promyelocytic leukaemia protein (Pml) and the NAD-dependent deacetylase sirtuin-1 (SIRT1), which helps in β -cell proliferation resulting in attenuation of β -cell development. Elevated plasma glucose is clearly associated with induction of oxidative stress. Moreover, recent study has established that lowering of the glucose concentration also reversibly increases ROS production in pancreatic β -cells. These observations suggest that the production of ROS is both necessary and at the same time possibly hazardous for normal β -cell function.

Diabetic: Complications Elevated blood glucose levels over prolonged period of time in uncontrolled diabetes mellitus can lead to a number of short and long-term macro and microvascular complications. Hyperglycaemia- induced oxidative stress in diabetic patients is the most explored hypotheses to explain the onset of complications. A study conducted in 2011 on 20,000 T2DM Indian patients showed the prevalence of various complications such as: neuropathy (33.6%), cardiovascular (23.6%), renal (21.1%), eye (16.6%) and foot ulcer (5.1%).

Cardiovascular disease: There are ample evidences to show that patients with diabetes mellitus are at high risk for several Cardiovascular Disorders (CVDs). CVDs are the leading causes of diabetes-related morbidity and mortality. Diabetes mellitus patients have elevated triglycerides, low HDL cholesterol and abnormalities in the structure of lipoprotein particles. The LDL cholesterol is predominantly present in small, dense form in diabetic patients and is more atherogenic than the large dense LDL particles present in healthy subjects because these can more easily penetrate which increases their susceptibility to oxidation and attachment to the arterial walls. Oxidised LDL is pro-atherogenic as it is recognised by the immune system as 'foreign', and causes several abnormal biological responses such as attracting leukocytes to the intima of vessel, improving the ability of leukocytes to ingest lipids and their differentiation into foam cells, and stimulating the proliferation of leukocytes, endothelial cells, and smooth muscle cells. These episodes instigate the formation of atherosclerotic plaque. In diabetic patients, LDL particles can also become glycated that increases the half-life of LDL particles and therefore, increases the ability of the LDL to promote atherogenesis. Dyslipidemia in diabetes promotes endothelial dysfunction and affects vasodilatory, anti-atherogenic, and anti-inflammatory properties of healthy endothelium and thus leads to atherosclerosis.

Diabetic nephropathy: Diabetic nephropathy is a public health problem worldwide that affects millions of people. Diabetes is a leading cause of Chronic Kidney Disease (CKD). Approximately 43% of diabetes mellitus patients in the United States have microalbuminuria, a marker of progression of CKD [3,4]. Hyperglycaemia in diabetes mellitus causes progressive structural changes in mesangium, glomerular basement membrane, and tubulointerstitial tissue of kidney and is considered as the driving factor for diabetic nephropathy. However, several other studies have demonstrated variability in the development of renal complications despite comparable hyperglycaemic control. The progression of diabetic nephropathy is complex and multifactorial. Uncontrolled diabetes mellitus results in non-enzymatic interaction of glucose with amino acids, groups of proteins, lipoproteins, and nucleic acids that leads to the formation of Advanced Glycosylation End Products (AGE); which is associated with pathophysiology of diabetic nephropathy through mechanisms that are either receptor-dependent or receptor-independent. It modifies basement membrane proteins, cross-links extracellular components and increases expression of type IV collagen. These alterations lead to structural changes of the surface charge, membrane permeability, proteolytic digestion, and membrane stability and disrupt intercellular interactions. This leads to impairment of tissue function and maintenance. AGEs interact with a wide array of receptors such as macrophage scavenger receptor type I and II, AGE-R1, AGE-R2, AGE-R3, Receptor for AGE (RAGE), and CD-36 on various cell types. RAGE activation leads to activation of several signal transduction pathways that lead to the generation of ROS and instigation of transcription factors, such as NF-kappa B that leads to the release of cytokines and growth factors including Transforming Growth Factor- β 1 (TGF- β 1), interleukin-1 β and interleukin-6, insulin-like growth factor-1, Tumour Necrosis Factor (TNF- α), and platelet-derived growth factor that activate many pro-inflammatory conditions.

Diabetic neuropathy: A common complication of type 1 and type 2 diabetes is neuropathic pain. Distal Symmetrical Polyneuropathy (DSPN) is the most common clinical form of diabetic neuropathy. DSPN affects toes and distal foot and is found in more than 90% of the diabetic patients. Diabetic Neuropathic Pain (DNP) is characterised by continuous tingling, burning, sharp, shooting, and lancinating pain, which can substantially affect the quality of life of the patients. The pathogenesis of DNP is not fully understood but several risk factors are known to be associated with DNP including hyperglycaemia, older age, longer diabetes duration, drinking alcohol and cigarette smoking.

Diabetic retinopathy: Chronic hyperglycaemia in diabetes mellitus triggers the several signaling pathways, including protein kinase C, activation of polyol pathway, elevated AGEs etc. that eventually lead to the functional and structural impairment to retinal cells. Diabetic retinopathy is the most common micro vascular complication of diabetes. Currently, diabetic retinopathy affects almost 100 million people worldwide and is set to become an ever-increasing health burden. It falls into two categories: the earlier stage of Non-Proliferative Diabetic Retinopathy (NPDR) and the advanced stage of Proliferative Diabetic Retinopathy (PDR). The clinical features in NPDR patients are micro aneurysm, retinal hemorrhage and intraregional micro vascular abnormalities,

while PDR is characterized by the hallmark feature of pathologic preretinal revascularization. A major additional categorization in diabetic retinopathy is diabetic macular edema, which is an important manifestation that characterises the most common cause of vision loss in patients with diabetic retinopathy. Diabetic foot ulcers: Approximately 6% of people with diabetes are affected by foot disease that includes infection, ulceration, or destruction of tissues of the foot. It can damage patients' quality of life and affect social participation and livelihood. Oxidative stress as a therapeutic target for management of diabetes mellitus: Oxidative stress is associated with many diseases linked with metabolic or vascular disorders. Thus, diabetes represents an ideal candidate for studying the significance of oxidative stress and its implication as potential target for treatment of the disease. Inhibiting the free radical formation by antioxidants serves as a novel therapeutic strategy to reduce oxidative stress and prevent diabetes-related vascular complications. The therapeutic efficacy of antioxidants has been evaluated in several randomised controlled trials and the study outcomes are summarised in. Many adjuvants with strong pharmacotherapy potential for diabetes management have been shown to possess antioxidant properties in addition to their primary pharmacological actions. The antioxidant properties of these agents may be the contributing factor for their therapeutic efficacy.

Conclusion

Free radical production in body is a continuous process as part of normal function. Though, excess free radical production instigating from endogenous or exogenous sources might play a role in onset of diabetes and its complications. Oxidative stress in diabetes causes over production of mitochondrial superoxide in endothelial cells of both large and small vessels, as well as in the myocardium and leads to many micro and macro vascular complications. The inhibition and scavenging of reactive oxygen species and reactive nitrogen species formation offer novel therapeutic strategy for management of oxidative stress and prevention of subsequent pathologic complications associated with diabetes mellitus. Antioxidants play important role in neutralisation of free radicals and reduce the associated tissue damage by scavenging them and promote their decomposition. Therefore, supplementation of antioxidants may be a valuable strategy for controlling diabetes complications and enhancing antioxidant capacity. Despite the potential advantages of antioxidant pharmacotherapy, additional systematic randomised trial is required to explore and assess the efficacy and safety scores of the current therapeutic strategy. In future, more research into the pathophysiology of oxidative stress and well-planned antioxidant therapy, especially on mechanistic approach in diabetic patients will be the main target area of research to get any fruitful conclusion. Conflict of interest: The authors declare no conflict of interest regarding the publication of this paper.

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