Review Article

'Oxidative stress'-A new target in the management of diabetes mellitus

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Abstract

Diabetes mellitus (DM) is a chronic condition that poses a mammoth challenge for the healthcare system in developing as well as developed nations. Diabetes mellitus is associated with damage to the vasculature which leads to microvascular and macrovascular complications. Oxidative stress is a consequence of glucotoxicity and lipotoxicity, which are associated with diabetes. Glucotoxicity and lipotoxicity play a part in the pathogenesis of β-cell dysfunction. The hyperglycemic state in DM leads to oxidative stress which further hampers insulin secretion. In diabetes, the biological antioxidants also get depleted along with a reduction in glutathione (GSH), an increase in the oxidized glutathione (GSSG)/GSH ratio, and a depletion of non-enzymatic antioxidants. This results in the formation of a viscous circle of hyperglycemia leading to increased oxidative stress that further hampers insulin secretion which in turn results in hyperglycemia. Antioxidants are efficacious in reducing diabetic complications. The antioxidants produced biologically fall short, hence external supplements are required. In this review, the authors have discussed the relationship between oxidative stress in DM and the advantages of antioxidant supplements in controlling blood glucose levels and also in deaccelerating the complications related to DM.

Keywords: Antioxidants, diabetes mellitus, oxidative stress, supplements

Introduction

Chronic oxidative stress has been associated with inflammation and has been recognized to affect the pathophysiological changes which lead to the development of several non-communicable diseases (NCDs). The NCDs include diabetes mellitus, cardiovascular diseases, neurodegenerative disorders, and cancer. Oxidative stress can cause extensive damage to the cellular structure which can disrupt cellular function and result in the initiation and progression of NCDs.[1] The vascular complications in diabetes mellitus have been linked to increased oxidative stress and inflammatory state among other causes. The hyperglycemic state is responsible for disturbing the balance of oxidants and antioxidants produced at a cellular level. However, an increase in oxidative stress plays a role in the development of complications associated with diabetes mellitus.[2]

Primary care physicians (PCPs) are the first point of contact for many diabetic patients. PCPs have a vital role to play in the Indian healthcare architecture owing to the population size and prevalence of diabetes mellitus. PCPs are capable of providing the required care and consultation to the growing diabetic populous of India if their training and infrastructure requirements are met.[3] For managing diabetic patients, in

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addition to hypoglycemics, supplements may provide a beneficial advantage of managing blood glucose levels.

In this review, the authors have discussed the relationship between oxidative stress in DM and the advantages of antioxidant supplements in controlling blood glucose levels and also in deaccelerating the complications related to DM.

Epidemiology of Diabetes Mellitus (DM)

Diabetes mellitus is a chronic condition that poses a mammoth challenge for the healthcare system in developing as well as developed nations. The global burden of diabetes has been experiencing a rising trend due to an increase in urbanization, sedentary lifestyles, and aging population.[4,5] There also has been an increase in the prevalence of diabetes mellitus in younger adults. The survival length has also experienced an extension because of early detection and improvement in management options.[5]

Type 2 diabetes mellitus (T2DM) makes up 87 to 91% share of the global diabetes burden.[4] Diabetes mellitus is in ninth position on the list of major causes of death worldwide. Asia is a hotspot for the global type 2 diabetes mellitus epidemic.[6] Saeedi *et al.*,[5] in 2019 using the Analytical Hierarchy Process (AHP) scoring criteria, studied adults between 20-79 years of age from 255 sources of diabetes prevalence data covering 138 countries. The analysis estimated there were 46,30,00,000 diabetics in 2019. The prevalence in women was estimated to be 9.0% and 9.6% in men. The prevalence was also found to be higher in high-income countries. India ranks second in this analysis with an estimated 77.0 million people with diabetes in 2019. The India State-Level Disease Burden Initiative reported that there were 65.0 million cases of diabetes in our country in the year 2016. The crude prevalence rate in India was reported to have increased by 39.4% from 5.5% in 1990 to 7.7% in 2016. These figures were reported for adults aged 20 years or older. Diabetes has contributed to 3.1% of all deaths in India from 1990 to 2016.[7] The global prevalence is anticipated to surge up to 578 million in 2030 and up to 700 million in 2045.[5]

Diabetes mellitus is associated with macrovascular and microvascular complications which are a result of damaged vasculature. The prevalence of diabetic retinopathy in Indian populations has been determined to be ranging from 10.3% to 21.2% in the diabetic population in various studies.[8] The clinical prevalence of microalbuminuria has been reported to be between 26.9% to 36.3% in India.[8,9] The prevalence of neuropathy is between 19.5% to 29.5% in newly diagnosed T2DM patients and 27.8% among patients with known T2DM. Among patients with T2DM, more than 65% die of cardiovascular disease and 80% of those can be linked to coronary artery disease (CAD).[9]

Free Radicals and Antioxidant Mechanism in Normal Physiology

Free radicals are generated as a result of either exogenous sources (alcohol, smoke, air, certain drugs, etc.) or endogenously due to enzymatic and nonenzymatic reactions. The major free radical groups include oxygen free radicals and nitrogen free radicals.[10] Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are the major free radical groups that partake in regulating fundamental cellular processes like insulin secretion under physiological conditions.[10,11]

In the physiological state, the production of free radicals is nearly balanced by the antioxidant defense system. The cells cannot eliminate ROS/RNS completely since they are useful in controlled amounts. An imbalance can be caused due to decreased antioxidant levels or increased oxidants levels or both. Furthermore, if the cells fail to adapt to the imbalance, the cells are damaged. The damage can result in the breaking of DNA strands, protein oxidation, lipid peroxidation, etc.[10] The damage caused by ROS is liked to the pathobiochemical mechanism of various diseases including diabetes.[12] The damage from oxidative stress targets important cell organelles. The damage extends to DNA strand breakage, lipid peroxidation, and protein oxidation. Cells damaged by oxidative stress can be repaired or replaced. However, when the oxidative stress is severe, it results in apoptosis and ultimately necrosis.[10]

Antioxidants produced biologically, called endogenous antioxidants counter oxidative stress. They function at the targeted macromolecule by preventing, reducing, or repairing oxidative damage. Endogenous antioxidants are classified into two categories: enzymatic and non-enzymatic. The major enzymatic antioxidants include superoxide dismutase, glutathione peroxidase, glutathione reductase, and catalase among many others. Superoxide dismutase (SOD), a group of metalloproteins, catalyze superoxide to hydrogen peroxide (H_2O_2) and molecular oxygen. The role of SODs in modulating the pathophysiology of several disease processes has been confirmed in preclinical studies. The glutathione system consists of reduced glutathione (GSH) and the enzymes responsible for countering the oxidative species. Catalase is found predominantly in peroxisomes and its main function is to decompose H_2O_2 to water and molecular oxygen. Nonenzymatic antioxidants include low-molecular-weight molecules such as vitamins C and E.[10]

Role of Oxidative stress in Pathogenesis of DM

Oxidative stress is caused by glucotoxicity and lipotoxicity, which are associated with diabetes. They play a part in the pathogenesis of β-cell dysfunction. Hyperglycemia and hyperlipidemia follow the principal pathogenesis of diabetes and exert additional toxic effects on β-cells.[13] Furthermore, chronic increased level of intracellular ROS in adipocytes subsequent to mitochondrial dysfunction leads to insulin resistance by attenuating insulin signaling.[14] Insulin activity is adversely affected by the generation of ROS such as H_2O_2 and superoxide anions. The β-cells of the pancreas deteriorate due to the ensued oxidative stress, subsequently, insulin secretion decreases.[15]

ROS production in pancreatic cells is resultant of the mitochondrial respiratory chain and oxidation of nicotinamide adenine dinucleotide phosphate (NADPH). In the process of glucose-stimulated insulin production, an increase in glycolytic flux increases tricarboxylic acid (TCA) cycle activity which increases the adenosine triphosphate (ATP) production in mitochondria. The glycolytic flux is associated with an increase in mitochondrial oxidative activity. This process is required to insure adequate insulin secretion as a response to increased blood glucose levels.[16]

Peripheral insulin resistance impairs the metabolism of glucose. At the molecular level, there is an increase in glycolytic flux as well as ROS production within β-cells of the pancreas. Mitochondrial generation of ROS and protein kinase C (PKC) are stimulated by increased intracellular Ca^{2+}. PKC further causes the generation of superoxide and other species via NADPH oxidase-dependent pathway. Increased ROS production has potential pathological consequences.[16]

Stimulation of endothelial cells by physical, chemical, or humoral stimuli activates endothelial nitric oxide synthase (eNOS) to convert L-arginine to nitric oxide (NO) and L-citrulline.[17] For the functions of relaxing and contracting the blood vessels, the endothelial cells produce an array of chemicals like NO, prostacyclin (PGI_2), thromboxane A_2 (TXA_2), leukotrienes, superoxide anions, prostaglandins, etc., The balance between the relaxing and contracting factors is regulated by a number of chronic factors which are modulated by stress resulting in the upregulation of endothelial NOS (eNOS). ROS generated from mitochondrial respiratory chains regulate the release of pro-inflammatory cytokines, metalloproteinases, and adhesion molecules and also inhibit activities of NO, endothelial-derived hyperpolarizing factors (EDRFs), and prostacyclins.[18] The balance between NO and ROS brings homeostasis to NO bioavailability. An increase in ROS levels leads to eNOS producing superoxide. Superoxide further reduces NO bioavailability and NO is converted to peroxynitrite ($ONOO^-$). Peroxynitrite has a deleterious effects on the vasculature.[19] Peroxynitrite production alters normal endothelial functions and is associated with the pathogenesis of vascular complications of DM.[17]

Diabetes is responsible for microvascular changes which result in extracellular matrix protein synthesis, and capillary basement membrane thickening. These are the pathognomonic characteristics of diabetic microangiopathy. These changes coupled with advanced glycation end products, oxidative stress, low-grade inflammation, and neovascularization of vasa vasorum further cause macrovascular complications. Hyperglycemia is the major cause of microvasculopathy and seems to further be involved in the causation of macrovasculopathy.[8] The damage to the vasculature gives rise to the complications associated with diabetes mellitus. The macrovascular complications include cardiovascular diseases and the microvascular complications include nephropathy, neuropathy, and retinopathy. These complications are fairly common in patients with DM and pose at least a 10-20 times higher risk of microvascular complications and a 2-4 times higher risk of developing macrovascular complications as compared to people without DM.[6] Patients with DM are also at a 2.5 times risk of developing ischemic stroke due to oxidative stress-induced microvascular dysfunction.[20]

Thus, a hyperglycemic state in DM leads to oxidative stress which further leads to hampered insulin secretion. In diabetes, the biological antioxidants also get depleted along with a reduction in GSH, an increase in the oxidized glutathione (GSSG)/GSH ratio, and depletion of non-enzymatic antioxidants.[21] This results in the formation of a viscous circle of hyperglycemia leading to increased oxidative stress and further hampering insulin secretion which in turn results in hyperglycemia. Another crucial challenge for physicians is reducing hyperglycemia while avoiding hypoglycemia. Frequent short-term glycemic variations can induce hypoglycemia. Hypoglycemia is hypothesized to induce the generation of oxidative stress and cardiac complications.[22]

Oxidative Stress and Complication of DM

Role of free radicals in endothelial dysfunction

Endothelial dysfunction is a repercussion of an increase in oxidative stress within the vascular wall mostly attributable to the uncoupling of eNOS. An increase in ROS production results in the upregulation of eNOS-mediated superoxide. The delicate balance is essential for the ability of blood vessels to preserve standard homeostasis. Increased ROS production and a shift in balance from NO to ROS signaling represent common characteristics of vascular disease.[19] Endothelial-derived NO functions to maintain the tone of normal vascular smooth muscles, modulation of inflammatory and immune responses, regulation of blood pressure, inhibition of cell proliferation of vascular smooth muscles, regulation of endothelial integrity and vascular permeability, inhibition of oxidation of low-density lipoproteins (LDL) among others.[17] Endothelial dysfunction consequentially hampers the blood supply due to disturbance in the homeostasis between the vasodilators and vasoconstrictors. Endothelial dysfunction is thus. associated with increased risk of hypertension, hyperlipidemia, hyperglycemia, insulin resistance, obesity, and inflammation.[23]

Oxidative stress and cardiovascular complications

At the cellular level, increased glucose levels in the blood induce mitochondrial dysfunction.[24] In cardiomyocytes, mitochondrial dysfunction adds to the production of ROS, uncoupling of the electron transport chain (ETC), and reduction in ATP production. Thus, induced glucotoxicity results in the creation of advanced glycation end-products (AGEs). AGEs are a group of modified proteins and/or lipids that can cause cell damage. Fatty acids via the proliferator-activated receptor alpha (PPARα) pathway cause metabolic inflexibility and reduced cardiac efficiency. The accumulated toxic lipids alter the cellular structure and cause dysfunction of cardiomyocytes and ultimately death.[25]

Due to increased ROS levels, endothelial dysfunction ensues and leads to the development of atherosclerosis. This can lead to loss of myocardial dysfunction and ultimately heart failure due to ischemia linked to atherosclerosis. Diabetes levies added oxidative stress to the heart. The increased cardiac oxidative stress leads to receptor-induced activation of NADPH oxidase 2 (Nox2) and mitochondrial redox mismatch. Oxidation of mitochondrial NADPH upscales H_2O_2 production, which plays a causal role in contractile dysfunction, arrhythmia, and ultimately maladaptive cardiac remodeling through hypertrophy and cell death.[26]

ROS/RNS and insulin resistance

ROS and reactive nitrogen species (RNS) are produced in the cells and in appropriate concentrations, contributing to the regulation of normal cellular functions like insulin secretion. However, increased levels of ROS and RNS lead to cellular damage. Both of these free radical species are identified as mediators for β-cell damage in insulin-dependent DM. ROS and RNS via multiple pathways alter cellular function and viability and ultimately induce apoptosis. ROS and RNS have also been identified as mediators for cytokine-induced β-cell damage.[11]

The surplus fatty acids are metabolized via β-oxidation, ensuing mitochondrial electron transport overload and amplified production of metabolic by-products and ROS. ROS activates the stress response kinases (JNK, p38, PKC) which can directly impair insulin receptor signaling via serine phosphorylation of insulin receptor substrate 1 (IRS-1). Tyrosine phosphorylation of IRS-1 is thus inhibited as a response to insulin binding. This further blocks downstream insulin signaling through PI3K/PDK1/Akt and, thus also blocks GLUT-4 translocation and glycogen synthase activation. Hence, there is a reduction in insulin-stimulated glucose transport and glycogen synthesis. This entire cascade is responsible for impaired glucose disposal and insulin hypersecretion as a compensatory mechanism.[27] The functioning of PI3K depends on the binding of the two Src-homology 2 (SH2) domains in the regulatory subunits to tyrosine-phosphorylated IRS proteins. This causes the catalytic subunit to activate, which rapidly phosphorylates phosphatidylinositol 4,5-bisphosphate (PIP2) to form the lipid second messenger phosphatidylinositol (3,4,5)-triphosphate (PIP3). PIP3 employs Akt to start downstream signaling. Akt is known to phosphorylate and activate eNOS and thus produce NO, thereby linking insulin resistance with cardiovascular disease.[28]

Role of Antioxidant Supplements

Antioxidants have been proven to be effective in reducing diabetic complications. Antioxidants such as selenium, vitamin C, vitamin A, vitamin E, zinc, carotenoids, flavonoids, chromium, and lipoic acid consumed via food or dietary supplements are beneficial in combating oxidative stress.[29-31] Ginseng and green tea have also been recognized for their antioxidant activity.[32,33] The advantages of various antioxidants are summarised in Table 1.

Table 1: Advantages of various antioxidants

Antioxidant	Advantages
Zinc[34]	Reduces post-prandial glucose levels Exerts glycemic control
Selenium[35]	Glycemic control Reduction in HbA1c
Chromium[29]	Stimulates glucokinase Reduces fasting blood glucose levels
Vitamin A[36]	Protects against insulin resistance Essential for maintaining the cell function and mass of pancreatic β-cells
Vitamin C[37]	Beneficial effect on glucose concentrations
Vitamin E[38]	Improves glycemic control Prevents development of diabetic retinopathy and cardiovascular complications
Carotenoids[39]	Protects against complications of diabetes mellitus including nephropathy, neuropathy and retinopathy
Flavonoids[30]	Useful in combating the complication of diabetes (neuropathy, retinopathy, and nephropathy)
Ginseng[32]	Lowers blood glucose Stimulates insulin secretion
Green tea[33]	Improves glucose tolerance Exerts beneficial effects on cardiovascular physiology

Dysregulated redox balance in the local or systemic antioxidant defense systems is involved in the pathogenesis of diabetes and its complications. The oxidative stress outweighs the endogenous antioxidant generation and scavenging capabilities. The resultant vascular damage at macro and micro levels needs to be countered externally. Hence, a consistent supplement with multiple antioxidants may help in reducing oxidative stress and thus complications.[31,40,41] Diabetic patients should include a recommended dietary allowance (RDA) of vitamins and minerals in their daily intake. This will permit the nonenzymatic and enzymatic antioxidant systems to counter oxidative stress.[42] MacFarquhar *et al.*,[43] 2010 reported 201 cases of selenium toxicity wherein, the product in question contained 200 times the labeled concentration leading to deleterious effects.

Antioxidants have an extensive array of biological as well as pharmacological benefits. Oxidation is a complicated process with multiple pathways leading to the formation of free radicals. A mixture of compounds, which have different targets to combat the process would result in greater bioactivity as compared to a single compound. The activity of one antioxidant may also be dependent on the other. The efficiency of antioxidants can be increased by using antioxidant combinations in which the antioxidants have a synergistic effect.[44]

A diet rich in antioxidants is also reported to decrease oxidative stress markers observed in T2DM and improve insulin sensitivity in patients.[45] Counseling patients for lifestyle modifications by PCPs will help the patients manage their condition better.[46]

Summary and Conclusion

Free radicals in the physiological state help in a fundamental cellular processes. Insulin secretion is one of such processes

is adversely affected when homeostasis is knocked off the balance. Oxidative stress leads to impairment of the insulin secretion mechanism which results in hyperglycemia which further triggers more ROS production, forming a vicious circle. The burden of oxidative stress in diabetes mellitus goes beyond the scavenging abilities of the inbuilt antioxidant mechanism of the cells. The antioxidants produced biologically fall short, hence external supplements are required. The external supplements lend a helping hand to control blood glucose levels and also help in deaccelerating the complications related to diabetes mellitus. Research has shown that long-term and an adequate doses of supplements with multiple antioxidants exert a synergistic effect by covering the multiple pathways of oxidative stress. The summary of the key points reviewed in the manuscript is presented in Table 2. Considering the numerous advantages of antioxidants, further research and clinical studies should be encouraged to support the existing data for the management of diabetes mellitus and its complications.

This review presents a consolidated view on the relation between oxidative stress in diabetes mellitus. The advantages of antioxidant supplements in controlling blood glucose levels and also in deaccelerating the complications related to diabetes mellitus have been highlighted.

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Key messages

There is a clear connection between oxidative stress and diabetes mellitus. Antioxidant supplements along with a standard glycemic control approach confer the much-needed advantage for blood glucose control as well as the management of complications.

Table 2: Summary

Oxidative stress is an important pathophysiologic factor in the development of:
Endothelial dysfunction
Insulin resistance
Diabetes
Cardiovascular complications of diabetes
Major antioxidants which can be beneficial in diabetes patients can be classified as:
Minerals: Zn, Se, Cr
Vitamins: A, C, E
Bio-actives: Carotenoids, Flavonoids
Functional foods: Ginseng, Green tea
Antioxidant supplements have been shown to improve:
Endothelial function
Insulin sensitivity
Glycemic Parameters
Markers of cardiovascular health

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Conflicts of interest

There are no conflicts of interest.

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