Atir Ali *et al*, International Journal of Pharmaceutical Sciences & Medicine (IJPSM),
Vol.8 Issue. 3, March- 2023, pg. 1-19

ISSN: 2519-9889
Impact Factor: 5.9

FREE RADICALS AND DIABETES MELLITUS

Atir Ali*[1]; Mohit Kumar[2]; Nidhi Srivastava[3]; Mohd Muntazim Khan[4]; Mohammad Asif Khan[5]

Author's address affiliations-
*[1]Community Pharmacist, Syed Medical Store, Tilhar, UP, India
[2]Associate Professor, ACME Institute of Pharmacy Bareilly, UP, India
[3]Assistant Professor, Arya Group of Institutions, Nawabganj Bareilly, UP, India
[4]Department of Animal Sciences, MJPRU Campus Bareilly, UP India
[5]Associate Professor, Institute of Pharmacy, Shri Ramswaroop Memorial University, Lucknow-Deva Road, UP, India

DOI: 10.47760/ijpsm.2023.v08i03.001

Corresponding author's details-
Atir Ali
Community Pharmacist, Syed Medical Store, Tilhar, UP, India
Email id: syedatirtil@gmail.com

ABSTRACT:
Oxidative stress or free radicals has been found in many studies to participate in progression of diabetes mellitus which plays an important role during diabetes, including impairment of insulin action and increase in complicated incidence. This review was based on the detection of roles of free radicals in the progression of diabetes mellitus thru using different sites like PubMed, Medline, Scopus etc. Endothelial cells also contain high amounts of aldo-keto reductase, and are thus prone to increased polyol pathway activation. Moreover, a large body of evidence supports hypothesis that hyperglycaemia or diabetes leads to vascular diacylglycerol accumulation and subsequent PKC activation, causing a variety of cardiovascular defects. Increase in the levels of oxygen and nitrogen free radicals (ROS/RNS) has been linked with lipid peroxidation, non-enzymatic glycation of proteins and oxidation of glucose which contributes toward diabetes mellitus and its complications. Most of the studies have shown relationship between oxidative stress and diabetes along with their complications related to heart, liver kidney and eye. Thus, oxidative stress seems to be more worrying in metabolic disorders specially NIDDM. It concludes that metabolic oxidation is the strongest factor behind insulin dependent and non-insulin dependent diabetes mellitus.

Keywords: Oxidative stress, non-insulin dependent diabetes mellitus, free radicals, antioxidants

ISSN: 2519-9889
Impact Factor: 5.9

INTRODUCTION

As a collection of metabolic illnesses, diabetes mellitus is defined by hyperglycaemia (high blood sugar) and inadequate insulin production or activity inside the body [1]. Glucose, sulphonylureas, and arginine are all triggers that can cause the beta cells in the islets of Langerhans in the pancreas to produce the protein (hormone) insulin [2]. Elevated blood sugar levels over time can cause both macro- and micro-vascular problems, such as atherosclerosis, retinopathy, nephropathy, and retinopathy. In addition to hyperglycaemia, additional variables, such as hyperlipidaemia and oxidative stress, play a significant role in the development of diabetes and increase the risk of complications [3-5]. Hyperglycaemia due to abnormalities in insulin action or insulin secretion or both characterise the metabolic illnesses known collectively as diabetes mellitus. Epidemic levels of diabetes have made it one of the world's leading health concerns. Throughout the illness process, hyperglycaemia typically results in microvascular problems, and diabetic patients are at an increased risk for rapid progression of atherosclerotic macrovascular disease [6-8].

Types of Diabetes Mellitus

Diabetes is classified into 2 types majorly, as below-

Type I Diabetes/ Juvenile onset/ IDDM

Type II Diabetes/Adult onset/NIDDM

1. *Type I diabetes (Insulin dependent)* is due to immune mediated beta-cells destruction, leading to insulin deficiency. It occurs mainly in younger people. And it is also called juvenile onset diabetes as the name suggests it occurs in younger people and it can be only treated by using insulin. Type 1 Diabetes is characterized by autoimmune destruction of Insulin producing cells in the pancreas by CD4+ and CD8+ T cells and Macrophages infiltrating the islets. Several features characterize Type 1 diabetes mellitus as an autoimmune disease [9-12]:

- Presence of immuno-competent and accessory cells in infiltrated Pancreatic islets;
- Association of susceptibility to disease with the class II (immune Response) genes of the major histocompatibility complex (MHC; Human leucocyte antigens HLA);
- Presence of islet cell specific autoantibodies;
- Alterations of T cell mediated immunoregulation, In CD4+ T cell compartment;
- The involvement of monoclines and TH1 cells producing Interleukins in the disease process;

ISSN: 2519-9889
Impact Factor: 5.9

- Response to immunotherapy and;
- Frequent occurrence of other organ specific auto- immune

Diseases in affected individuals or in their family members. Approximately 85% of patients have circulating islet cell antibodies, And the majorities also have detectable anti-insulin antibodies before Receiving insulin therapy. Most islet cell antibodies are directed against Glutamic acid decarboxylase (GAD) within pancreatic B cells [13-14]. The autoimmune destruction of pancreatic β -cells, leads to A deficiency of insulin secretion which results in the metabolic Derangements associated with T1DM. In addition to the loss of insulin Secretion, the function of pancreatic α -cells is also abnormal and There is excessive secretion of glucagons in T1DM patients. Normally, Hyperglycemia leads to reduced glucagons secretion, however, In patients with T1DM, glucagons secretion is not suppressed by Hyperglycemia. The resultant inappropriately elevated glucagon Levels exacerbate the metabolic defects due to insulin deficiency. Although insulin deficiency is the primary defect in T1DM, there is Also a defect in the administration of insulin. Deficiency in insulin Leads to uncontrolled lipolysis and elevated levels of free fatty acids In the plasma, which suppresses glucose metabolism in peripheral Tissues such as skeletal muscle. This impairs glucose utilization and insulin deficiency also decreases the expression of a number of Genes necessary for target tissues to respond normally to insulin such As glucokinase in liver and the GLUT 4 class of glucose transporters in Adipose tissue explained that the major metabolic derangements, Which result from insulin deficiency in T1DM are impaired glucose, Lipid and protein metabolism [15-17].

2. ***Idiopathic diabetes*** is the type 1 diabetes with no known etiologies and is strongly inherited. It occurs in people with unknown cause. And it can be treated by using certain type of medication and in the episode of very high or elevated level of glucose it can also only controlled by insulin [18].

3. ***Type II diabetes (non-Insulin dependent)*** **i**s due to insulin Secretory defect and insulin resistance. It occurs in elderly person and person with obesity. It can be controlled by certain medications and life style changes. In type 2 diabetes these mechanisms break down, with the Consequence that the two main pathological defects in type 2 diabetes Are impaired insulin secretion through a dysfunction of the pancreatic B -cell, and impaired insulin action through insulin resistance [19]. In situations where resistance to insulin predominates, the mass of B -cells undergoes a transformation capable of increasing the insulin Supply and compensating for the excessive and anomalous demand. In absolute terms, the plasma insulin concentration (both

ISSN: 2519-9889
Impact Factor: 5.9

fasting and Meal stimulated) usually is increased, although "relative" to the severity of insulin resistance, the plasma insulin concentration is insufficient to Maintain normal glucose homeostasis [20]. Keeping in mind the intimate Relationship between the secretion of insulin and the sensitivity of Hormone action in the complicated control of glucose homeostasis, it is Practically impossible to separate the contribution of each to the etio-Pathogenesis of DM2 [20]. Insulin resistance and hyperinsulinemia eventually lead to impaired Glucose tolerance. Except for maturity onset diabetes of the young (MODY), the mode of inheritance for type 2 diabetes mellitus is Unclear. MODY, inherited as an autosomal dominant trait, may result from mutations in glucokinase gene on chromosome 7p. MODY is Defined as hyperglycemia diagnosed before the age of twenty-five years and treatable for over five years without insulin in cases where islet cell Antibodies (ICA) are negative. Insulin resistance the primary events are believed to be an initial deficit in insulin Secretion and in many patients' relative insulin deficiency in association with peripheral insulin resistant [20-21]. Resistance to the action of Insulin will result in impaired insulin mediated glucose uptake in the periphery (by muscle and fat), incomplete suppression of hepatic Glucose output and impaired triglyceride uptake by fat. To overcome the insulin resistance, islet cells will increase the amount of insulin Secreted. Endogenous glucose production is accelerated in patients with type 2 diabetes or impaired fasting glucose. Because this increase Occurs in the presence of hyper insulinemia, at least in the early and Intermediate disease stages, hepatic insulin resistance is the driving Force of hyperglycemia of type 2 diabetes [22].

4. Gestational diabetes mellitus is any form of intolerance to Glucose with onset or first recognition of pregnancy. It occurs only at the time of gestation and disappear as delivery occurred or after labour. Gestational diabetes mellitus (GDM) is a heterogeneous pathogenic condition affecting 2-5% of all pregnant women during pregnancy in other data is 5-6% . GDM and T2DM share a common pathophysiological background, including β -cell dysfunction and IR. In addition, women with GDM are at increased risk of developing T2DM later in life. The pancreatic β- cells failure and impairment is the primary characteristic of GDM. In this group of patients with diabetes, there is a genetic predisposition triggered by increased IR during pregnancy leading to malfunction of the pancreatic β -cells. The clustering of the GDM within family members suggestive of genetic predisposition to the development of this disease. Furthermore, women with MODY gene mutations are reported to have GDM more often. In addition, the mutations in other genes include glucokinase (GCK), HLA antigens, insulin receptor (INSR), insulin-like growth factor-2 (IGF2), HNF4A, insulin gene (INS-VNTR), plasminogen activator inhibitor 1 (PAI-1), potassium inwardly rectifying channel subfamily J, member 11

ISSN: 2519-9889
Impact Factor: 5.9

(KCNJ11), hepatocyte nuclear factor-4a (HNF4A) and 1α (HNF1A) suggest the susceptibility to increase the risk of GDM in certain patients [23-24].

The stimulators or the inducers of IR and phosphorylate insulin receptor substrate (IRS) proteins are activated in uncontrollable method several kinases, including inhibitor of nuclear factor κB kinase β (IKK β), c-Jun N-terminal kinase (JNK), mammalian target of rapamycin (mTOR), protein kinase C (PKC) and ribosomal S6 protein kinase (S6K). Substance P is a potent cytokine and is considered one of the crucial activators that contribute in the development of IR by impairment of insulin signalling. The genetic variants in TCF7L2 is the strongest gene associated with GDM risk among other minor alleles of rs7903146 (TCF7L2), rs1225 5372 (TCF7L2), rs1799884 (-30G/A, GCK), rs5219 (E23K, KCNJ11), rs7754840 (CDKAL1), rs4402960 (IGF2BP2), rs10830963 (MTNR1B), rs1387153 (MTNR1B) and rs1801278 (Gly972Arg, IRS1) significantly associated with a higher risk of GDM. There are 12 SNPs from 10 genes are associated GDM [25].

The E23K polymorphism of KCNJ11 seems to predispose to GDM in Scandinavian women and the polymorphism of TCF7L2 (rs7903146 C/T) gene, and the G972R polymorphism of the IRS1 gene, seems to predispose to GDM in Greek women. In women of Han nationality in north China, the defect in sulfonylurea receptor-1 (SUR1) gene (cc and AA) may contribute to insulin hypersecretion, which might be the cause of increased body weight and decreased IS and genotype cc of SUR1 is connected with severe type of GDM [26].

In animals but not in human, Galanin inhibits glucose-stimulated insulin release. In the human, the initial postprandial rise of glucose and insulin are suppressed by galanin administration. Galanin and IL-6 were found to be significantly associated with IR markers in GDM, thus may play important roles in the regulation of glucose hemostasis. The higher level of plasma galanin is a novel biomarker for the prediction of GDM. In late pregnancy the relative proinsulin secretion is mainly related to IR and does not necessarily reflect β -cell function. T2DM is not independently associated with hyperproinsulinemia as measured by the proinsulin-to-C-peptide ratio. While, in pregnant women, the increased in IR is associated with decreased proinsulin to C-peptide ratio, independently of glucose tolerance status. The islet amyloid pancreatic polypeptide hypersecretion is characteristic for pregnancy and might partially decrease hyperinsulinemia in pregnancy by inhibiting insulin secretion. The β- cells dysfunction and IR are the core in the pathogenesis of T2DM and both are mediated by Adiponectin. Therefore, in late pregnancy the Adiponectin is an independent factor correlated with β - cells dysfunction. All of these are secreted by placenta independently [27].

ISSN: 2519-9889
Impact Factor: 5.9

The fall of IS during pregnancy is counteracted by increase maternal insulin secretion to maintain glucose control. The insufficient insulin secretion to counteract the pregnancy-related decrease in IS contributing in development of DM. Women at high risk of GDM should have a prior conception plan to prevent DM by normalize body weight, regular physical exercise, reducing excess intake of animal protein and soft drinks, planning of pregnancy in younger ages, avoiding pollutant exposition and smoking cessation [28].

Pathophysiology of diabetes

Whenever somebody takes the meal, there is rise in blood glucose levels that stimulates insulin secretion resulting in an Increase in transportation, biotransformation and storage in Muscles and fat tissues. In fasting conditions, the glucose in Blood is provided by liver that is used by the brain, without any dependency on insulin [29].

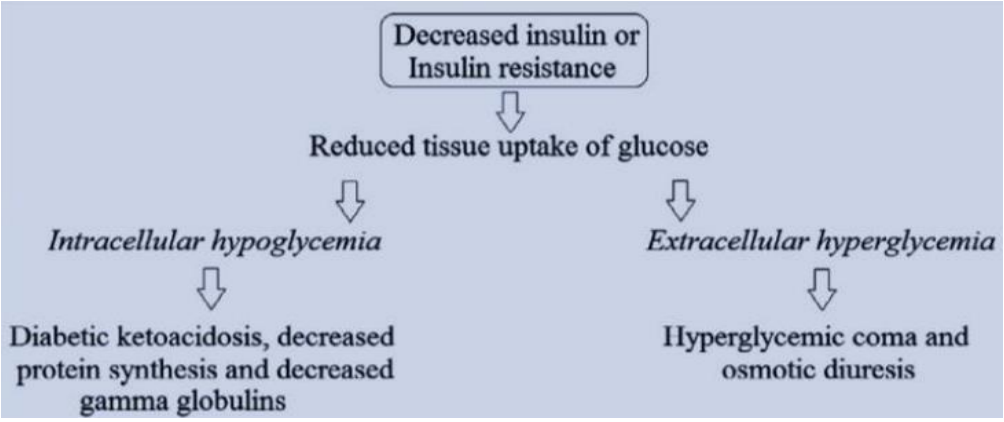

Fig 1. Pathophysiology of diabetes mellitus

Besides the storage of glucose, Insulin also inhibits the secretion of glucagon and lowers the concentration of serum fatty acids leading to a decline in liver glucose production. 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 (causing cachexia, Polyphagia, and impaired wound healing), while the extracellular hyperglycemia leads to hyperglycemic coma and osmotic dieresis.

ISSN: 2519-9889
Impact Factor: 5.9

Pathogenesis of Type I diabetes mellitus (IDDM)

In Insulin dependent diabetes mellitus (IDDM) there is a deficiency of insulin secretion due to the autoimmune destruction of beta pancreatic cells that leads to metabolic disturbances associated with IDDM. The end stage of b-cell destruction represents the onset of clinical disease leading to type 1 diabetes mellitus in which there are infiltrating monocytes, lymphocytes and a mixture of pseudoatrophic islets with some cells secreting somatostatin, glycogen and pancreatic polypeptide which then, consequently through immunogenic process, induces the disease and autoimmunity, genetic makeup and environmental factors are responsible for islets cell destruction [30].

Pathogenesis of Type II diabetes mellitus (NIDDM):

In Non-Insulin dependent diabetes mellitus (NIDDM) there are certain mechanisms broken 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. In this type of diabetes, multiple genetic defects, and certain environmental factors especially obesity are responsible for beta cell defects and peripheral tissue insulin resistance respectively.

Complications of diabetes mellitus:

Diabetes is such a sort of disorder in which the patients are at all the time on risk of complications. Complications may be macrovascular (coronary heart disease, peripheral vascular disease and stroke), microvascular (neuropathy, retinopathy and nephropathy) and both micro- and macrovascular (diabetic foot). The mortality and morbidity of diabetes are associated more with macrovascular degeneration as compared to the risks of microvascular complications in older people [31].

In general, complications of diabetes mellitus can be categorized into two groups

a. Metabolic acute complications:

These are short term and include hypoglycemia, ketoacidosis and hyperosmolar non-ketonic coma.

b. ***Systemic late complications:***

These are long term chronic sort of complications that include diabetic nephropathy, microangiopathy, diabetic neuro- and retinopathy, atherosclerosis and infections.

ISSN: 2519-9889
Impact Factor: 5.9

Macrovascular complications

The central pathological mechanism in macrovascular complications is atherosclerotic disease. Atherosclerosis occurs as a result of chronic inflammation and injury to the arterial wall in the peripheral or coronary vascular system. This damages cause accumulation of oxidized lipids from LDL particles in the endothelial wall of arteries, whose rupture leads to acute vascular infarction. Additionally, platelet adhesion and hypercoagulability also occurs in type 2 diabetes, increasing the risk of vascular occlusion. It has been proposed that increased superoxide production is the central and major mediator of endothelial tissue damage, causing direct inactivation of two antiatherosclerotic enzymes, endothelial nitric oxide synthase and prostacyclin synthase and that the activation of oxidative stress pathways is involved in the pathogenesis of complications [32].

Endothelial cells also contain high amounts of aldo-keto reductase, and are thus prone to increased polyol pathway activation. Moreover, a large body of evidence supports hypothesis that hyperglycemia or diabetes leads to vascular diacylglycerol accumulation and subsequent PKC activation, causing a variety of cardiovascular defects. PKC activation has been associated with vascular alterations such as increases in permeability, contractility, extracellular matrix synthesis, cell growth and apoptosis, angiogenesis, leukocyte adhesion, and cytokine activation and inhibition. Hyperglycemia-induced activation of PKC has also been implicated in the overexpression of the fibrinolytic inhibitor, plasminogen activator inhibitor-1 (PAI-1) [74]. In smooth muscle PKC hyperactivity is associated with decreased NO production and has been shown to inhibit insulin-stimulated expression of eNOs in endothelial cells.

Introduction to Free Radicals

Free radicals are reactive chemical entities that are short lived species containing one or more unpaired electrons. They can also be considered as necessary evil for signaling involved in normal process of differentiation and migration. The free radicals induce damage to cells by passing the unpaired electron resulting in oxidation of cell components and molecules. They are generally very unstable and very much reactive.

Types of Free Radicals

Free radicals can be classified into following three types:

Reactive oxygen species (ROS)

Reactive oxygen species are highly reactive chemical molecules formed due to the electron receptivity of O_2 . Examples of ROS include peroxides, superoxide, hydroxyl radical, singlet oxygen, and alpha-oxygen.

Atir Ali *et al*, International Journal of Pharmaceutical Sciences & Medicine (IJPSM),
Vol.8 Issue. 3, March- 2023, pg. 1-19

ISSN: 2519-9889
Impact Factor: 5.9

Reactive Nitrogen Species (RNS):

Reactive nitrogen species are a family of antimicrobial molecules derived from nitric oxide and superoxide produced via the enzymatic activity of inducible nitric oxide synthase 2 and NADPH oxidase respectively [33].

Reactive chlorine species (RCS):

It oxidizes other molecules i.e., chloramines.

Biological roles of free radicals

As discussed earlier, free radicals are said to be necessary evil, as they play role in origin and evolution of life. These are important for activating different signaling pathways inside the cell, such as the Mitogen activated protein kinase (MAPK) and extracellular-signal-regulated kinase (ERK) pathways that alter gene expression, as well as in coordination with superoxide dismutase initiates cell death. For instance, RNS produced by neurons act as neurotransmitters and those generated by macrophages act as mediators of immunity. These are also responsible for leukocyte adhesion, thrombosis, angiogenesis and vascular tone. Similarly, ROS is involved in gene transcription, single transduction and regulation of other activities in cell [34].

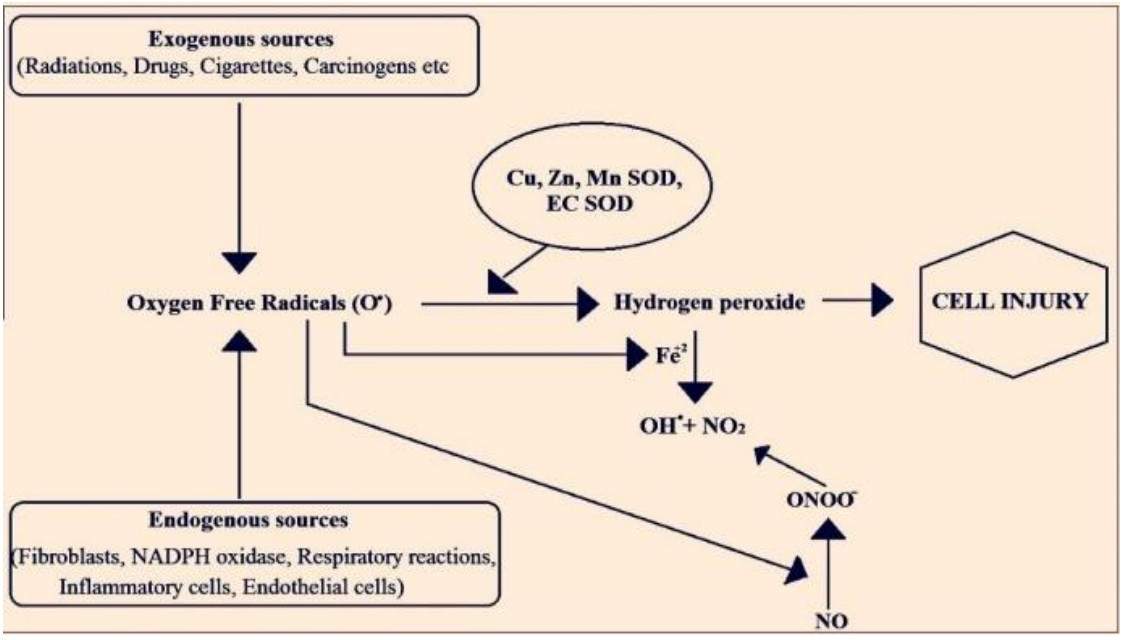

Fig 2. Biological roles of free radicals

Atir Ali *et al*, International Journal of Pharmaceutical Sciences & Medicine (IJPSM),
Vol.8 Issue. 3, March- 2023, pg. 1-19

ISSN: 2519-9889
Impact Factor: 5.9

Production and scavenging of free radicals

Both exogenous and endogenous substances produce free radicals in cells and its surroundings. They can be produced from non-enzymatic reactions of organic compounds with oxygen as well as those initiated by ionizing radiations. This process may also occur in mitochondrion by oxidative phosphorylation. Different sources include radiations, ROS, RNS, Neutrophils and macrophages production, chemicals, smoking of cigarettes, beedi, cigars and industrial effluents.

Now in order to scavenge the deleterious effects of these free radicals, the body has different mechanisms to produce antioxidants, endogenous or exogenous, that will neutralize the elevated number of free radicals and keep the cells protected against their toxic effects and contributing toward the prevention of diseases.

Oxidative stress and antioxidants

It is a universal truth that oxygen is the major factor that has made the life finite. It is one of the important components of aerobic life. However, in some circumstances, this oxygen may be a killer of cells when it generates reactive species that causes necrosis and ultimately the cell death. RNS and RCS also cause oxidation by the generation of certain mechanism that interferes with the normal physiological processes inside the cell.

Oxidative stress can be defined as any disturbance in the balance of antioxidants and pro-oxidants in favour of the later due to different factors such as aging, drug actions and toxicity, inflammation and/or addiction. It is in general, excess formation or/and insufficient removal of highly reactive molecules such as reactive nitrogen species (RNS) and reactive oxygen species (ROS) Oxygen is highly reactive specie that has the ability to become part of potentially harmful and damaging molecules (free radicals) [35].

Lungs	Asthma, chronic bronchitis
Kidneys	Glomerulonephritis, chronic renal failure
Joints	Arthritis, rheumatism
Brain	Alzheimer's disease, Parkinson's disease, memory loss, depression, stroke
Eyes	Cataract, retinal diseases
Fetus	Preeclampsia, IU growth restriction
Heart vessels	Arteriosclerosis, hypertension, ischemia, cardiomyopathy, heart failure
Multi-organs	Cancer, diabetes, inflammation infection, aging

Fig 3. Oxidation induced organs damage

ISSN: 2519-9889
Impact Factor: 5.9

The term ‘‘antioxidant’’ can be labelled for any substance whose availability, even in minute concentration inhibits or delays the oxidation of a substrate. Different types of biological antioxidants include, for instance, Glutathione (oxidized/reduced), Vitamin C & E, cystine, etc.

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. ROS level elevation in diabetes may be due to decrease in destruction or/and increase in the production by catalase (CAT – enzymatic/nonenzymatic), 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. According to epidemiological studies, diabetic mortalities can be explained notably by an increase in vascular diseases other than hyperglycaemia.

Hyperglycaemia and free fatty acid intake are among the causes for oxidative stress conditions. Hence, it may not be surprising that diabetic subjects tend to have more oxidative cell and organism environments than healthy subjects, i.e., an increase in ROS generation. Moreover, diabetic patients present a decrease in antioxidant defences. The antioxidant enzyme levels are affected by diabetes, which further increase oxidative stress. Oxidative stress has been proposed as a major participant in the pathophysiology of diabetic complications. Nevertheless, regarding diabetes onset and development, oxidative stress has also shown to affect the two major mechanisms failing during diabetes: insulin resistance and insulin secretion [36].

Oxidative stress processes in insulin resistance

ROS and RNS affect the insulin signalling cascade. As with other ROS effects, low doses play a physiological role in insulin signalling. After insulin stimulation of its receptor in adipocytes, H2O2 is produced via NADPH oxidase, which by inhibits PTP1B catalytic activity, thus increasing tyrosine phosphorylation.

Disturbs in cellular redistribution of insulin signaling components may alter the insulin cascade, a process mediated by NF-κB. A decrease in GLUT4 gene transcription and increase in GLUT1 (insulin independent glucose transporter) has also been observed, as well as increases in phosphorylation of IRS protein in an insulin receptor-independent fashion (perhaps by the stress kinases). Altogether, hyperglycemia and insulin resistance may also lead to altered mitochondrial function, and insulin action impairment by cytokines in response to metabolic stress. An increase in the hexosamine pathway has also been linked to insulin resistance. Moreover, it has been proposed that this pathway acts as a cellular sensor for the glucose excess. From that point of

ISSN: 2519-9889
Impact Factor: 5.9

view, insulin resistance may be a protective mechanism from the glucose excess entrance [37].

Oxidative stress processes in insulin secretion

Pancreatic beta-cells are especially sensitive to ROS and RNS, because their natural enzymatic antioxidant defences are lower compared to other tissues such as liver. Moreover, they lack the ability to adapt their low enzyme activity levels in response to stress such as high glucose or high oxygen. Glucose enters to the beta-cell in an insulin independent fashion, because besides providing energy, glucose sensing in the beta-cell is crucial for insulin secretion. It has been suggested that hyperglycemia can generate chronic oxidative stress by the glucose oxidation pathway, leading to an excess in mitochondrial superoxide production, which further activates uncoupling protein-2 (UCP-2). This protein lowers ATP/ADP relationship through proton leak in the beta-cell, which reduces insulin secretion.

ROS also increase the stress signaling pathways in the beta cells, such as NF-κB activity, which potentially leading to beta-cell apoptosis, and the JNK pathway which has been related to suppression of insulin gene expression, possibly by reduction of PDX-1 DNA binding activity, a major regulator of insulin expression. It has also been shown that the activation of the hexosamine pathway in beta-cells leads to suppression of PDX-1 binding to the insulin and other genes involved in insulin secretion, perhaps contributing to the beta-cell dysfunction present in diabetes mellitus. As in other cell types, NO in beta-cells has physiologic roles. NO may regulate glucokinase activity by s-nitrosilation in the beta-cell, and possibly increase insulin secretion. However, NO excess and concomitant NRS may cause apoptosis through caspase-3 activation and decrease in ATP levels. Besides ROS hyperproduction, excess mitochondrial metabolism resulting from hyperglycemia in the beta-cell may also alter mitochondrial shape, volume and behavior, uncoupling K-ATP channels from mitochondrial activity and thus altering glucose-induced insulin secretion.

Pathophysiology 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. According to latest research, lipid is not only but also the apolipoprotein component of LDL that forms insoluble aggregates oxidatively due to hydroxyl radical-induced cross-linkage between apo-B monomers that is responsible for oxidative damage in diabetic complications. In diabetes mellitus, main sources of oxidative stress are mitochondria. During oxidative

ISSN: 2519-9889
Impact Factor: 5.9

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. 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.

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. A variety of pathological conditions are induced by oxidative stress such as Rheumatoid arthritis Diabetes mellitus and cancer. Free radical and oxidative stress induced complications from DM include coronary artery disease, Neuropathy, nephropathy, retinopathy and stroke.

Although large amounts of cellular radical generation may be Harmful, should there be a substantial rise in free radical Generation or a reduction in free radical elimination from the cells, oxidative cellular stress occurs. Therefore, it is essential to balance free radical generation with elimination. to date, there are sufficient experimental and clinical evidences that point to the increased formation of reactive oxygen species (ROS) in diabetes and that the development of diabetes is strongly linked to oxidative stress. Oxidative stress causes elevated ROS and/or reactive species of oxygen (RNS) which include charged species like hydroxyl radical and superoxide and uncharged Species including peroxide of hydrogen and singlet oxygen. The autooxidation of glucose; changes in redox balance Decreases in low-molecular-weight antioxidant substances Like glutathione (GSH) and vitamin E; and impaired antioxidant defence operations, such as SOD and CAT, may be Plausible causative factors of oxidative stress in diabetes. Additionally, high- glucose-generated ROS is causally linked to elevated glucose and other metabolic abnormalities That are crucial to the development of diabetic complications. However, the precise mechanisms by which oxidative stress can lead to the progression of diabetic problems remain Unknown.

The role of free radicals and oxidative stress in the pathogenesis and development of diabetic retinopathy, nephropathy, neuropathy, and rapid coronary artery disease has also been confirmed with convincing evidence. In fact, several experiments have Shown that increased extra- and

ISSN: 2519-9889
Impact Factor: 5.9

intracellular glucose levels result in oxidative stress, both in experimental diabetes animals and in diabetic patients.

A cascade of ROS leaking from the mitochondria can be a source of oxidative stress which contributes to the (1) development of type 1 diabetes (T1DM) via apoptosis of pancreatic beta cells and (2) onset Of T2DM through insulin resistance. The fundamental Processes in the development of diabetes are complicated, Since hyperglycaemia may also be due to the cause-effect relationship of enhanced oxidative stress. Oxidative stress biomarkers are normally measured by lipid peroxidation Indicators and protein oxidation, both in T1DM and T2DM. Normally, oxidative stress in diabetes is contributed by Various mechanisms, including excessive oxygen radical Formation from the autooxidation of glucose, glycated Protein formation, and antioxidant enzyme glycation which Restrict the ability of antioxidants to detoxify the free radicals. In contrast to these mechanisms, two other mechanisms Have been proposed to be responsible for producing oxygen Radicals in diabetes. First, Jain indicated that elevated glucose Concentrations can boost cytochrome P450-like activity due To the production of excessive nicotinamide adenine dinucleotide phosphate oxidase (NADPH) generated by glucose Metabolism [55]. Secondly, ketosis, a classic and specific Example of T1DM, may also enhance the generation of free Radicals in diabetic patients. Many reports have attributed the common pathogenic element in endothelial and beta-cell dysfunction to oxidative stress. For example, beta-cell dysfunction caused by Prolonged exposure to high glucose raised free fatty acid (FFA) levels. Beta cells are especially susceptible to ROS Because they are low in enzymes such as CAT, glutathione Peroxidase (GPx), and SOD; they are also low in free radical Quenching (antioxidants). It is therefore not surprising that Oxidative stress can damage mitochondria and significantly Blunt insulin secretion. It has been shown that oxidative Stress caused by a limited exposure from beta- cell preparations To hydrogen peroxide (H2O2) can increase the output of protein cycline- dependent kinase inhibitor 1 (p21) and decrease Insulin messenger ribonucleic acid (mRNA), cytosolic adenosine triphosphate (ATP), and calcium flux in the cytosol and mitochondria. In fact, many experimental data have demonstrated different kinds of vascular cells can generate ROS under hyperglycaemic situations. ROS levels are tightly controlled by the antioxidant and nonenzyme antioxidant protective measures in normal and healthy cells. However, excessive ROS concentrations Are contributed by hyperglycaemia in diabetes, leading to A significant complication of DM. In the case of diabetes or insulin resistance, a higher oxidative glucose metabolism itself increases the mitochondrial production of O2• Which is then converted to OH• and H2O2. In addition to glucose, ROS generation by mitochondrial FFA is Also augmented. Overall, the overexpression and activation of mitochondrial inner membrane

ISSN: 2519-9889
Impact Factor: 5.9

Uncoupling enzymes (UCPs) have been suggested to contribute to an increase in superoxide production under diabetic conditions.

Biomarkers of oxidative stress in diabetes mellitus

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. Any alteration in their levels will make the cells prone to oxidative stress and hence cell injury.

Catalase (CAT)

Catalase is regulator of hydrogen peroxide metabolism that can, in excess, cause serious damage to lipids, RNA and DNA. CAT converts H2O2 catalytically into water and oxygen and thus neutralizes it. In case of catalase deficiency, beta cell of pancreas that contain large amount of mitochondria, undergoes oxidative stress by producing excess ROS that leads to b-cells dysfunction and ultimately diabetes.

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 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 affected enhancing oxidative stress in diabetes.

Lipids

Diabetes mellitus produces disturbances in the lipid profile of body making the cells more susceptible to lipid peroxidation. 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. Lipid hyperperoxides (LHP) through Intermediate radical reactions produce such fatty acids that generate highly reactive and toxic lipid radicals that form new LHP. A critical biomarker of oxidative stress is Lipid peroxidation which is the most explored area of research when it comes to ROS. Malondialdehyde (MDA) is formed as a result of lipid peroxidation that can be used to measure lipid peroxides after reacting it with thiobarbituric acid.

ISSN: 2519-9889
Impact Factor: 5.9

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.

Free Radicals and Diabetes Mellitus

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 the transfer of their free unpaired electron causes the oxidation of cellular machinery. In order to encounter the deleterious effects of such species, body has got endogenous antioxidant systems or it obtains exogenous antioxidants from 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 project was to summarize the basics of oxidative stress in diabetes mellitus.

CONCLUSION

Oxidative stress has been demonstrated in many studies to participate in the progression of diabetes which plays important role during diabetes, including impairment of insulin action and elevation of the complication incidence. Antioxidants have already shown to be prospective in the treatment of diabetes both type 1 and type 2. Increase in the levels of oxygen and nitrogen free radicals (ROS/RNS) has been linked with lipid peroxidation, non-enzymatic glycation of proteins and oxidation of glucose which contributes toward diabetes mellitus and its complications. Most of the studies have shown relationship between oxidative stress and diabetes along with their complications related to heart, liver kidney and eye.

It concludes that metabolic oxidation is the strongest factor behind insulin dependent and non-insulin dependent diabetes mellitus.

ISSN: 2519-9889
Impact Factor: 5.9

FUNDING

Nil.

CONFLICT OF INTEREST

None.

REFERENCES

[1]. Al Homsi, M.F., Lukic, M.L., 1992. An Update on the pathogenesis of Diabetes Mellitus. Department of Pathology and Medical Microbiology (Immunology Unit), Faculty of Medicine and Health Sciences, UAE University, Al Ain, United Arab Emirates. American Diabetes Association, 2004. Diagnosis and classification of diabetes. Diabetes Care 27 (1), S5 –S10.

[2]. Asfandiyarova, N., Kolcheva, N., Ryazantsev, I., Ryazantsev, V.,2007. Risk factors for stroke in type 2 diabetes mellitus. Diab. Vasc.Dis. Res. 3, 57 – 60.

[3]. yepola, O.R., Brooks, N.L., Oguntibeju, O.O. 2014. Oxidative Stress and Diabetic Complications: The Role of Antioxidant Vitamins and Flavonoids. <http://dx.doi.org/10.5772/57282>.

[4]. ansal, A.K., Bilaspuri, G.S., 2011. Impacts of oxidative stress and antioxidants on semen functions (review article). Vet. Med. Int. Butterfiel et al, 1998. Structural and functional changes in proteins induced by free radical-mediated oxidative stress and protective action of the antioxidants N-tert-butyl-alpha-phenylnitrone and vitamin E. Ann. N.Y. Acad. Sci. 854, 448–

[5]. 462.Ceriello, A., 2006. Oxidative stress and diabetes-associated complications. Endocr. Pract. 12 (l), 60–62.

[6]. ho, K.-H., Wolkenhauer, O., 2003. Analysis and modelling of signal transduction pathways in systems biology. Biochem. Soc. Trans. 31 (6), 1503 –1509. Defronzo, R.A., Lily, Ferrannini E., 1988. Lecture 1987, the triumvirate: beta cell, muscle, liver. A collusion responsible for NIDDM.Diabetes 37, 667 –687.

[7]. roge, Wulf, 2011. Free radicals in the physiological control of cell function. Physiol. Rev. 82, 47–95.

[8]. l Faramawy, S.M., Rizk, R.A., 2011. Spectrophotometric studies on antioxidants-doped liposomes. J. Am. Sci. 7, 363 –369.

[9]. Erejuwa, O.O., 2012. Oxidative stress in diabetes mellitus: is there a role for hypoglycemic drugs and/or antioxidants. Oxid. Stress Dis.,217 –246.

[10]. sterbauer, H., Schaur, R.J.r., Zollner, H., 1991. Chemistry and biochemistry of 4- hydroxynonenal, malonaldehyde and related aldehydes. Free Rad. Biol. Med. 11 (1), 81 –128.

[11]. ang, Yun-Zhong, Yang, Sheng, Wu, Guoyao, 2002. Free radicals, antioxidants, and nutrition. Nutrition 18, 872–879.

[12]. reidovich, I., 1999. Fundamental aspects of reactive oxygen species, or what's the matter with oxygen? Ann. N.Y. Acad. Sci. 893, 13.

[13]. ill, R.G., Haskins, K., 1993. Molecular mechanisms underlying diabetes and other autoimmune diseases. Immunol. Today, 49 –51.

[14]. iugliano, D., Ceriello, A., Paolisso, G., 1995. Diabetes mellitus, hypertension, and cardiovascular disease: which role for oxidative stress? Metabolism 44 (3), 363 –368.

[15]. alliwell, B., 1994. Free radicals, antioxidants, and human disease: curiosity, cause, or consequence? Lancet 344, 721 –724.

[16]. Hatice, P. et al, 2004. Lipid peroxidation and resistance to oxidation in patients with type 2

ISSN: 2519-9889
Impact Factor: 5.9

diabetes mellitus. Tohuku J. Exp. Med. 203, 211–218.

[17]. Jamieson, Dana., 1986. The relation of free radical production to hyperoxia. Ann. Rev. Physiol. 48, 703–719.

[18]. Johansen, Jeanette Schultz et al, 2005. Oxidative stress and the use of antioxidants in diabetes. Cardiovas. Diabetol. 4, 5.Joshi, S.R., Parikh, R.M., Das, A.K., 2007. Insulin-history, biochemistry, physiology and pharmacology. J. Assoc. Phys. India 55 (L),19.Kangralkar, V.A., Patil, S.D., Bandivadekar, R.M., 2010. Oxidative stress and diabetes: a review. Int. J. Pharm. Appl. 1 (1), 38 – 45.Lipinski, B., 2001. Pathophysiology of oxidative stress in diabetes mellitus. J. Diabetes its Complications 15 (4), 203 –210.

[19]. Loghmani, E., 2005. Diabetes Mellitus: Type 1 and Type 2. In: Stang, J., Story, M. (Eds)., Guidelines for Adolescent Nutrition Services 2005.Maritim, A.C., Sanders, R.A., Watkins, J.B.,

[20]. 2003. Diabetes, oxidative stress, and antioxidants: a review. J. Biochem. Mol. Toxicol. 17 (1),24–38.

[21]. Mark Percival, 1996. Antioxidants, Clinical Nutrition insights.NUT031 1/96 Rev. 10/98. Matough, F.A., Budin, S.B., Hamid, Z.A., Alwahaibi, N., Mohamed, J., 2012. The role of oxidativestress and antioxidants in diabetic complications. Sultan Qaboos Univ. Med. J. 12 (1), 5 – 18.Michael, J.C., James, M.C., Robbins, VinayK, 2000. The pancreas. In:Pathalogic Basis of Disease, sixth ed. Harcourt Publisher, pp. 902 –929.Mohan, Harsh, 2002. Textbook of Pathology, fourth ed. Jaypeepublishers.

[22]. M. Valko, D. Leibfritz, J. Moncol, M. T. Cronin, M. Mazur, And J. Telser, "Free radicals and antioxidants in normal physiological functions and human disease, " The International Journal of Biochemistry & Cell Biology, vol. 39, no. 1,pp. 44 – 84, 2007.

[23]. J. S. Johansen, A. K. Harris, D. J. Rychly, and A. Ergul, " Oxidative stress and the use of antioxidants in diabetes: linking Basic science to clinical practice, " Cardiovascular Diabetology, vol. 4, no. 1, p. 5, 2005.

[24]. P. Rösen, P. Nawroth, G. King, W. Möller, H. J. Tritschler, And L. Packer, "The role of oxidative stress in the onset and Progression of diabetes and its complications: a summary of A Congress Series sponsored by UNESCO-MCBN, the American Diabetes Association and the German Diabetes Society," Diabetes/Metabolism Research and Reviews, vol. 17, no. 3, pp. 189–212, 2001.

[25]. V. M. Victor, M. Rocha, R. Herance, and A. Hernandez Mijares, "Oxidative stress and mitochondrial dysfunction in Type 2 diabetes, " Current Pharmaceutical Design, vol. 17, No. 36, pp. 3947–3958, 2011.

[26]. R. A. Kowluru and P.-S. Chan, "Oxidative stress and diabetic Retinopathy," Experimental Diabetes Research, vol. 2007, Article ID 043603, 2007.

[27]. D. M. Niedowicz and D. L. Daleke, "The role of oxidative Stress in diabetic complications," Cell Biochemistry and Biophysics, vol. 43, no. 2, pp. 289 –330, 2005.

[28]. J. Cederberg, S. Basu, and U. J. Eriksson, "Increased rate of Lipid peroxidation and protein carbonylation in experimental Diabetic pregnancy," Diabeto logia, vol. 44, no. 6, pp. 766 –774, 2001.

[29]. S. Wolff, "Diabetes mellitus and free radicals: free radicals, Transition metals and oxidative stress in the aetiology of diabetes mellitus and complications, " British Medical Bulletin Vol. 49, no. 3, pp. 642–652, 1993.

[30]. D. Giugliano, A. Ceriello, and G. Paolisso, "Diabetes mellitus, Hypertension, and cardiovascular disease: which role for oxidative stress?," Metabolism, vol. 44, no. 3, pp. 363 –368, 1995

[31]. S. K. Jain, "Hyperglycemia can cause membrane lipid peroxidation and osmotic fragility in human red blood cells," Journal of Biological Chemistry, vol. 264, no. 35, pp. 21340 –21345,1989.

[32]. S. K. Jain, K. Kannan, and G. Lim, "Ketosis (acetoacetate) can Generate oxygen radicals and cause

ISSN: 2519-9889
Impact Factor: 5.9

increased lipid peroxidation and growth inhibition in human endothelial cells," Free Radical Biology & Medicine, vol. 25, no. 9, pp. 1083 –1088,1998.

[33]. J. L. Evans, I. D. Goldfine, B. A. Maddux, and G. M. Grodsky,"Are oxidative stress -activated signaling pathways mediators Of insulin resistance and β-Cell Dysfunction?, " Diabetes, Vol. 52, no. 1, pp. 1–8, 2003.

[34]. T.-H. Lu, C.-C. Su, Y.-W. Chen et al., "Arsenic induces pancreatic β-cell apoptosis via the oxidative stress-regulate Mitochondria-dependent and endoplasmic reticulum stress-Triggered signaling pathways," Toxicology Letters, vol. 201,No. 1, pp. 15 –26, 2011.

[35]. P. Maechler, L. Jornot, and C. B. Wollheim, "Hydrogen peroxide alters mitochondrial activation and insulin secretion In pancreatic beta cells," Journal of Biological Chemistry, Vol. 274, no. 39, pp. 27905–27913, 1999.

[36]. T. Nishikawa, D. Edelstein, X. L. du et al., "Normalizing mitochondrial superoxide production blocks three pathways of Hyperglycaemic damage, " Nature, vol. 404, no. 6779,pp. 787 –790, 2000.

[37]. J. L. Evans, I. D. Goldfine, B. A. Maddux, and G. M. Grodsky,"Oxidative stress and stress -activated signaling pathways: a Unifying hypothesis of type 2 diabetes," Endocrine Reviews, Vol. 23, no. 5, pp. 599–622, 2002.

