

Role of Oxidant Alteration of Biomolecules in Diabetes and Other Associated Diseases

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Received: 14 Oct 2017/Revised: 19 Nov 2017/Accepted: 13 Dec 2017

ABSTRACT- Reactive oxygen species (ROS) are products of normal cellular metabolism and are known to act as second messengers. Physiological conditions, ROS participate in the maintenance of cellular 'redox homeostasis' in order to protect cells against oxidative stress through various redox-regulatory mechanisms. Oxidative stress resulting from enhances free-radical formation and/or a defect in antioxidant defences has been implicated in the pathogenesis of diabetes and its associated complications. Diabetes mellitus comprises a group of metabolic disorders that share the common phenotype of hyperglycemia, association with the biochemical alteration of glucose and lipid peroxidation. Increase the level of oxidative stress along with deranging different metabolisms; one of the Long term complications of diabetes mellitus is diabetic retinopathy, which is a leading cause of acquired blindness. Many of the recent landmarks in scientific research have shown that in human beings, oxidative stress has been implicated in the progression of major health problems by inactivating the metabolic enzymes and damaging important cellular components, oxidizing the nucleic acids, leading to cardiovascular diseases, eye disorders, joint disorders, neurological diseases (Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis), atherosclerosis, lung and kidney disorders, liver and pancreatic diseases, cancer, ageing, disease of the reproductive system including the male and female infertility etc. In this review, we had the importance of endogenous antioxidant defense systems, the intense medical management; these strategies include dietary measures (antioxidants) their relationship to several pathophysiological processes and their possible therapeutic implications *in vivo* condition.

Key-words- Oxidative stress, Reactive oxygen species, Diabetic mellitus, Diabetic complications, Free radicals, Associated diseases, Lipid peroxidation

INTRODUCTION

Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Raised blood glucose, a common effect of uncontrolled diabetes, may, over time, lead to serious damage to the heart, blood vessels, eyes, kidneys and nerves. More than 400 million people live with diabetes.

Diabetes is widely recognized as one of the leading causes of death and disability worldwide. [1] WHO estimates that, globally, 422 million adults aged over 18 years were living with diabetes in 2014. [2] In 2000, the World Health Organization (WHO) recorded a total of 171 million people for all age groups worldwide (2.8% of the global population) who have diabetes, and the numbers are expected to rise to 366 million (4.4% of the global population) by 2030. [3] Unless urgent preventive steps are taken, it will become a major health problem.

The Indian Diabetes Federation (IDF) estimated 3.9 million deaths for the year 2010, which represented 6.8% of the total global mortality. [4] Insulin is a protein (hormone) synthesized in beta cells of pancreas in response to various stimuli such as glucose, sulphonylureas, and arginine however glucose is the major determinant. [5] Sidewise to hyperglycemia, there are several other factors that play great role in pathogenesis of diabetes such as hyperlipidemia and oxidative stress leading to high risk of complications. [6] Prolonged exposure of hyperglycemia increases the generation of free radicals and reduces capacities of antioxidant defence system. [7] It is the mainly frequently cause of blindness in people aged 35-75 years. Poor glycaemic control and oxidative stress have been credited to the development of complications like diabetic retinopathy. The retina has high content of polyunsaturated fatty acid (PUFA) and glucose oxidation relative to any other tissue. Hyperglycemia and dyslipidemia in diabetes mellitus stimulate increased lipid peroxidation and ROS formation, an important mechanism in the pathogenesis of diabetic retinopathy. [8] Hyperglycaemia generates ROS, which in turn cause damage to the cells in many ways. Damage to the cells ultimately results in secondary complications in diabetes mellitus. [9,10]

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Quick Response Code	Website: www.ijlssr.com
	 DOI: 10.21276/ijlssr.2018.4.1.6

The pleural fluid MDA and ADA concentration was found to be raised in tubercular patients; might be due to reduced immunity level in disease state; Thus it is concluded that MDA can used a marker of oxidative stress in type 2 DM ^[11,12]. The alteration in the function of endothelium along with antioxidant/pro-oxidant imbalance in hypertension can lead to detrimental consequences and long term adverse effects like atherosclerosis and cardiovascular disease. ^[13]

Oxidative Stress- Oxidative stress describes the condition wherein an excessive production of ROS overwhelms endogenous antioxidant defense mechanisms. The resultant elevation in ROS levels has a detrimental effect on cellular function, a consequence of ROS-induced damage to lipid membranes, enzymes and nucleic acids. ^[14] Risk factors for cardiovascular disease (CVD), including type 2 diabetes, are characterized by excess vascular production of ROS. One of the earliest consequences of oxidative stress in human subjects is impaired endothelium-dependent vasodilatation. ^[15]

Table 1: Types of ROS, source of synthesis and the damage caused by the production of ROS

Name of the ROS	Sources/where and how produced	Damage caused by the particular ROS
Hydrogen peroxide(H ₂ O ₂)	Dismutation of (•O ₂ ⁻) by SOD	Causes membrane damage
Organichydrope roxide (ROOH)	Radical reactions with cellular components	Lipid peroxidation &DNA
Hydroxyl radical(•OH)	Fenton reaction	Attack most cellular components and damage them
Superoxide ion (•O ₂ ⁻)	Auto-oxidation reactions and by the ETS	Can release Fe ²⁺ from iron sulfur proteins and ferretin Precursor of Fe catalysed •OH formation

Alterations of Bimolecules

Effects on glucose metabolism- Uncontrolled IDDM leads to increased hepatic glucose output. First, liver glycogen stores are mobilized then hepatic gluconeogenesis is used to produce glucose. Insulin deficiency also impairs non hepatic tissue utilization of glucose. In particular in adipose tissue and skeletal muscle, insulin stimulates glucose uptake. This is accomplished by insulin mediated movement of glucose transporters proteins to the plasma membrane of these tissues. Reduced glucose uptake by peripheral tissues in turn leads to a reduced rate of glucose metabolism. In

addition, the level of hepatic glucokinase is regulated by insulin. Therefore, a reduced rate of glucose phosphorylation in hepatocytes leads to increased delivery to the blood. Other enzymes involved in anabolic metabolic metabolism of glucose are affected by insulin. The combination of increased hepatic glucose production and reduced peripheral tissues metabolism leads to elevated plasma glucose levels. When the capacity of the kidneys to absorb glucose is suppressed, glucosuria ensues. Glucose is an osmotic diuretic and an increase in renal loss of glucose is accompanied by loss of water and electrolyte. The result of the loss of water (and overall volume) leads to the activation of the thirst mechanism (polydipsia). The negative caloric balance, which results from the glucosuria and tissue catabolism leads to an increase in appetite and food intake that is polyphagia. ^[16]

Glycemic Index (GI)- GI is meant to measure the change in blood glucose following the ingestion of food containing a specific amount of CHO and compare it with a reference standard such as glucose or white bread. GI is ratio between the increase in blood glucose over the fasting levels observed for 2-hour, following ingestion of a set amount of carbohydrate (50g) in the test food and the response to glucose or white bread containing similar amount of carbohydrate in the same individual. The increments are calculated from the measurement of area under the curve (AUC) in the graph drawn as in glucose tolerance test GI= ACU following the test meal/AUC after 50g of glucose or equivalent amount of white bread x 100.

Glycemic load (GL)- The overall blood glucose response is determined not only by the GI value of a food but also by the amount of carbohydrate in the food. Thus the concept of GL has been developed. The product of Glycemic index and value of its carbohydrate content is the glycemic load. This represents both the quantity and quality of carbohydrate consumed. Food prepared from whole grains products as whole meal wheat (flour), oats, Jowar, Rai and Ragi have low glycemic index. In addition these are rich in fiber, antioxidants and phytochemicals. Legumes, (grams) and beans have low GI and higher protein as well as viscous soluble fiber contents. Food items with GL of 60% or below is to be preferred for patients with diabetes or prediabetes. Several prospective studies have found an inverse association between whole grain consumption and incidence of diabetes and CHD. Dietary recommendations for lowering blood cholesterol with a view to reduce cardio vascular morbidity and mortality have focused largely on diets low in fat and high in carbohydrates.

Effect on lipid metabolism- One major role of insulin is to stimulate the storage of food energy in the form of glycogen in hepatocytes and skeletal muscle, following the consumption of a meal. In addition, insulin stimulates hepatocytes to synthesize and store triglycerides in adipose tissue. In uncontrolled IDDM there is a rapid mobilization of triglycerides leading to increased levels of

plasma free fatty acids. The free fatty acids are taken up by numerous tissues (except the brain) and metabolized to provide energy. In the absence of insulin, malonyl COA levels fall, and transport of fatty acyl-COA into the mitochondria increases. Mitochondrial oxidation of fatty acids generates acetyl COA that can be further oxidized in the TCA cycle. However, in hepaticocytes the majority of the acetyl COA is not oxidized by the TCA cycle but is metabolized into the ketone bodies (acetoacetate and β -hydroxybutyrate). These ketone bodies are used for energy production by the brain, heart and skeletal muscle. In IDDM, the increased availability of free fatty acids and ketone bodies exacerbates the reduced utilization of glucose, furthering the ensuing hyperglycaemia. Production of ketone bodies in excess of the body's ability to utilize them leads to ketoacidosis. A spontaneous breakdown product of acetoacetate is the acetone that is exhaled by the lungs, which gives a distinctive odor to the breath. Normally, plasma triglycerides are acted upon by lipoprotein lipase (LPL) that requires insulin. LPL is a membrane bound enzyme on the surface of the endothelial cells lining the vessels, which allows fatty acids to be taken from circulating triglycerides for storage in adipocytes. The absence of insulin results in hypertriglyceridemia. [16]

Dietary saturated fats down regulates hepatic LDL receptors and therefore reduce receptor mediated clearance of LDL particles from circulation. Replacement of saturated fats with carbohydrates or with unsaturated fats such as MUFA/PUFA may unregulate hepatic LDL receptors and thereby reduce LDL cholesterol levels. Thus there is a general consensus about the importance of reducing the cholesterol raising saturated fats in the diets of individuals with diabetes. IT is recommended that PUFA comprise <10% of the total calories, because of concern over the effect of PUFA on serum HDL cholesterol levels and their possible carcinogenic effects. The remainder of fat energy should be provided by MUFA. Our body requires two essential fatty acids- linoleic acid (18:2, n-6) and alpha linolenic acid (18:3, n-3) fatty acids as they are not synthesized in the body. These fatty acids play an important role in the body as they are precursors for prostaglandins and other biologically active long chain PUFA. It is recommended that the ratio of n-6/ n-3 fatty acids should be below 10 and 3% of the energy should be derived from EFA. Therefore intake of fat should also meet the requirements of these essential fatty acids. Fish oils are rich in Omega -3 polyunsaturated fatty acids (w3PUFA) in contrast to the vegetable oils which contain w6PUFA. They are more effective triglyceride lowering agents than vegetable oils.

Effects on protein- Insulin regulates the synthesis of many genes, either positively or negatively, which affect overall metabolism. Insulin has an overall effect on protein metabolism, increasing the rate of protein synthesis and decreasing the rate of protein degradation. Thus insulin deficiency will lead to increased catabolism of protein. The increased rate of proteolysis leads to elevated concentrations of amino acids in plasma.

Glycogenic amino acids serve as precursors for hepatic and renal glyconeogenesis, which further contributes to the hyperglycemia seen in IDDM [16].

Protein in Indian Diets is very different as the regular protein intake is usually from vegetable sources and the daily consumption is about 0.60 m/kg body weight. The protein requirements are enhanced in growing children and during pregnancy. Protein will have to be restricted in nephropathy. Ingested protein stimulates insulin secretion in people with Type 2 diabetes. There appears to be a synergistic effect when protein is ingested with glucose. Since the dietary protein does not raise the blood glucose concentration and stimulates insulin secretion some workers suggest increasing the protein content of meals for people with Type 2 diabetes if lower post meal glucose levels are a treatment goal. Therefore, in lean body weight individuals a modest increase in proteins may be desirable. Arginine and leucine improve insulin secretion and lead to a better metabolic control.

Some of the Human Disorders Clinically Linked to Oxidative Stress- Oxidative stress has been implicated in several diseases including cancer, atherosclerosis, malaria, chronic fatigue syndrome, rheumatoid arthritis and neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, and Huntington's disease, Amyotrophic lateral sclerosis (ALS), Asthma, Pulmonary Fibrosis, Lung Cancer, Cataract, Autoimmune Uveitis (AIU), Retinitis Pigmentosa (RP), Rheumatoid Arthritis, Acute Lymphoblastic Leukemia (ALL), Temporomandibular (TMB) Joint Disorders, Systemic Lupus Erythematosus (SLE), Wilson's Disease, and others.

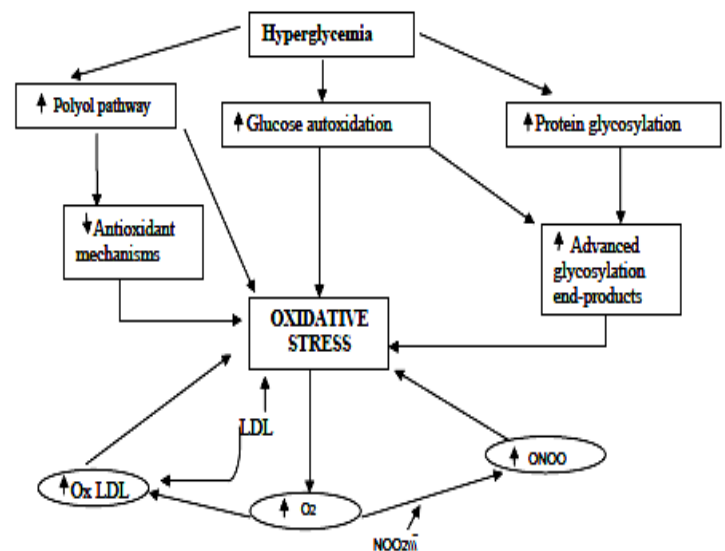


Fig. 1: Pathogenesis of hyperoxidative stress in non-insulin dependent diabetes. In boxes are shown mechanisms that are directly related to hyperglycemia. In circles are some mechanisms that result from the reaction of free radicals e.g. superoxide ($O_2^{\bullet-}$) with lipoproteins (e.g. small, dense low-density lipoprotein) and nitric oxide (NO^-), oxidized LDL (ox-LDL), peroxynitrite ($^{\ominus}ONOO$)

Deleterious effects of oxidative stress on human health Oxidative stress indicators in Diabetes mellitus-

The concept of raised level of oxidative stress (increased generation of free radicals) in DM was derived principally from *in vitro* experiments. One of such investigations involved the use of cultured human umbilical vein endothelial cells incubated in variable glucose concentrations followed by monitoring the generation of ROS by a measure of cellular level of nitro tyrosine.

The proposed HbA1c diagnostic criteria have greater diagnostic than FPG and 2-h OGTT regarding the diagnosis of diabetes mellitus. [17] It is gold standard marker for HbA1c can be used as a potential dual marker of glycemic control and dyslipidemia in type 2 diabetes mellitus [18].

Taken together, a possible mechanism we infer here that due to the pharmacological and compensatory effect, EGb761 can preserve more Mg and glucose level in the non-ischemic brain. Also, this biological phenomenon, at least in part, may be helpful for the non-ischemic brain not only in preserving more Mg and glucose level, but also in preventing the non-ischemic brain from further serious cerebral ischemic challenge. [19]

The prevalence of insulin resistance in these students was high (40%), which makes them prone to future development of metabolic syndrome and cardiovascular complications. Central obesity measured by WC >= 90cm was significantly associated with insulin resistance measured by HOMA-IR cut-off >= 2, but not with BMI or alcoholism. WC >= 90cm is therefore a strong indication for screening students for insulin resistance to prevent future complications. [20]

This study emphasizes the need for early identification of the risk factors leading to excessive BMI, body fat% and initiation of preventive measures in order to prevent the deterioration of cardiovascular performance in 11 to <13 years old school going Bengali boys. [21] The methodological analysis on obesity clearly indicates that prevention is better than cure. Present review tries to focus on the different aspects allied with the obesity. [22]

Diabetic retinopathy- Diabetic retinopathy is a vision threatening disease characterized by neurodegenerative features associated with general vascular changes. It remains uncertain how these pathologies relate to each other and their net contribution to retinal damage. There are numerous biochemical pathways, which help in the development of the neurovascular injury in DR. As a result, biomarkers which reveal dissimilar pathways are released locally and into the circulation. Early identification of these biomarkers could be in favor of predicting and efficient management of DR. Among these biomarkers are the ones related to inflammatory response, oxidative stress and retinal cell death. Diabetes increases oxidative stress, which plays a key regulatory role in the development of its complications. [23]

The retina has increase content of polyunsaturated fatty acids and has the elevated oxygen uptake and glucose oxidation relative to any different tissue. This

phenomenon renders retina more sensitive to oxidative stress and is inversely associated to glycemic control. Hyperglycemia is a long period in retinopathy raise level of HbA1c. [24] Hyperglycemia induced ROS creation is measured a causal link between elevated glucose and the pathways of development of diabetic complications. [25,26] When compared, oxidative stress is still higher in diabetic patients with complications than patients without complications. Although other factors play an equally important role, if not more, in the pathogenesis of diabetic complications, oxidative stress plays a significant role in diabetes and its complications [27].

Pathogenesis of DR- Chronic elevation in circulating blood glucose damages blood vessels, which results in many micro and macrovascular complications. DR is one of the major microvascular complications affecting the vision and is the leading cause of blindness in working-age adults. [27] It progresses from mild nonproliferative abnormalities, characterized by increased vascular permeability, to nonproliferative diabetic retinopathy (NPDR), characterized by vascular closure, to proliferative diabetic retinopathy (PDR), characterized by the growth of new blood vessels in the retina and the posterior surface of the vitreous. It is a multifactorial condition for which the pathophysiology is incompletely. [28] Oxidative stress in diabetes mellitus, increasing over time may play a role in the pathogenesis of diabetic retinopathy. [29]

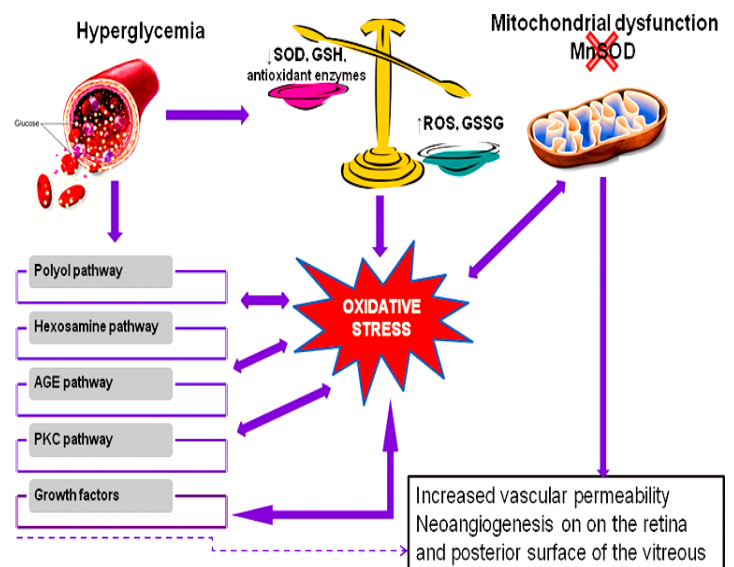


Fig. 2: Major pathways implicated in the development of diabetic retinopathy [26]

Oxidative Stress and Kidney Disease

Diabetic Nephropathy- Current years, diabetes and diabetic kidney disease continue to increase worldwide. In the USA, diabetes-associated kidney disease is a major cause of all new cases of end stage kidney disease. All diabetic patients are considered to be at risk for nephropathy. Today we have not specific markers to expect development of end-stage renal disease. Clinically control of blood sugar level and blood pressure regulations are important two parameters to the

prevention of diabetic nephropathy.^[30] There are huge amount of *in vitro* and *in vivo* studies regarding explanation of mechanism of diabetes mellitus induced nephropathy. All of these mechanisms are a consequence of uncontrolled elevation of blood glucose level. Currently the proposed mechanism is the glomerular hyper filtration/hypertension hypothesis. According to this hypothesis, diabetes leads to increased glomerular hyperfiltration and a resultant increased glomerular pressure. This increased glomerular pressure leads to damage to glomerular cells and to development of focal and segmental glomerulosclerosis.^[31] The calcium phosphate nanoparticles are nontoxic and biodegradable can be used to deliver drug, genes activators or siRNA or combination or multidrug if the challenges are met. further investigations must done using drug targeting precise molecular pathway in DN^[33] and evaluation of evidence gave by expert and author work on pathophysiological role of TRPC 6 and the medicinal drugs which regulate or restrain TRPC6 or its downstream molecular target propose that TRPC6 is unique molecular target.^[34]

Oxidative Stress and Heart Disease- Traditional vascular risk factors, including hyperlipidemia (cholesterol, LDL, etc.), hypertension, cigarette smoking, diabetes, overweight, physical inactivity, age, male sex and familial predisposition, only partly explain the excess risk of developing cerebrovascular and Coronary Heart Disease (CHD).

Oxidative stress created on the biomolecule of Cholesterol, saturated fats and excessive amounts of sodium have been identified as factors of high blood pressure and Cardiovascular disease.^[36] Several lines of evidence demonstrate that oxidative stress plays an important role in the pathogenesis and development of cardiovascular diseases, including hypertension, dyslipidemia, atherosclerosis, myocardial infarction, angina pectoris, and heart failure^[35-37].

Oxidative Stress and Eye Disease- Oxidative stress has been implicated in the pathogenesis of several eye conditions such as cataract, macular de-generation, diabetic retinopathy and retinitis pigmentosa, corneal disease.^[38-43]

Cataract surgery- Cataract one might not expect the lens to be site wherein oxidative stress plays a major part in pathologic conditions; metabolic activity here is quite low, because the lens is mostly crystalline protein with a paucity of cell organelles, such as mitochondria, which are the center of so much oxidative stress in the rest of the body. Yet, in fact, the lens is perhaps the most oxidatively stressed tissue in the body. Lens issue is, after all, exposed to light all the time that the eyelids are open, and this means that photo-oxidation occurs at a high rate with major effects.

DNA is also a target of oxidative stress, and DNA damage and apoptosis occur in lens epithelial cells exposed to oxidative stress, a factor causing cataract in

experimental rodents^[44] ultraviolet B (UVB) irradiation causes DNA fragmentation and apoptotic cell death in oxidative stress induced immortalized lens cell lines when the stressor was UV irradiation, whereas necrosis occurred when the stressor was hydrogen peroxide or t-butyl hydroperoxide.^[45]

Glaucoma- Glaucoma if one approach glaucoma as an optic neuropathy in which damage to the optic nerve and subsequent ganglion cell loss is the key feature, oxidative stress can readily be built into the picture of disease initiation and progression. Retinal ganglion cell death in glaucoma has been shown to be directly associated with the generation and effects of ROS^[46]. Axonal injury caused by increased intraocular pressure and resulting ganglion cell apoptosis results in the generation of ROS that can then contribute to the death of previous undamaged ganglion cells. Experiments demonstrating reduced apoptosis under the influence of ROS scavengers, such as SOD and catalase, show that oxidative stress is an important if not crucial factor in cell loss through apoptosis. ROS can also act as cell signaling molecules, which leads to glial cell dysfunction and also the stimulation of antigen presentation^[47].

Oxidative Stress and Lung Disease

Cigarette smoke and inhaled oxidants- Inhalation of volatile substances in cigarette smoke, as well as fine particulate matter, may increase ROS levels in the lungs^[48-50]. Inhalation of cigarette smoke and airborne pollutants, either oxidant gases such as O₃ and sulphur dioxide (SO₂), or particulate air pollution, results in direct lung damage as well as the activation of inflammatory responses in the lungs. Cigarette smoke is a complex mixture of over 4700 chemical compounds, including high concentrations of oxidants (1014 oxidant radicals/puff)^[51]. The cellular mechanisms resulting in oxidative stress induced by smoking are complex and poorly understood. However, there is striking evidence for oxidative stress and an imbalance between oxidants and antioxidants in smokers^[52].

Oxidative stress and Bronchial asthma- Bronchial asthma is a chronic inflammatory disease of the airways that is characterized by airway eosinophilia, goblet cell hyperplasia with mucus hypersecretion and hyperresponsiveness to inhaled allergens and non-specific stimuli, which usually induce increased vascular permeability resulting in plasma exudation^[53].

Oxidative stress and acute lung injury- Acute lung injury is a disease process characterized by diffuse inflammation of the lung parenchyma. Oxidant-mediated tissue injury is likely to be important in the pathogenesis of ALI. Lung injury due to hyperoxia is a commonly used model for the study of ALI in animals. ROS are generated as a by-product of the activation of neutrophils and macrophages. In addition, the requirement by many patients with ALI for a high fraction of inspired oxygen (FiO₂) may predispose to oxidative stress. Decreased

levels of GSH, a major endogenous scavenger of ROS, have been observed in the alveolar fluid of patients with ARDS. In response to various inflammatory stimuli, lung endothelial cells, alveolar cells and airway epithelial cells, as well as activated alveolar macrophages, produce both NO and O₂•⁻.^[54]

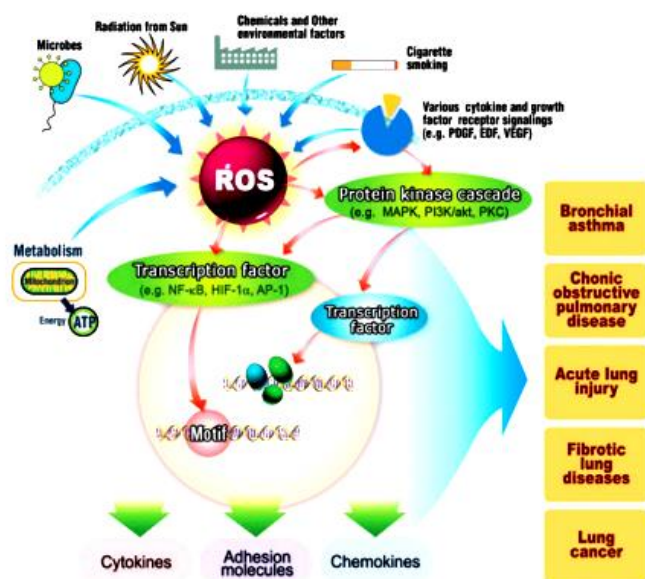


Fig. 3: General overview of the role of reactive oxygen species in lung diseases

CONCLUSIONS

In conclusion, there is considerable evidence that induction of oxidative stress is a key process in the onset of diabetic complications. The precise mechanisms by which oxidative stress may accelerate the development of complications in diabetes are only partly known. Several studies indicate oxidative stress is present in the dysfunction of insulin action and secretion that occur during diabetes, as well as in the development of diabetic complications. oxidative stress is not the primary cause of diabetes, but rather a consequence of nutrient excess, given that oxidative stress is a natural response to stress, in this case, to glucose and/or lipid overload. This fact is to be kept in mind, when planning strategies for prevention of diabetes mellitus and other associated diseases for better quality of life.

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**How to cite this article:**

Verma MK, Verma P. Role of Oxidant Alteration of Biomolecules in Diabetes and Other Associated Diseases. *Int. J. Life Sci. Scienti. Res.*, 2018; 4(1):1542-1549. DOI:10.21276/ijlssr.2018.4.1.6

Source of Financial Support: Nil, **Conflict of interest:** Nil