The Role of Oxidative Stress in Diabetes Mellitus: A 24-year Review

Ilechukwu CC[1*], Ebenebe UE[2], Ubajaka CF[2], Ilika AL[2], Emelumadu OF[2], Nwabueze SA[2]

ABSTRACT

Background: ***Diabetes mellitus is a widespread and devastating disease. Diabetes is associated with several mechanisms of tissue damage, one of which is oxidative stress. Oxidative stress and oxidative damage to tissues are common end points to chronic diseases such as atherosclerosis, diabetes and cardiovascular diseases. Oxidative stress plays an important role in the pathogenesis of and the complications of diabetes. Hyperglycaemia results in overproduction of oxygen free radicals which contributes to the progression of diabetes.***

Objective: ***This review aims at determining the role of oxidative stress in diabetes and diabetic complications.***

Method: ***Relevant literatures were reviewed from medical journals, library search, Pub Med search, Google search and other internet search engines (Google Scholar, Hinarii, Ask.com) from 1987 to 2011.***

Results: ***Several studies demonstrated that oxidative stress plays a role in the progression of diabetes and also in the development and progression of diabetic complications.***

Conclusion: ***Increasing evidence has implicated a role for oxidative stress in progression of diabetes and diabetes associated complications. Antioxidant therapy has been effective in management of diabetes and diabetic complications. In addition, physical exercise and insulin therapy can also improve diabetes through the reduction of oxidative stress.***

Keywords: ***Oxidative stress, free radicals, antioxidants, diabetes, diabetic complications.***

INTRODUCTION

Diabetes mellitus is a group of metabolic diseases in which a person has high blood sugar either because the pancreas does not produce enough insulin or because cells do not respond to insulin that is produced or both[1]. This high blood sugar (fasting plasma glucose equal or greater than 126mg/dL or blood glucose equal or greater than 200mg/dL 2 hours post-prandial) produces the classical symptoms of polyuria, polydipsia and polyphagia[1]. Although the aetiology of this disease is not well defined, viral infection, autoimmune disease, and environmental factors have been implicated[1]. Diabetes Mellitus is a health problem that is increasing rapidly[2]. In 1995, the International Diabetes Federation estimated the prevalence of diabetes to be approximately 135 million patients worldwide. More recently in 2010, it was estimated that around 285 million people were diabetic and this number is predicted to reach 438 million by 2030, accounting for 7.7% of the population aged 20-79[2].

TYPES OF DIABETES

There are 3 main types of diabetes mellitus

1. Insulin dependent diabetes mellitus (IDDM) or type 1 diabetes or juvenile diabetes.
2. Non-insulin dependent diabetes mellitus (NIDDM) or type 2 diabetes or adult–onset diabetes.
3. Gestational diabetes[3].

Type 1 diabetes

Type 1 diabetes results from the body's failure to produce insulin. Type 1 diabetes is characterized by loss of the insulin producing beta cells of the islets of Langerhans in the pancreas, leading to insulin deficiency. This type can be further classified as immune mediated or idiopathic. There is no known preventive measure against type 1 diabetes. Type 1 diabetes can affect children or adults, but was traditionally termed "juvenile diabetes" because a majority of these diabetes cases were in children[3].

Type 2 diabetes

Type 2 diabetes results from insulin resistance, a condition in which cells fail to use insulin properly sometimes combined with an absolute insulin deficiency. Type 2 is the most common type of diabetes, the defective responsiveness of body tissues to insulin is believed to involve the insulin receptors in the early stage of type 2 and the predominant abnormality is reduced insulin sensitivity. At this stage hyperglycemia can be reversed by a variety of measure and medications that improve insulin sensitivity or reduce glucose production by the liver[3].

Gestational diabetes

Gestational diabetes occurs when pregnant women without previous diagnosis of diabetes develops a high blood glucose level[3]. It may precede development of types 2 diabetes mellitus but it usually resolves after delivery[3]. It resembles type 2 diabetes mellitus. Gestational diabetes is fully treatable but requires careful medical supervision throughout the pregnancy.

[1]Department of Community Medicine, Anambra State University Teaching Hospital, Awka
[2]Department of Community Medicine, Nnamdi Azikiwe University Teaching Hospital, Nnewi
Correspondence: Dr. CC Ikechukwu, Department of Community Medicine, Anambra State University Teaching, Awka
Email: chijiokeilechukwu@gmail.com

It occurs in 2-5% of all pregnancies and may improve or disappear after delivery[3]. About 20-50% of affected women develop type 2 diabetes later in life[3].

Oxidative stress

Oxidative stress is an imbalance between the production of reactive oxygen species and a biological systems ability to readily detoxify the reactive intermediates or to repair the resulting damage[4]. It has been established that oxidative stress is among the major causative factors in the induction of many chronic and degenerative disease including atherosclerosis, ischaemic heart disease, ageing, diabetes mellitus, cancer, immunosuppression, etc[5]. Disturbances in the normal redox state of cells can cause toxic effects through the production of peroxides and free radicals that damages all components of the cell, including proteins, lipids, and DNA[6]. Some reactive oxygen species (hydrogen peroxide (H_2O_2), superoxide anion ($^{\cdot}O_2^-$), hydroxyl anion (OH)act as cellular messengers in redox signaling; thus oxidative stress can cause disruption in normal mechanisms of cellular signaling[7].

Effects of oxidative stress

Chemically oxidative stress is associated with increased production of oxidizing species or a significant decrease in the effectiveness of antioxidant defenses such as glutathione, catalase, superoxide dismutase, gamma-glutamyl transferase, vitamins A, C and E[8]. However, more severe oxidative stress can cause cell death and even moderate oxidation can trigger apoptosis while more intense stresses may cause necrosis[8].

The production of reactive oxygen species is the destructive aspect of oxidative stress. Such species include free radicals and peroxides. Free radicals are atoms or molecules that have an unpaired electron spinning an outer layer of the nucleus or the peripheral layer[8]. Under severe levels of oxidative stress that cause cell death, the damage causes ATP depletion preventing controlled apoptotic death and causing the cell to fall apart or disintegrate[8].

Free radicals produced during aerobic metabolism, in the body can cause oxidative damage of amino acids, lipids, proteins and DNA[9]. The family of free radicals generated from the oxygen is called reactive oxygen species (ROS) which cause damage to other molecules by extracting electrons from them in order to attain stability. The human body is exposed to free radicals from outside the body (exogenous) and inside the body (endogenous)[9].

Some of the external factors that lead to free radicals are smog, cigarette smoke, radiation, excessive consumption of alcohol and even sunlight. On the other hand, some factors that lead to free radicals come from within the body. The cells need oxygen to produce the energy they need to work properly. In the process known as mitochondria respiration, the cells take in oxygen, burn it and release energy; during the process free radicals are produced. Oxidative stress occurs when free radicals produced exceeds the body's ability to neutralize them[9]. Oxidative stress helps in development and progression of diabetes and its complications[7].

Hyperglycaemia, diabetes, oxidative stress and lipid peroxidation

Hyperglycaemia is a connector between diabetes and diabetic complications[10, 11].

In the review done by Rolo et al[10], four of the most important molecular mechanisms have been involved in hyperglycemia–induced tissue damage: activation of protein kinase C isoforms through de novo synthesis of the lipid, second diacylglycerol increased hexosamine pathway flux, increased advanced glycation end product formation and increased polyol pathway flux[10].

Hyperglycaemia induces over production of superoxide. In fact, diabetes is typically associated with increased generation of free radicals and/or impaired antioxidant defense qualifications representing a central contribution for reactive oxygen species in the onset, progression and pathological consequences of diabetes[11]. Early recognition, treatment, and prevention of the metabolic syndrome present a major challenge for health care professionals confronting an epidemic of overweight and sedentary lifestyle[12].

The study done by Gopaul et al[13], reported plasma levels of a specific non-enzymatic peroxidation product of arachidonic acid esterified 8-cpi-PGF_2 alpha, from healthy and non insulin dependent diabetes mellitus individual as an index of oxidative stress in vivo. Furthermore it studied some data which indicated that non-insulin dependent diabetes mellitus is connected with increased plasma lipid peroxidation[13].

Diabetic complications and oxidative stress

In the review written by Haidera et al[14], it has been found that diabetes is an important risk factor for the development of problems such as coronary heart disease, peripheral arterial disease, hypertension, stroke, cardiomyopathy, nephropathy, and retinopathy. Furthermore, a linking element among all these complication could be excess production of reactive oxygen species[14].

Cardiovascular complications are major causes of death in diabetes[15]. Oxidative stress is a regular characteristic of diabetes complications when the action of antioxidant systems is overwhelmed by additional production of reactive oxygen species[15].

The factors that increase the possibility of cardiovascular disease that come from insulin resistance are obesity, dyslipidemia, and hypertension[16]. In the study done by Bacha et al[16], Obesity is often associated with insulin resistance and the components of the metabolic syndrome. In the review done by Yamagishi et al[17], cardiovascular disease is the cause of disabilities and death in diabetes. In addition diabetes is linked with a high increase in the risk of atherosclerotic vascular disorders, including coronary, peripheral artery and cardiovascular disease[17].

Hypertension normally coexists with diabetes, and this considerably enlarges the probability of vascular complications[18]. In the review done by Sowers et al[18], it was stated that hypertension is approximately twice as frequent in patients with diabetes compared with patients without the disease[18].

Diabetes – associated atherosclerosis and role of oxidative stress

Atherosclerosis is one of the major causes of mortality and morbidity in patients with diabetes[19].The building of fat and cholesterol along the walls of arteries is progressive; it thickens and hardens forming calcium deposits and may eventually block the arteries. Blockage of the arteries and /or rupture of vulnerable plaques are a common cause of heart attack and stroke. Diabetes has been shown to accelerate the clinical course of atherosclerosis in the coronary arteries (Coronary artery disease, including myocardial infarction), lower extremities (peripheral arterial disease) and extra cranial carotid arteries (cerebrovascular disease, including stroke)[19].

An understanding of the underlying mechanisms that accelerate diabetes associated atherosclerosis is important in the search for treatment to protect against or retard the progression of the disease[19]. The abnormal metabolic state associated with diabetes, which includes chronic hyperglycaemia, dyslipidaemia and insulin resistance can alter the function of multiple cell types including endothelial cells, smooth muscle cells and platelets[19].

Diabetic Cardiomyopathy and the role of ROS in diabetic cardiomyopathy

The study done by Kannel et al[20] showed that diabetic men and women had a 2- and 5- fold greater incidence of heart failure respectively even after taking into account other common risk factors such as coronary artery disease, age blood pressure, weight and cholesterol. Diabetic cardiomyopathy is characterized by early diastolic dysfunction and late systolic impairment, and is accompanied by a wide range of structural abnormalities and pathophysiological impairments[21].

Hyperglycaemia is known to up-regulate the production of Angiotensin II, which is the overt hormone of the renin-angiotensin system (RAS). This has a profound effect on the myocardium given that most of the cellular components of the RAS including angiotensinogen, renin and the angiotensin II, (AT,) receptors are found in myocytes[21]. The biochemical pathways leading to endothelial dysfunction and inflammation due to the overproduction of ROS appear to play a causal role in the pathogenesis of diabetic cardiomyopathy[21].

Diabetic nephropathy and the role of ROS in diabetic nephropathy

Diabetic nephropathy is classically defined as the increase in protein excretion in the urine[22]. The early stage of Diabetic nephropathy is characterized by a small increase in urinary albumin excretion (microalbuminuria), while overt diabetic nephropathy is defined as the presence of macroalbiuminuria or proteinuria[22]. Structural changes associated with diabetic nephropathy are the expansion of glomerular mesengial area, mesengial cell hypertrophy and thickening of the glomerular basement membrane leading to a progressive reduction in the filtration surface of the glomerulus, a process known as glomerulosclerosis[23].

Despite intensive glucose control and blockade of the RAS diabetic nephropathy continues to progress in significant proportion of patients and often lead to an organ failure and the need for dialysis and for kidney transplantation[24]. Therefore the development of a novel targeted therapeutics is warranted to reduce or eliminate kidney disease in diabetic patients[24].

An up regulation of ROS in diabetes has been implicated in the pathogenesis of kidney injury[25]. In the diabetic kidney enhanced glucose uptake occurs in many of the cell populations including glomerular epithelial cells, mesengial cells and proximal tubular epithelial cells, leading to the excessive production of intracellular ROS, making these cells particularly susceptible to the diabetic milieus[25].

Cerebrovascular disease and diabetes

Diabetes mellitus is a common disease distinguished by adjustments in micro vessels in multiple tissues ensuing

in retinopathy, nephropathy and neuropathy[26]. The pathogenesis directly correlates with hyperglycemia, the direct glucose toxicity, hypercoagulability, oxidative stress and endothelial dysfunctions also play roles. In the study done by Niiya et al[27], it was shown that there is accumulating evidence that advanced glycation end products (AGEs) are relevant to the formation of vascular complications in diabetes mellitus.

Oxidative stress, central nervous system and mitochondrial

Oxidative stress takes place within the brain when the production of reactive oxygen species takes precedence over the capability of the endogenous antioxidant structure to eliminate excess oxygen species afterwards directing the cellular injury[28]. Cellular characteristics of the brain indicate that oxidative stress is very harmful to the brain[28]. The brain, for instance, needs a very high amount of oxygen, 20% of the entire body requirement[28]. The brain tissue is made up of large amount of unsaturated fatty acids which can be metabolized by oxygen free radicals and therefore oxidative stress in the brain is deleterious[28].

Mitochondria are a very important organelle that has some roles in the cell, which are amino acid biosynthesis, fatty acid oxidation, and steroid metabolism[29]. Furthermore, mitochondria preserve the cellular energy reserves with ATP production by the electron transport of the respiratory chain[29]. In addition it is recognized to be a very important source of superoxide radicals and other reactive oxygen species that are connected with oxidative stress[29].

Mitochondrial dysfunction has been anticipated to be the intermediary between neurodegeneration in the central nervous system and peripheral nervous system and it has been linked to be a serious transformer of diabetic complication in neurons[30].

Oxidative stress in insulin resistance and diabetes

Insulin resistance occurs when cells no longer respond well to insulin[31]. Several clinical and experimental studies have indicated hyperglycaemia yield in the generation of reactive oxygen species, in the end leading to increased oxidative stress in variety of tissues[31]. It has also been known that oxidative stress has the ability to lower insulin sensitivity and damage the insulin-producing cells, the B-cells of Islets of Langerhan in the pancreas[31]. Adipose tissues and muscle are the significant tissues participating in insulin resistance. Oxidative stress modifies the signaling pathway within a cell installing insulin resistance[31]. In the review done by Evans et al[31], in both type 1 and type 2 diabetes, diabetic complications in target organs arise from chronic elevations of glucose[31].

Generally the following agents cause insulin resistance; obesity, hormone (insulin) excess, reactive oxygen species (ROS) and reactive nitrogen species (RNS), pregnancy and lifestyle not physically active and mitochondrial dysfunction[32]. Because genes are the fundamental molecular basis of inheritance and thus the cornerstone of evolution- a model explaining insulin resistance is based at the gene level and a certain mitochondrial DNA polymorphism is invoved[32].

Oxidative stress, antioxidant and diabetes

Antioxidants are substances that inhibit the destructive effects of oxidative stress. Antioxidant can be exogenous examples include antioxidant vitamins like vitamin A, C and E or endogenous, examples include reduced glutathione, and antioxidant enzymes like catalase, superoxide dismutase, glutathione peroxidase and glutathione reductase. Antioxidant both exogenous and endogenous can be effective in preventing free radical formation by scavenging them or promoting their decomposition[33]. Antioxidants may protect the body against ROS effects either by preventing the formation of ROS or by the interruption of ROS attack, or by scavenging the reactive metabolites or by converting them to less reactive molecules[34].

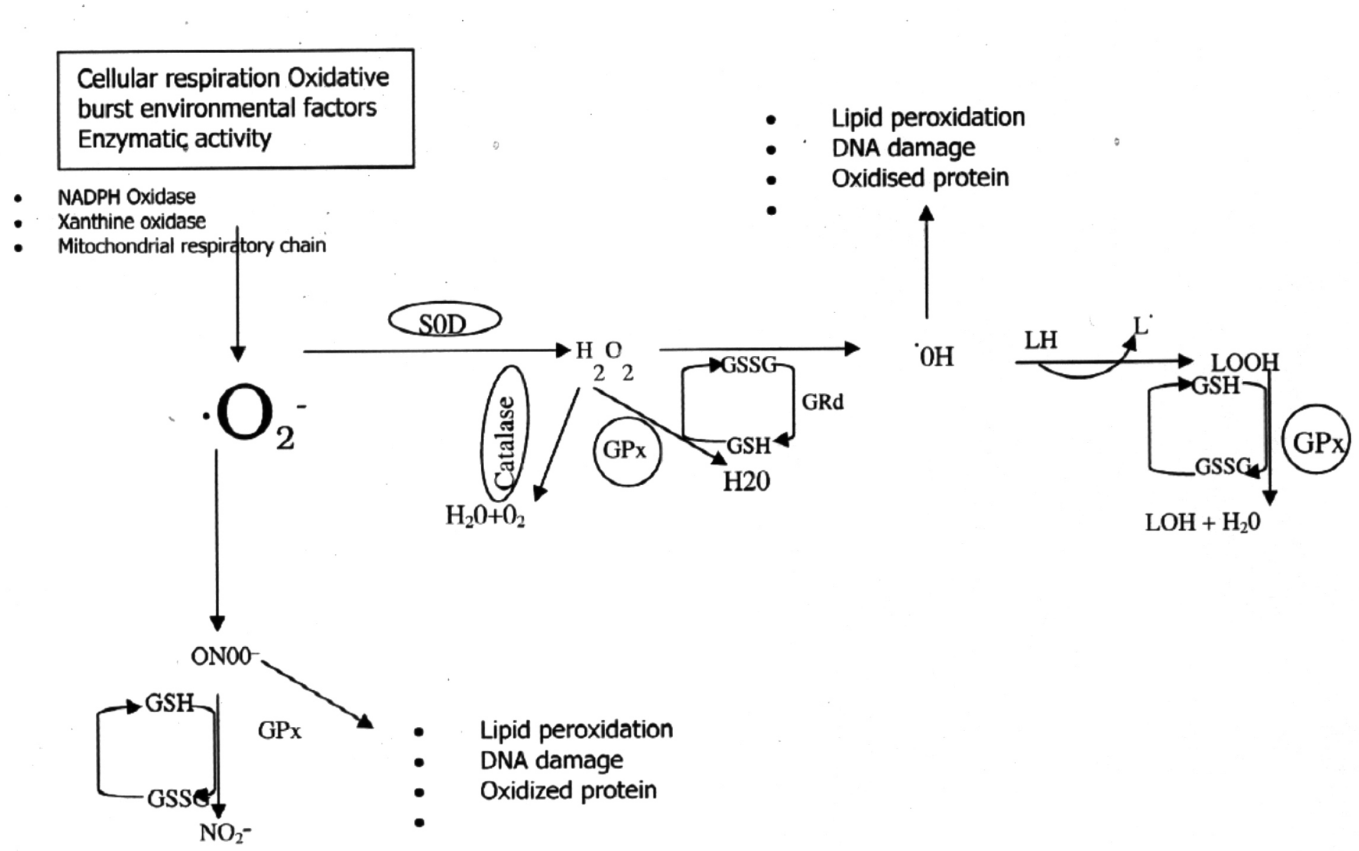

Fig1: Removal of Reactive Oxygen Species (ROS) by antioxidant defense systems

Superoxide radical ($\cdot O_2^-$) is generated in low levels under physiological states but its production is greatly enhanced under pathological situations via enzymes such as NADPH oxidase, xanthine oxidase, and dysfunctional mitochondrial respiratory chain. $\cdot O_2^-$ is neutralized to water via a two-step process involving superoxide dismutase in the first step and glutathione peroxidase (GPX) or catalase in the second step. Increased production of O_2 and /or impairment of antioxidant defense systems lead to a build-up of the intermediate hydrogen peroxide (H_2O_2). H_2O_2 forms the toxic oxygen species hydroxyl anion (OH) via Fenton biochemistry, which is highly reactive and causes lipid peroxidation forming lipid hydrogen peroxides (LOOH). The functional importance of GPX resides in its ability to remove H_2O_2 and LOOH and neutralized these to water and lipid alcohol, respectively. Additionally, the increase in $\cdot O_2^-$ also favours the formation of peroxynitrite ($ONOO^-$) which reduces the bioavailability of nitric oxide (NO) GPX also functions to neutralize $ONOO^-$[35].

Insulin Therapy

Insulin therapy is an essential requirement for people with diabetes type 1 and also important for type 2 diabetic subjects[36]. In the past the only way person could get insulin in their body was by hypodermic syringe. Nowadays the insulin pump is available. Another way of getting insulin is by inhalation, which is currently being researched on. The amount of insulin needed in the body consist of how much a person exercise and by how much a person sleeps. Good sugar control helps in preventing the diabetic complications[36].

CONCLUSION

Oxidative stress has been demonstrated to participate in the progression of diabetes. Oxidative stress plays an important role during diabetes, including impairment of insulin action and elevation of the complication incidence. Antioxidants have been shown to be protective in the treatment of diabetes both type 1 and type 2.

RECOMMENDATIONS

The following are our recommendations:

Antioxidants which work as inhibitors in the destructive effects of oxidation are needed for stopping the development of diabetes and diabetic complications, therefore intake of foods rich in antioxidants is highly recommended.

Physical exercise and insulin therapy that improve the diabetes have also been associated with their antioxidant effects and are therefore recommended to provide more effective therapeutics choices for this devastating disease[37].

Modifications of lifestyle through increased physical activity and reduced intake of calories can help lower the number of future cases of diabetes.

People should eat the right type of food by reducing intake of calories and eating more of fruit, green vegetables which are rich in antioxidants and food that contain fiber like garden egg. Regular blood glucose test is advocated so that one can monitor his or her sugar level to reduce diabetes.

REFERENCE

1. Sander S, Anderson AK, Barbu A, et al. Novel Experimental strategies to prevent the development of type 1 diabetes mellitus. Ups Journal of Medical Science. 2000; 105(2): 17-34.
2. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Research and Clinical Practice. 2010; 87:4-14.
3. David GG. Greenspan's Basic and Clinical Endocrinology 9th ed. New York: McGraw–Hill Medical; 2011.
4. Gutteridge JMC. Free radicals in disease processes: A complication of cause and consequence. Free Radical Resource. 1995; 19:141-148.
5. Squadriatto GI, Polor WA. Free radical; Oxidative Chemistry of Nitric oxide: the roles of super oxide, peroxynitrite and $C0_2$. Biology and Medicine. 1998; 25:392-403.
6. Amer J, Ghoti H, Rachmilewitz E, Foren A., Levin C, Fibach E. Red Blood cells platelets and polymorphonuclear nuetrophils of patients with sickle cell disease exhibit oxidative stress that can be ameliorated by antioxidants. British Journal of Haematology. 2006; 132(1): 108-113.
7. Ha H, Leo HB. Reactive Oxygen species as glucose signaling molecules in mesangial cells cultured under high glucose. Kidney International Supply. 2000; 77:519-25.
8. Simona DM, Zhao-Zhong C, Kenneth M. Oxidative stress and Diabetes. Harlem Children Society. 2008; 1:1-153.
9. Haliwell B. How to characterize an antioxidant: An update. Biochemical Society Symposium. 1995; 61:73-101.
10. Rolo AP., Palmeira CM. Diabetes and Mitochondrial function: role of hyperglycaemia and oxidative stress. Toxicology Applied pharmacology. 2006; 212:167-178.
11. Brownlee M. Biology and Molecular cell biology of Diabetes Complications. Nature. 2001; 414:813-820.
12. Lakka HM, Laaksonen DE, Lakka TA, et al. The metabolic syndrome and total cardiovascular disease mortality in middle-aged men. Journal of the American Medical Association. 2002; 299: 2709-2716.
13. Gopaul NK, Anggard EE, Mallet AI, Betteridge DJ, Wolff SP, Novroo3- Zadeh J. Plasma–8-epi-PGF2 alpha levels are elevated in individual with non-insulin dependent diabetes mellitus. Federation of European Biochemical Societies. 1995; 368: 225-229.
14. Haidara MA, Yassim HZ, Rateb M, Ammar H, Zorkani MA. Role of oxidative stress in development of cardiovascular compilation in diabetes mellitus. Current Vascular Pharmacology. 2006; 4: 215-227.
15. Jones DP. Extracellular redox State; refining the definition of oxidative stress in aging. Rejuvenation Resource. 2006; 9: 169-181.
16. Bacha F, Saad R, Gungor N, Arslanian SA. Are obesity related metabolic risk factors modulated by the degree of insulin resistance in adolescents? Diabetes Care. 2006; 29: 1599-1604.
17. Yamagishi S, Nakamura K, Matsin, Takenka K, Jinnouchi Y, Imaizumi T. Cardiovascular Disease in diabetes. Mini Review of Medicinal Chemistry. 2006; 6:313-318.
18. Sowers JR, Epstein M, Frohlich ED. Diabetes, Hypertension, and Cardiovascular disease: An update. Hypertension. 2001; 37: 1053-59.
19. de Haan JB, Cooper ME. Targeted antioxidant therapies in hyperglycaemia endothelial dysfunction. Frontiers in Bioscience (scholar edition). 2011; 3: 709-29.
20. Kannel W, Hjortland M, Castelli W. Role of diabetes in congestive heart failure; the Framingham study. American Journal of Cardiology. 1994; 34: 29-34.
21. Hayat SA, Patel B, Khattar RS, Malik RA. Diabetes Cardiomyopathy: Mechanisms,Diabetes and treatment. Clinical Science. 2004; 107: 539-57.
22. Zelmanovitz T, Gerchman F, Bathazar A, Thomazelli F, Matos J, Canani L. Diabetic nephropathy. Diabetology and Metabolic Syndrome. 2009; 1: 10-26.
23. Gilbert RE, Cooper ME. The Tubucointrestitium in progressive diabetic kidney disease: More than an aftermath of glomerular injury? Kidney International. 1999; 56: 1627-37.
24. Barit D and Cooper ME. Diabetic patients and kidney protection: an attainable target. Journal of hypertension. 2008; 26: 33-7.
25. Forbes JM, Coughlan MT, Cooper ME. Oxidative stress as a major culprit in kidney disease in diabetes. Diabetes. 2008; 57: 1446-54.

26. Gigante E. Diabetic nephropathy: Oral anti-diabetic agents or insulin? Italian Journal of Nephrology. 2006; 34: 564-67.
27. Niiya Y, Abumiya T, Schichinohe H, et al. Susceptibility of brain micro vascular endothelial cells to advanced glycation end products induced tissue factor up regulation is associated with intracellular reactive oxygen species. Brain Resource. 2006; 1108: 179-187.
28. Miyajima H, Takahashi Y, Kono S. Aceruloplasminemia, an inherited disorder of iron metabolism. Biometals. 2003; 16: 205-213.
29. Jang VY, Song JH, Shon Yk, Han ES, Lec CS. Protective effect of boldine on oxidative mitochondria damage in streptozotocin–induced diabetic rats. Pharmacology Resource. 2000; 42: 361-371.
30. Schapira AH. Mitochondrial dysfunction in neurodegenerative disorders. Biochemistry and Biophysics Journal. 1998; 1366:225-233.
31. Evans JL, Goldfine ID, Maddux BA, Grodsky G M. Are oxidative stress–activated signaling pathways mediators of insulin resistance and beta cell dysfunction? Diabetes. 2003; 52: 1-8.
32. Lee HK, Park KS, Cho YM, Lee YY, Pak YK. Mitochondria based model for fetal origin of adult disease and insulin resistance. Annals of New York Academy of Science. 2005; 1042: 1-18.
33. Tiwari A. Imbalance in antioxidant defense and human diseases: multiple approach of natural antioxidant therapy. Current Science. 2004; 86(8):1-11.
34. Sen CK. Oxygen toxicity and antioxidants state of the art. International Journal of Physiological Pharmacology 1995; 39: 177-96.
35. Recknagel RO, Glende EA, Waller RL, Lowrey K. Lipid peroxidation, Biochemistry, measurement, and significance in liver cell injury:In Plaa G.L and Hewitt W.R. (E.d), Toxicology of the liver. Raven, press: New York, USA;1987. Pp. 362-369.
36. Borghouts LB, Keizer HA. Exercise and insulin sensitivity: a review. International Journal of Sports and medicine. 2000; 21: 1-12.
37. Koro CE, Bowlin SJ, Burgeosis N, Fedder DO. Glycaemic control from 1988 to 2000 among US adult diagnosed with type 2 diabetes: a preliminary report. Diabetes Care. 2004; 27: 17-20.