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Management of diabetes and its complications through the role of antioxidants: Review

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ABSTRACT

Diabetes is a chronic disease and affects a large rate of the population around the world. It is characterized by absolute or relative deficiencies in insulin secretion and/or insulin action and is associated with chronic hyperglycemia and disturbances of carbohydrate, lipid, and protein metabolism. It is a multi-faceted metabolic disorder in which increased oxidative stress plays a key role in the pathogenesis of this debilitating disease. The imbalance between the reactive types (RS) and the antioxidants leads to the production of a condition called (oxidative stress) which causes the development of the condition to diabetes. This review has reported the beneficial effects of antioxidant (vitamins A, C, E, alpha lipoic acid, GSH and catalase) on the complications of diabetes. The use of antioxidants reduces oxidative stress and relieves complications of diabetes,while clinical trials are less clear. The aim of this review was to summarize the role of antioxidants in the management of diabetes and its complications through their free radical scavenging properties.

1. Introduction

Diabetes mellitus is a multi-faceted metabolic disorder in which increased oxidative stress plays a key role in the pathogenesis of this debilitating disease. The prevalence of diabetes among adults worldwide has increased significantly so that the number of adults with diabetes is expected to increase from 135 million in 1995 to 300 million in 2020. Diabetes is the fourth leading cause of death globally [1]. Recent studies indicate that 171 million people worldwide suffer from diabetes in 2000 and the number of people with diabetes is expected to rise to 366 million by 2030 [2].Diabetes is defined as an imbalance in the process of glucose metabolism, which leads to a high level of sugar (glucose) in the blood abnormally for various reasons, and occurs due to a defect in the secretion of insulin from the pancreas. The amount of insulin that is secreted may be less than required or there is a complete cessation of the intestine and called in this case (Insulin insufficiency) or where the amount of excreted is large in some cases, but there is resistance in the tissue and the cell inhibits the function of insulin and called in this case (insulin resistance). Insulin is a hormone that regulates blood sugar. Over time, high sugar causes significant damage to the body, especially the blood vessels and nerves[3].

Several complications arise from diabetes as complications of nephropathy,retinopathy,neuropathyand micro vascular, chronic hyperglycemia has a central role in the damaging effects on tissues[4].The term oxidative stress indicates a shift towards a pro-oxidant environment in the balance between oxidant species formation and antioxidant defences. Chemical compounds capable of producing potential toxic reactive oxygen species (ROS) are known as pro-oxidants and compounds detoxifying them are termed as antioxidants. Free radicals are reactive chemical species having a single unpaired electron in an outer orbit. This unstable configuration provides energy which is released through reactions with adjacent molecules such as proteins, lipids, carbohydrates and nucleic acids. Most free radicals that damage biological systems are oxygen free radicals [5]. If the increased oxidative stress is inversely linked to insulin resistance, it should be improved in insulin action with antioxidant treatment. In vivo studies on experimental animals and small clinical trials in humans, they have provided support for this concept[6],which significantly improved insulin sensitivity when they were used as medicine for diabetic rats with α-lipoic acid, a physiological antioxidant [7]; and in clinical trials, they have confirmed that α-lipoic acid improved insulin resistance by ~25% in subjects with T2DM[8],also have been shown to improve insulin sensitivity in diabetic patients with other antioxidants, e.g, vitamin C and E and N-acetylcysteine[9].

2. Oxidative stress and antioxidants

Oxygen is one of the important components of life. However, in some circumstances, this oxygen may be a killer of cells when it generates reactive species that causes necrosis, organ damage [10] and ultimately the cell death. Reactive nitrogen and carbon species also cause oxidation by the generation of certain mechanism that interferes with the normal physiological processes inside the cell [11]. Oxidative stress can be defined as a disturbance in the balance between oxidants and antioxidants due to different factors such as aging, drug actions and toxicity, inflammation and/or addiction [12]. Oxidative stress outcomes from an imbalance between radical generating and radical-scavenging systems, which indicates the reduced activity of antioxidant defenses or increased the free radicals production or both [13].As associated with damage to a wide range of molecular species including lipids, proteins, and nucleic acids[14]. Moreover, oxidative stress results from increased ROS and/or reactive nitrogen species (RNS)[15].

The potential sources of oxidative stress in diabetes might include auto-oxidation of glucose, changes in redox balances, decreased antioxidants concentrations in tissue, such as reduced glutathione (GSH) and vitamin E,vitamin C and weaken activities of antioxidant defense enzymes such ascatalase (CAT) and superoxide dismutase (SOD)[16].Several studies have shown that oxidative stress results from increased concentration of glucose inside and outside the cell[17-18]. The etiology of oxidative stress in diabetes arises from a diversity of mechanisms such as excessive oxygen radical production from auto-oxidation of glucose[19].In recent discussions of disease mechanisms, free radicals and antioxidants have become common terms[20].Antioxidants are natural substances that may prevent or delay some types of cell damage. Antioxidants are found in many foods, including fruits and vegetables. There are several nutrients in food that contain antioxidants. Vitamin C, vitamin E, and beta carotene are among the most commonly studied dietary antioxidants. There are several species or molecules, endogenous (internally synthesized) or exogenous (consumed), that plays a role in antioxidant defense and may be considered as biomarkers of oxidative stress. Antioxidants can be divided as either chain breaking antioxidants or preventive antioxidants, based on their mechanism of action [21]. Different types of biological antioxidants include glutathione, vitamin C and E, cysteine, and many others. Also, many plant-derived substances are known as phytonutrients or phytochemicals that possess antioxidant properties. Phenolic compounds such as flavonoids are such chemicals. These are found in several fruits, vegetables and green tea extracts.

3. Free radical

A free radical can be defined as any molecular species which is able of an independent presence that contains an unpaired electron in an atomic orbital. Many radicals are unstable and highly reactive. The presence of an unpaired electron results in certain common properties that are shared by most radicals. They can give an electron to or take an electron from other molecules, therefore, conduct as oxidants or reluctant[22].Free radicals attack significance molecules leading to cell hurt and homeostatic disruption. The aims of free radicals include all kinds of molecules in the body, among them, lipids, nucleic acids, and proteins are the major targets[23].Free radicals are derived either from essential metabolic processes in the human body or from outer sources such as exposure to X-rays, air pollutants, cigarette smoking, and industrial chemicals[24]. Free radical formation occurs continuously in the cells because ofenzymatic and non-enzymatic reactions[25].

4. Oxidative stress and its relation to diabetes and it's a complication

The oxidative stress is thought to be a reason in the development of atherosclerosis, heart failure, lichen planus, vitiligo, cancer, Parkinson's disease, Alzheimer's disease, sickle cell disease, myocardial infarction, autism, chronic fatigue syndrome and renal failure[26-28].

5. Oxidative Stress and Diabetic Retinopathy

The propagation of diabetic retinopathy is increasing worldwide due to rising numbers, and prolonged survival, of diabetic patients. Oneof the most important causes of blindness in adults diabetic is retinopathy. If diabetic retinopathies do not stop, new vessels growing finallyretinal separation will be occurred[29].The appearance of this disease depends on the period diabetes and rarely develops in the first year of diabetes but the rise happening in the rate the injury over time. The retina has a high content of polyunsaturated fatty acids and has the elevated uptake of oxygen and also highest oxidation of glucose. As a result, the retina is more prone to oxidative stress. The relationship between hyperglycemia, oxidative stress and changes in the redox homeostasis is the main phenomenon in the pathogenesis diabetic retinopathy[30]. It has been shown that oxidative stress participates not only in the development of diabetic retinopathy but also in the resistance of it even after the control on glycemic. The reason may be that diabetic retinopathy is resistant to inverse due to ROS that is not easily removed and the accumulation of damaged molecules[2, 29].When oxidative stress shows an imbalance between excess forming and \or impaired removal of ROS, the antioxidant defense system of the cell is the crucial part of the overall oxidative stress experienced by a cell[31]. In diabetes deficiency in retina shows that the activities of antioxidant defense enzymes are responsible for scavenging free radicals and maintaining redox homeostasis such as SOD, glutathione peroxidase, catalase and glutathione reductase[16]. Further, the cell is armed with intracellular antioxidant, GSH that is the main defense of the cell. It can act as scavenger ROS and modify intracellular redox state.Thus, prevention of retinopathy must the diet of patients contain recommended vitamins (non-enzymatic) and enzymatic antioxidant system respond to oxidative stress observed in diabetic patients.

6. Oxidative Stress and Diabetic Nephropathy

Diabetic Nephropathy exists in about one-third patients with insulin-dependent diabetes and is one of the significant micro vascular complications, and an important cause of chronic kidney disease and end-step renal failure globally[32].Recent studies have indicated that ROS plays the intermediate role in the development diabetic nephropathy. The rise glucose directly increases lipid peroxidation and hydrogen peroxide production.As it was noted, ROS is always produced in physiological situation and effectively eliminated by several intra and extracellular, antioxidant systems. Various studies on experimental models of both immune and non-immune glomerular injury demonstrated that ROS is to be the first factor in the pathogenesis of these disorders and showed that the kidney is sensitive to oxidative stress[33]. Hyperglycemia is not only because of generation of more ROS but also the cause of the decrease of the scavenging enzymes[34].Studies have shown that Albuminuria that is a marker of glomerulopathy in diabetes has higher levels of lipid peroxides in plasma, urine, an index that Lipid Peroxidation of Unsaturated Fatty Acids is one of the radical reactions and increased oxidative stress[35]. This indicates that oxidative stress increases in

diabetic kidneys.

The recent studies indicated that evidence is now available about the effect of oxidative stress in the development of diabetic complications.Recently it has been proposed that a treatment with antioxidants is available now; insights into the mechanisms leading to the oxidative stress generation in diabetes and these results have led to more estimates of new antioxidant molecules that in the future may inhibit at an early stage, the mechanism leads to diabetic complications[24,36].

7. Oxidative Stress and Diabetic neuropathy

Hyperglycemia plays a crucial role in the evolution and development of diabetic neuropathy. With the increased oxidative stress that accompanies diabetes one of the mechanisms by which hyperglycemia causes neural degeneration[37]. Diabetic neuropathy is the most common cause of cut off and failure of the independent system[30].In nerve, the confluence of metabolic and vascular impairment result in neuron defect and loss of neurotrophicsupport and in the long-term can mediate neuron, glial cell and Schwann cell apoptosis of the peripheral nervous system[38].

Various studies with experimental diabetes have shown that neurotrophin-3 (NT-3), nerve growth factor (NGF), insulin-like growth factor-I (IGF-I) and colliery neutrophil factor have been decreased and were associated with presence of neuropathy[39]. Management of NGF restores neuropeptide levels and sensitive amplitudes in experimental diabetes[40],inparallel, IGF-I administration prevent the development of neuropathy and reverses impaired nerve renewal and NT-3 normalizes nerve conduction slowing[41-42].When oxidative stress is inducing in nerves of non-diabetic animals by giving pro-oxidants, reduction in NGF and NT-3 are observed like those reported in animals with experimental diabetes[43].Therapy by usingantioxidant in experimental diabetic neuropathy prevents the observed decreases in nerve NGF and restores nerve function[44]. Antioxidant therapy also returns normal blood inflow and nerve conduction velocities in experimental diabetes[45-46].Interestingly, neurotropic factors may also serve as antioxidants and this function may participate in their role as possible therapeutic in diabetic neuropathy[47]. To avert the complications of diabetes including neuropathy, many studies have been done using antioxidant factor and some of them have shown hopeful results.Controlling the Patients antioxidant level also may clear development of disorder that could be reducing by changing the therapeutic antioxidant diet[31, 48]. Then, so that we can control the level of blood glucose, medications like antioxidants that are targeted against oxidative stress stay most promising way to prevent neuropathy.

8. Effect of antioxidants on diabetes

An antioxidant is a molecule that inhibits the oxidation of other molecules, and a substance which slows down the damage that can be caused to other substances by the effects of oxygen. Food which contains antioxidants are thought to be very good for diabetes. Initially, anti-oxidation was used to store food, but later the biologists realized the significance of antioxidants in health, that was in the 1960s publications of vitamins and flavonoids[49].However,many congress and reviews indicate the rising interest in the roles of the body's antioxidants system working together in human cells against reactive oxygen species, their connection with several of the processes of the cellular and their possible therapeutic effects[50].Antioxidant defense technique includes both enzymatic and non-enzymatic strategies. Common antioxidants involve the vitamins A, C, and E, glutathione, alpha-lipoic acid, mixed carotenoids, and the enzymes catalase, glutathione peroxidase, superoxide dismutase and glutathione reductase. Other antioxidants include, coenzyme Q10, many bioflavonoids, antioxidant minerals (zinc, manganese, copper, and selenium), and the cofactors (vitamins, B2, B6, B12, folic acid,). They work with each other against different types of free radicals[51-52].Through normal physiological processes, antioxidants affect signal transduction and regulation of proliferation and the immune response during normal physiological processes. While ROS have relating cancer, CVD, and diabetic complications, antioxidants have shown a possibility treatment for the preventing and therapy of these diseases, especially given the puzzling links observed between diets high in vegetables and fruits (and potential antioxidants) and reduced risks of cancer[53].

9. Evidence from experimental and clinical studies

Numerous studies have been conducted using antioxidants in experimental diabetes models. Through some observable biomarkers are measured the effects of antioxidants on oxidative stress. These Markers include an enzymatic activity of the level of reactive substance with thiobarbituric acid (TBARS), as well as enzymatic activities for GSH-PX, SOD, GSH-RX, Are indirect measurements of free radicals[54].The effects of the high toxicity of Hydroperoxides on cell both directly and through degeneration to highly toxic hydroxyl radicals. which they may also interact with transition metals like copper or iron to form stable aldehydes such as malondialdehyde that will harm cell membranes. Peroxyl radicals can work on remove hydrogen from lipids; producing hydroperoxides that work propagate the free-radical pathway[26].Thiobarbituric acid reactive substances (TBARS) are the indirect evidence of concentrated free-radical production. where diabetes is stimulated in some animals (rats) with alloxan or streptozotocin (STZ) leading to an increase in thiobarbituric acid reactive substances (TBARS), Preventing the forming of hydroxyl radicals would be an effective means to decrease hydroxyl-induced damage, According to previous studies, many compounds were tested as antioxidants in some diabetic animals with varying success. such as melatonin, boldine, -lipoicacid, andnicotinamid[55-57].

The effects of treatments with antioxidants such as vitamin C, lipoic acid, and vitamin E Specifically, vitamin E normalizes retinal PKC activity and blood inflow in the vascular tissue of diabetic rats[58].A study examined whether it was dietary supplementation with vitamin E would reduce occurrence of diabetic retinopathy in rat model. The diabetic group received vitamin E supplements (400 mg/day)

while the control group consists of fifty the pregnant rats and fad a normal diet. Find that supplementation with vitamin E in this experimental study reduces the incidence of neural tube defects by more than 75 percent[59].Protective effect to the vitamin E against diabetic embryopathythese findings suggest that vitamin E reduces this oxidative load, and thus may potentially serve as a dietary prophylaxis in the future. Also In another study to define the impact of vitamin E on oxidative stress and cell membrane in the brains of diabetes-induced rats. Suggest that vitamin E was found to be efficient for the antioxidant defense system. They noted a decrease in the generation of oxidative damaging substances such as the carbonyl value, a decrease of the accumulation of ROS such as superoxide radicals, maintenance of membrane in the brains of the rats, and improved lipid composition a significantly[60].In a previous study, has been suggested that vitamin C administered alone or in conjunction with vitamin E reduced the fall in ulnar nerve conduction velocity[61]. Also in another study suggested that triple antioxidant therapy (α-lipoic acid and vitamin C, vitamin E) in diabetes eases the experimental oxidative stress for reduces haemoglobinglycation in vivo and methemoglobinformation in vitro[62]. An experimental study has shown that high doses of vitamin C can improve some a side of endothelial disorders in diabetes[63].

Examination of the protecting effects of antioxidant combination (α-lipoic acid, vitamin E and C) on the complete cholesterol and lipid levels and the fatty acid composition of brain tissues in diabetic and non-diabetic rats showed that the treatment with a triple collection of antioxidants reservation the arachidonic acid level in the brains of diabetic and non-diabetic rats. Moreover, both insulin treatment and antioxidants have beneficial impacts on the D-6 desaturase system and unsaturated fatty acid levels. Antioxidants effects may have protective effects on unsaturated fatty acids, decrease oxidative stress, and impairing cell membrane lipid peroxidation, the progression to LDL oxidation, and decreaseendoneurial blood flow, thereby vascular dysfunction and reducing peripheral nerve[64].A study showed that the impact of vitamin E with supplementation to diabetic mice. The effect was observed; vitamin E in this model delay coronary atherosclerosis speeding up by DM, this has been shown to be due to a decrease in oxidative stress[65]. Another study reported that maternal diabetes inhibited Pax3 expression which increases neural tube defects causes neuropathy of mouse or rat embryos is prevent by N-acetyl-cystenine, vitamin E, vitamin C[66].

10. Clinical studies

Many clinical studies have examined the effect of antioxidants on diabetics, theyhave shown the results disparity from study to another. In which several studies recommend that vitamin C administration has useful effects on glucose and lipid metabolism in T2DM patients. A clinical study has done; it has been confirmed that vitamin C supplementation is efficient in decreasing sorbitol gathering in the RBC of diabetes. The effects of this study showed that within 30 days, vitamin C supplementation at each dose normalized sorbitol levels in those with diabetes. Another study investigated the effect of two separate doses of vitamin C supplements during a 58 day experimental on the adults with T1DM;it has been found that vitamin C also helped to reduce capillary fragility which also contributedto complications from diabetes[67.A previous study confirmed that type 2 diabetes patients, who were given two different doses 500 mg or 1000 mg daily of vitamin C for 42 days, it has been indicated a study that daily consumption 1000 mg supplementary vitamin C may be useful in reducing lipids and blood glucose in patients with type 2 diabetes and therefore degrading the risk of complications[68].

In a study conducted to evaluate the ability of oral supplementation of vitamin E (900 mg\day) in T2DM patients over a four-month period, as shown during the blood glucose assays which done both before and after the supplementation period, found that supplementation of vitamin E reduced insulin resistance and improve glucose uptake[69].Some studies have also shown that vitamin E may be a beneficial addition to reducing oxidative stress in T2DM. This was confirmed by a previous study in which glycosylated haemoglobin and other proteins were reduced with each 600 or 1200 mg/day of vitamin E for two months[70].As shown by study the capacity of tocopherols to decrease oxidative stress and it also indicate the possible benefits of vitamin E supplementation in type 2 diabetes patients. In people with type 2 diabetes[71]. A clinical study was conducted to evaluate patients with type 1 diabetes T1DM. There were two groups; one group received a high dose of vitamin E supplementation (1,800 IU/day) while the other group received a placebo. The results showed that oral vitamin E treatment showed its effectiveness in improving renal function in patients and normalizing retinal hemodynamic abnormalities with T1DM, particularly those with short disease period. This implies that vitamin E supplementation may produce an additional interest in reducing the risks for growing diabetic nephropathy or retinopathy[72].Other studies have shown a relationship between low vitamin E status and increased risk of type 1 and 2 diabetes [73-74].

They suggested that there were no good effects on the condition of vitamin E or use of supplements, this aim wasnot common[75].Additionally, As shown by a study, the use of 600 IU vitamin E supplementation which did not reduce the risk of the development of type 2 diabetes over placebo at a 10-year consecutive[76]. However, most data supported a potential link between vitamin E status and the risk of diabetes especially type 2 diabetes. Oxidative stress is central to factor dysfunction to b-cell in type 2 diabetes and this effect can be moderated by antioxidants.

As an antioxidant, vitamin E improves results associated with pancreas physiology in diabetes which may improve functional results of diabetes[75, 77].This reports that kidney function of diabetic animals can be improved by vitamin E. In a trial including supplementation with vitamins C and E together, those given the antioxidants had a significantly less concentration of urinary microalbumin secretion in comparison to the placebo group[78]. it has been found thatvitamin E status has to affect human diabetics also. Plasma vitamin E to lipid rate was less in diabetics than

controls, and this outcome was even more vocalized in diabetics with neuropathy. In this study, plasma vitamin E to lipid ratio was also inversely linked to a result of neuropathy. Animal studies have expressed that supplementation with vitamin E slows the rise of nerve dysfunction[79]. The majority of studies in this review support the role of antioxidant supplements in reducing the risk of diabetes complications, but some studies have failed to prove useful antioxidant supplements in reducing the effects of diabetic complications.

Table 1: Some clinical trials to role antioxidant supplements in preventing complications diabetes.

Antioxidant supplementation	Target	Study outcome
Vitamin C [80]	Type 2 diabetes	Chronic vitamin C administration has beneficial effects upon glucose and lipid metabolism.
Vitamin E [81]	Type 2 diabetes	Important role in delaying the onset of the diabetic complications and slowing down the development the complications.
Vitamin E [69]	Type 2 diabetes	That give of pharmacologic doses of vitamin E is a beneficial tool to reduce oxidative stress and improve insulin action.
Vitamin E [82]	Type 2 diabetes	Significantly beneficial a reduction approximately 60% of plasma LDL oxidation in diabetic patients.
Vitamin E [83]	Diabetes mellitus (DM)	Decreased cardiovascular effects in people with diabetes.
Vitamin C and E [84]	Type 2 diabetes	significance beneficial, decreasing the FBS, TC, SC, LDL and HbA1c
Vitamin C [85]	Type 2 diabetes	Beneficial in the treatment of type II DM, supplementation of vitamin C reduces FBG, PPBG, and improves HbA1c. Hence, good glycemic control.
Vitamin A, C and E[86]	Type 1 diabetes	No significance beneficial in reduction oxidative damage
Vitamins E andC [87]	Diabetes mellitus	No significant associations were observed between risk of retinopathy and intake of major dietary antioxidants

11. Conclusion

In conclusion, this review emphasized the role of antioxidants in management of diabetes and its complications. Diabetes mellitus is accompanied by increased oxidative stress, which is considered an underlying mechanism for inflammation and endothelial dysfunction. This has prompted several clinical trials with antioxidant supplements in diabetic individuals to prevent long-term complications. Several explanations for a lack of clinical benefit for the use of anti-oxidants in diabetes have been proposed: first, physiologic concentrations of ROS are required for biochemical processes such as immunity and defence against microorganisms, cellular differentiation and growth arrest, apoptosis and intracellular signal transduction including insulin signalling. Supplementation with antioxidants may deleteriously affect these processes. Second, the effects of some of antioxidants are not confined to their antioxidant properties; for example, vitamin E participates in the expression of some genes. The current recommended mineral and vitamin intakes for people with diabetes mellitus are like those for healthy subjects; patients should be encouraged to obtain such nutrients primarily from natural sources and/or fortified foods rather than supplements [88-89]. Routine vitamin or mineral supplementation is not generally recommended due to a lack of evidence related to demonstrable benefits and long term safety in diabetic individuals. Importantly, there is currently no published evidence that any anti-oxidant strategy prolongs life span in diabetic patients or improves glucose control achieved by current management strategies. As evident from literature, exploration of the potentials of natural antioxidants such as vitamins A, C and E have been helpful in the negation of excess ROS production and acts as counteractive agents against hyperglycaemia-induced oxidative damage in the body. Further studies are needed to establish the various mechanisms by which these vitamins produce their effects on diabetic conditions. In addition, since there are few studies on the antioxidant potentials of antioxidant vitamins using human subjects from available literature, more clinical studies are needed to support the claims from animal studies. Therefore, antioxidant proved by experimental study as well in clinical study could be used as a potential therapy formanagement of diabetes and its complications.

References

1. King H, Aubert RE, Herman WH. Global burden of diabetes, 1995–2025: prevalence, numerical estimates, and projections. Diabetes care. 1998;21(9):1414-31.
2. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes care. 2004;27(5):1047-53.
3. World Health Organization. Definition, diagnosis and classification of diabetes mellitus and its complications: report of a WHO consultation. Part 1, Diagnosis and classification of diabetes mellitus. (1999).
4. Bajaj S, Khan A. Antioxidants and diabetes. Indian journal of endocrinology and metabolism. 2012;16(Suppl 2):S267.

5. Rahman K. Studies on free radicals, antioxidants, and co-factors. Clinical interventions in aging. 2007;2(2):219.
6. Bikkad MD, Somwanshi SD, Nagane NS. Oxidative Stress in Type II Diabetes Mellitus. Biomedical Research. 2014;25:84-87.
7. Jacob S, Streeper RS, Fogt DL, Hokama JY, Henriksen EJ, Dietze GJ, Tritschler HJ. The antioxidant α-lipoic acid enhances insulin-stimulated glucose metabolism in insulin-resistant rat skeletal muscle. Diabetes. 1996;45(8):1024-9.
8. Jacob S, Ruus P, Hermann R, Tritschler HJ, Maerker E, Renn W, Augustin HJ, Dietze GJ, Rett K. Oral administration of RAC-α-lipoic acid modulates insulin sensitivity in patients with type-2 diabetes mellitus: a placebo-controlled pilot trial. Free Radical Biology and Medicine. 1999;27(3-4):309-14.
9. Hirashima O, Kawano H, Motoyama T, Hirai N, Ohgushi M, Kugiyama K, Ogawa H, Yasue H. Improvement of endothelial function and insulin sensitivity with vitamin C in patients with coronary spastic angina: possible role of reactive oxygen species. Journal of the American College of Cardiology. 2000;35(7):1860-6.
10. Vaziri ND, Dicus M, Ho ND, Boroujerdi-Rad L, Sindhu RK. Oxidative stress and dysregulation of superoxide dismutase and NADPH oxidase in renal insufficiency. Kidney Int. 2003; 63:179-85.
11. Weseler AR, Bast A. Oxidative stress and vascular function: implications for pharmacologic treatments. Current hypertension reports. 2010 Jun 1;12(3):154-61.
12. Sies H, editor. Oxidative stress. Elsevier; 2013 Oct 22.
13. Kangralkar VA, Patil SD, Bandivadekar RM. Oxidative stress and diabetes: a review. Int J Pharm Appl. 2010;1(1):38-45.
14. McCord JM. The evolution of free radicals and oxidative stress. The American journal of medicine. 2000;108(8):652-9.
15. Evans JL, Goldfine ID, Maddux BA, Grodsky GM. Are oxidative stress− activated signaling pathways mediators of insulin resistance and β-cell dysfunction?. Diabetes. 2003;52(1):1-8.
16. Haskins K, Bradley B, Powers K, Fadok V, Flores S, Ling X, Pugazhenthi S, Reusch J, Kench J. Oxidative stress in type 1 diabetes. Annals of the New York Academy of Sciences. 2003;1005(1):43-54.
17. Giugliano D, Ceriello A, Paolisso G. Diabetes mellitus, hypertension, and cardiovascular disease: which role for oxidative stress?. Metabolism-Clinical and Experimental. 1995;44(3):363-8.
18. West IC. Radicals and oxidative stress in diabetes. Diabetic Medicine. 2000;17(3):171-80.
19. Wolff SP. Diabetes mellitus and free radicals: free radicals, transition metals and oxidative stress in the aetiology of diabetes mellitus and complications. British medical bulletin. 1993;49(3):642-52.
20. Aruoma OI. Nutrition and health aspects of free radicals and antioxidants. Food and Chemical Toxicology. 1994 Jul 1;32(7):671-83.
21. Somogyi A, Rosta K, Pusztai P, Tulassay Z, Nagy G. Antioxidant measurements. Physiological Measurement. 2007;28(4):R41-55.
22. Cheeseman KH, Slater TF. An introduction to free radical biochemistry. British medical bulletin. 1993;49(3):481-93.
23. Lobo V, Patil A, Phatak A, Chandra N. Free radicals, antioxidants and functional foods: Impact on human health. Pharmacognosy reviews. 2010;4(8):118.
24. Bagchi K, Puri S. Free radicals and antioxidants in health and disease: a review. Eastern Mediterranean Health J. 1998; 4:350-360.
25. Liu T, Stern A, Roberts LJ, Morrow JD. The isoprostanes: novel prostaglandin-like products of the free radical-catalyzed peroxidation of arachidonic acid. Journal of biomedical science. 1999;6(4):226-35.
26. Halliwell B, Gutteridge JM. [1] Role of free radicals and catalytic metal ions in human disease: an overview. In Methods in enzymology 1990 (Vol. 186, pp. 1-85). Academic Press.
27. Vafa MR, Haghighatjoo E, Shidfar F, Afshari S, Gohari MR, Ziaee A. Effects of apple consumption on lipid profile of hyperlipidemic and overweight men. International journal of preventive medicine. 2011;2(2):94.
28. Baillie JK, Thompson AA, Irving JB, Bates MG, Sutherland AI, Macnee W, Maxwell SR, Webb DJ. Oral antioxidant supplementation does not prevent acute mountain sickness: double blind, randomized placebo-controlled trial. QJM: An International Journal of Medicine. 2009;102(5):341-8.
29. Aylward GW. Progressive changes in diabetics and their management. Eye. 2005;19(10):1115.
30. Rahimi-Madiseh M, Malekpour-Tehrani A, Bahmani M, Rafieian-Kopaei M. The research and development on the antioxidants in prevention of diabetic complications. Asian Pacific journal of tropical medicine. 2016;9(9):825-31.
31. Rafieian-Kopaei M, Baradaran A, Rafieian M. Plants antioxidants: From laboratory to clinic. Journal of nephropathology. 2013;2(2):152-3.
32. Lim AK. Diabetic nephropathy–complications and treatment. International journal of nephrology and renovascular disease. 2014;7:361.
33. Ardalan MR, Estakhri R, Hajipour B, Ansarin K, Asl NA, Nasirizade MR, Azar AN, Ghorbanihaghjou A, Vatankhah AM, Esmaili HA. Erythropoietin ameliorates oxidative stress and tissue injury following renal ischemia/reperfusion in rat kidney and lung. Medical Principles and Practice. 2013;22(1):70-4.
34. Nasri H, Baradaran A, Ardalan MR, Mardani S, Momeni A, Rafieian-Kopaei M. Bright renoprotective properties of metformin: beyond blood glucose regulatory effects. Iranian journal of kidney diseases. 2013;7(6):423.
35. Nasri H, Rafieian-Kopaei M. Kidney tubular cell protection; recent findings. Iranian journal of pediatrics. 2014;24(6):781-3.
36. Amini FG, Rafieian-Kopaei M, Nematbakhsh M, Baradaran A, Nasri H. Ameliorative effects of metformin on renal histologic and biochemical alterations of gentamicin-induced renal toxicity in Wistar rats. Journal of research in medical sciences: the official journal of Isfahan University of Medical Sciences. 2012;17(7):621.
37. Rahimi R, Nikfar S, Larijani B, Abdollahi M. A review on the role of antioxidants in the management of diabetes and its complications. Biomedicine & Pharmacotherapy. 2005;59(7):365-73.
38. Schmeichel AM, Schmelzer JD, Low PA. Oxidative injury and apoptosis of dorsal root ganglion neurons in chronic experimental diabetic neuropathy. Diabetes. 2003;52(1):165-71.
39. Apfel S. Neurotrophic factors and diabetic peripheral neuropathy. European neurology. 1999;41(Suppl. 1):27-34.
40. Tomlinson DR, Fernyhough P, Diemel LT. Role of neurotrophins in diabetic neuropathy and treatment with nerve growth factors. Diabetes. 1997;46(Supplement 2):S43-9.
41. Schmidt RE, Dorsey DA, Beaudet LN, Plurad SB, Parvin CA, Miller MS. Insulin-like growth factor I reverses experimental diabetic autonomic neuropathy. The American journal of pathology. 1999;155(5):1651-60.
42. Zhuang HX, Snyder CK, Pu SF, Ishii DN. Insulin-like growth factors reverse or arrest diabetic neuropathy: effects on hyperalgesia and impaired nerve regeneration in rats. Experimental neurology. 1996;140(2):198-205.
43. Hounsom L, Corder R, Patel J, Tomlinson DR. Oxidative stress participates in the breakdown of neuronal phenotype in experimental diabetic neuropathy. Diabetologia.

2001;44(4):424-8.
44. Obrosova IG, Fathallah L, Stevens MJ. Taurine counteracts oxidative stress and nerve growth factor deficit in early experimental diabetic neuropathy. Experimental neurology. 2001;172(1):211-9.
45. Cameron NE, Eaton SE, Cotter MA, Tesfaye S. Vascular factors and metabolic interactions in the pathogenesis of diabetic neuropathy. Diabetologia. 2001;44(11):1973-88.
46. Greene DA, Stevens MJ, Obrosova I, Feldman EL. Glucose-induced oxidative stress and programmed cell death in diabetic neuropathy. European journal of pharmacology. 1999;375(1-3):217-23.
47. Pan Z, Sampath D, Jackson G, Werrbach-Perez K, Perez-Polo R. Nerve growth factor and oxidative stress in the nervous system. InBrain Plasticity 1997 (pp. 173-193). Springer, Boston, MA.
48. Vincent AM, Russell JW, Low P, Feldman EL. Oxidative stress in the pathogenesis of diabetic neuropathy. Endocrine reviews. 2004;25(4):612-28.
49. Rowe LA. DNA damage-induced reactive oxygen species: A genotoxic stress response (Doctoral dissertation, Emory University).
50. Matés JM, Pérez-Gómez C, De Castro IN. Antioxidant enzymes and human diseases. Clinical biochemistry. 1999;32(8):595-603.
51. Fehér J, Csomós G, Vereckei A. Free radical reactions in medicine. Springer Science & Business Media; 2012.
52. Maritim AC, Sanders A, Watkins J3. Diabetes, oxidative stress, and antioxidants: a review. Journal of biochemical and molecular toxicology. 2003;17(1):24-38.
53. Seifried HE, Anderson DE, Fisher EI, Milner JA. A review of the interaction among dietary antioxidants and reactive oxygen species. The Journal of nutritional biochemistry. 2007;18(9):567-79.
54. Johansen JS, Harris AK, Rychly DJ, Ergul A. Oxidative stress and the use of antioxidants in diabetes: linking basic science to clinical practice. Cardiovascular diabetology. 2005;4(1):5.
55. Kedziora-Kornatowska KZ, Luciak M, Paszkowski J. Lipid peroxidation and activities of antioxidant enzymes in the diabetic kidney: effect of treatment with angiotensin convertase inhibitors. IUBMB life. 2000;49(4):303-7.
56. Pierrefiche G, Topall G, Courboin G, Henriet I, Laborit H. Antioxidant activity of melatonin in mice. Research communications in chemical pathology and pharmacology. 1993;80(2):211-23.
57. Montilla PL, Vargas JF, Túnez IF, Carmen M, Agueda M, Valdelvira M, Cabrera ES. Oxidative stress in diabetic rats induced by streptozotocin: protective effects of melatonin. Journal of pineal research. 1998;25(2):94-100.
58. Kunisaki MA, Bursell SE, Clermont AC, Ishii HI, Ballas LM, Jirousek MR, Umeda FU, Nawata HA, King GL. Vitamin E prevents diabetes-induced abnormal retinal blood flow via the diacylglycerol-protein kinase C pathway. American Journal of Physiology-Endocrinology and Metabolism. 1995;269(2):E239-46.
59. Sivan E, Reece EA, Wu YK, Homko CJ, Polansky M, Borenstein M. Dietary vitamin E prophylaxis and diabetic embryopathy: morphologic and biochemical analysis. American Journal of Obstetrics &Gynecology. 1996 Oct 1;175(4):793-9.
60. Hong JH, Kim MJ, Park MR, Kwag OG, Lee IS, Byun BH, Lee SC, Lee KB, Rhee SJ. Effects of vitamin E on oxidative stress and membrane fluidity in brain of streptozotocin-induced diabetic rats. Clinicachimicaacta. 2004;340(1-2):107-15.
61. Panjwani U, Yadav DK, Kumar A, Singh SB, Selvamurthy W. Effect of vitamin C and E supplementation in modulating the peripheral nerve conduction following cold exposure in humans. International journal of biometeorology. 2003;48(2):103-7.
62. Coleman MD, Fernandes S, Khanderia L. A preliminary evaluation of a novel method to monitor a triple antioxidant combination (vitamins E, C and α-lipoic acid) in diabetic volunteers using in vitro methaemoglobin formation. Environmental toxicology and pharmacology. 2003;14(1-2):69-75.
63. Mohora M, Greabu M, Muscurel C, Duţă C, Totan A. The sources and the targets of oxidative stress in the etiology of diabetic complications. Romanian J Biophys. 2007;17(2):63-84.
64. Özkan Y, Yilmaz Ö, Öztürk Aİ, Erşan Y. Effects of triple antioxidant combination (vitamin E, vitamin C and α-lipoic acid) with insulin on lipid and cholesterol levels and fatty acid composition of brain tissue in experimental diabetic and non-diabetic rats. Cell Biology International. 2005;29(9):754-60.
65. Otero P, Bonet B, Herrera E, Rabano A. Development of atherosclerosis in the diabetic BALB/c mice: prevention with vitamin E administration. Atherosclerosis. 2005;182(2):259-65.
66. Chang TI, Horal M, Jain SK, Wang F, Patel R, Loeken MR. Oxidant regulation of gene expression and neural tube development: Insights gained from diabetic pregnancy on molecular causes of neural tube defects. Diabetologia. 2003;46(4):538-45.
67. Cunningham JJ, Mearkle PL, Brown RG. Vitamin C: an aldose reductase inhibitor that normalizes erythrocyte sorbitol in insulin-dependent diabetes mellitus. Journal of the American College of Nutrition. 1994;13(4):344-50.
68. Afkhami-Ardekani M, Shojaoddiny-Ardekani A. Effect of vitamin C on blood glucose, serum lipids & serum insulin in type 2 diabetes patients. Indian Journal of Medical Research. 2007;126(5):471.
69. Paolisso G, D'Amore A, Giugliano D, Ceriello A, Varricchio M, D'onofrio F. Pharmacologic doses of vitamin E improve insulin action in healthy subjects and non-insulin-dependent diabetic patients. The American journal of clinical nutrition. 1993;57(5):650-6.
70. Matough FA, Budin SB, Hamid ZA, Alwahaibi N, Mohamed J. The role of oxidative stress and antioxidants in diabetic complications. Sultan Qaboos University Medical Journal. 2012;12(1):5.
71. Wu JH, Ward NC, Indrawan AP, Almeida CA, Hodgson JM, Proudfoot JM, Puddey IB, Croft KD. Effects of α-tocopherol and mixed tocopherol supplementation on markers of oxidative stress and inflammation in type 2 diabetes. Clinical chemistry. 2007;53(3):511-9.
72. Bursell SE, Clermont AC, Aiello LP, Aiello LM, Schlossman DK, Feener EP, Laffel L, King GL. High-dose vitamin E supplementation normalizes retinal blood flow and creatinine clearance in patients with type 1 diabetes. Diabetes care. 1999;22(8):1245-51.
73. Knekt P, Reunanen A, Marniemi J, Leino A, Aromaa A. Low vitamin E status is a potential risk factor for insulin-dependent diabetes mellitus. Journal of internal medicine. 1999;245(1):99-102.
74. Salonen JT, Nyyssonen K, Tuomainen TP, Maenpaa PH, Korpela H, Kaplan GA, Lynch J, Helmrich SP, Salonen R. Increased risk of non-insulin dependent diabetes mellitus at low plasma vitamin E concentrations: a four year follow up study in men. Bmj. 1995;311(7013):1124-7.
75. Pazdro R, Burgess JR. The role of vitamin E and oxidative stress in diabetes complications. Mechanisms of ageing and development. 2010;131(4):276-86.
76. Liu S, Lee IM, Song Y, Van Denburgh M, Cook NR, Manson JE, Buring JE. Vitamin E and risk of type 2 diabetes in the women's health study randomized controlled trial. Diabetes. 2006;55(10):2856-62.

77. Sena CM, Nunes E, Gomes A, Santos MS, Proença T, Martins MI, Seiça RM. Supplementation of coenzyme Q10 and α-tocopherol lowers glycatedhemoglobin level and lipid peroxidation in pancreas of diabetic rats. Nutrition research. 2008;28(2):113-21.
78. Farvid MS, Jalali M, Siassi F, Hosseini M. Comparison of the effects of vitamins and/or mineral supplementation on glomerular and tubular dysfunction in type 2 diabetes. Diabetes care. 2005;28(10):2458-64.
79. Ziegler D, Sohr CG, Nourooz-Zadeh J. Oxidative stress and antioxidant defense in relation to the severity of diabetic polyneuropathy and cardiovascular autonomic neuropathy. Diabetes care. 2004;27(9):2178-83.
80. Paolisso G, Balbi V, Volpe C, Varricchio G, Gambardella A, Saccomanno F, Ammendola S, Varricchio M, D'Onofrio F. Metabolic benefits deriving from chronic vitamin C supplementation in aged non-insulin dependent diabetics. Journal of the American College of Nutrition. 1995;14(4):387-92.
81. Jain AB, Jain VA. Vitamin E, its beneficial role in diabetes mellitus (DM) and its complications. Journal of clinical and diagnostic research: JCDR. 2012;6(10):1624.
82. Reaven PD, Herold DA, Barnett J, Edelman S. Effects of vitamin E on susceptibility of low-density lipoprotein and low-density lipoprotein subfractions to oxidation and on protein glycation in NIDDM. Diabetes care. 1995 Jun 1;18(6):807-16.
83. Hodis HN, Mack WJ, Dustin L, Mahrer PR, Azen SP, Detrano R, Selhub J, Alaupovic P, Liu CR, Liu CH, Hwang J. High-dose B vitamin supplementation and progression of subclinical atherosclerosis: a randomized controlled trial. Stroke. 2009;40(3):730-6.
84. Prajapat R, Bhattacharya I, Jakhalia A. Combined Effect of Vitamin C and E Dose on Type 2 Diabetes Patients. Adv in Diabetes and Metabolism. 2017;5(2):21-5.
85. Afkhami-Ardekani M, Vahidi AR, Borjian L, Borjian L. Effect of vitamin C supplement on glycosylated hemoglobin in patients with type 2 diabetes. J Shah Sad Univ. 2003;10(1):15-8.
86. Cazeau RM, Huang H, Bauer JA, Hoffman RP. Effect of vitamins C and E on endothelial function in type 1 diabetes mellitus. Journal of diabetes research. 2016; Article ID 3271293; 5.
87. Millen AE, Klein R, Folsom AR, Stevens J, Palta M, Mares JA. Relation between intake of vitamins C and E and risk of diabetic retinopathy in the Atherosclerosis Risk in Communities Study. The American journal of clinical nutrition. 2004;79(5):865-73.
88. Bantle JP, Wylie-Rosett J, Albright AL, Apovian CM, Clark NG, Franz MJ, Hoogwerf BJ, Lichtenstein AH, Mayer-Davis E, Mooradian AD, Wheeler ML. Nutrition recommendations and interventions for diabetes: a position statement of the American Diabetes Association. Diabetes care. 2008;31:S61-78.
89. Bisbal C, Lambert K, Avignon A. Antioxidants and glucose metabolism disorders. Current Opinion in Clinical Nutrition & Metabolic Care. 2010;13(4):439-46.

