Diabetes and Oxidative Stress: The Mechanism and Action

Robab Sheikhpour*

Department Of Biology, Science and Research Branch, Islamic Azad University, Tehran, Iran

*Correspondence:
Robab Sheikhpour, Department of Biology, Science and Research Branch, Islamic Azad University, Tehran, Iran.
Tel: (98) 913 152 2462
Email: r.sheikhpour@yahoo.com

Received: 5 August 2013
Accepted: 20 November 2013
Published in 28 December 2013

Abstract

Diabetes mellitus is one of the major metabolic disorders. Diabetes is recognized for severe complications including diabetic nephropathy, neuropathy and retinopathy. Long-lasting effect of hyperglycemia results in increased oxidative stress. Oxidative stress results from an imbalance between radical-generating and radical scavenging systems. Increased oxidative stress has been shown to be increased in both insulin-dependent (IDDM), and noninsulin-dependent (NIDDM) diabetes mellitus and it could cause initial β cell damage in type I diabetes, or impaired insulin production, release or function in type II diabetes. Therefore, people with diabetes may also have greater antioxidant requirements because of increased production of free radicals in hyperglycemia. In this article, oxidative stress, free radicals, antioxidants and various mechanisms of reactive oxygen species (ROS) formation such as polyol pathway, protein oxidation, advanced glycation endproducts and lipid peroxidation in diabetic patients will be surveyed.

Keyword: Diabetes, Lipid Peroxidation, Antioxidant, Oxidative Stress

Introduction

Diabetes mellitus is a group of metabolic diseases (1) caused by a combination of insulin resistance and impaired insulin secretion by pancreatic β cell (2,3). Today, more than 200 million people worldwide have type 2 diabetes. The total number of people with diabetes is expected to reach 370 million worldwide in 2030 (4). Studies showed that diabetic patients are more prone to oxidative stress (2). Oxidative stress results from increased free radical production or reduced activity of antioxidant defenses or both (2,5). Persistent hyperglycemia causes increased production of free radicals, especially reactive oxygen species (ROS), for all tissues (2). Increased ROS may disturb or modify various cellular functions and alter gene expression. The increased oxidative stress in noninsulin-dependent diabetes mellitus (NIDDM) is associated with an increased oxidative damage to DNA (2,6). It can cause initial β cell damage in type I diabetes, or impaired insulin production, release or function in type II diabetes (7).

Oxidative stress

Increased Free radical production is due to misbalance between generating and clearing free radical. This process causes oxidative stress (2,4,5). Overproduction of free radicals can destroy biomolecules such as lipids, proteins and DNA. Thus, it causes many diseases such as cancer, diabetes, cardiovascular diseases, aging and other

degenerative diseases in human (2,8). Mousa reported that diabetic patients suffer from enhanced oxidative stress and decreased antioxidant system (7).

Free radical species

Free radicals are very active and separate an electron from molecule, because of unpaired electron in their outer orbit. These compounds have a very significant task in biogenesis and useful effects on the organisms (8). Superoxide ($O2^{\cdot-}$), hydrogen peroxide (H_2O_2), hydroxyl radical ($OH^{\cdot}$) and nitric oxide ($NO^{\cdot}$) are free radicals that are essential for normal physiology. These radicals speed up cellular destruction in many diseases. These agents can attack proteins, lipids and DNA (9).

Superoxide ($O2^{\cdot-}$)

$O2^{\cdot-}$ is created during the oxidation of reduced nicotinamide adenine dinucleotide (NADH) to oxidized nicotinamide adenine dinucleotide (NAD) in mitochondria. Also, a byproduct of many enzymes that act as oxidases is $O2^{\cdot-}$. Almost four percent of electrons entering the respiratory chain are able to produce $O2^{\cdot-}$ (9). Superoxide plays a significant role in many diseases (10). One study showed that superoxide ion and H_2O_2 or both are increased in diabetic rats (11). Also, studies showed that the regulation of spontaneous NO can be under the action of superoxide ion (11).

Hydrogen peroxide (H_2O_2)

Superoxide ($O2^{\cdot-}$) in the presence of superoxide dismutase (SOD) can be converted to H_2O_2 (9). Studies have shown that 30% H_2O_2 solution has co-carcinogen activity in oral mucosa but solutions of 3% or less had no co-carcinogenic activity (12).

Hydroxyl radical ($OH^{\cdot}$)

H_2O_2 in the presence of free Fe^{2+} produce hydroxyl radical and Fe^{3+} (9). When transition metals such as Fe^{2+} and Cu^{2+} are presented, H_2O_2 can react with components such as glucose and its other metabolites and form hydroxyl radical (OH) that is the most reactive ROS (11,13).

Nitric oxide ($NO^{\cdot}$)

L-arginine can produce NO by nitric oxide synthase (eNOS) in vascular endothelial cells (14). NO regulates ion channels by guanylate cyclases and adjust vascular tone (9). Reaction of NO with oxygen produces nitrogen dioxide (NO2). Also, increased levels of nitric oxide have been observed in type 1 diabetes (15).

Mechanisms for increased oxidative stress in diabetes

The polyol pathway

Hyperglycemia induces the polyol pathway, resulting in induction of aldose reductase and production of sorbitol. Significance of the polyol pathway may differ among different tissues (2). The polyol pathway plays a significant role in diabetes complications (17). Induction of oxidative stress may occur through many different mechanisms, including depletion of NADPH and consequent disturbance of glutathione and nitric oxide metabolism (2).

Protein oxidation in diabetic patients

Free radicals modify amino acid side chains such as arginine, lysine, threonine and proline residues and produce protein carbonyls. High levels of protein carbonyl have been seen in plasma of diabetic patients. There is a direct correlation between protein oxidation and diabetes complications (2). One study showed that protein oxidation in diabetic patients is higher and total protein is lower than normal subjects. Also, another study showed that diabetic children have low levels of ceruloplasmin, ceruloglobulin and retinol binding protein (RBP) (2,15).

Advanced glycation endproducts

Advanced glycation or glycosylation end products are the products of glycation and oxidation (glycoxidation), which are increased with age. Large amounts of these components have been seen in the plasma of diabetic patients. Also, these components are enhanced with age. Studies showed that antioxidants can decrease glycosylation end products and cross-

linking. In addition, production of superoxide can be under glycation process (2).

Glutathione homeostasis

Free radicals may cause destruction of cellular components. Glutathione can reduce oxidative stress; so, it can be an antioxidant (2,18). Blood Glutathione levels are significantly decreased in different phases of type 2 DM such as early hyperglycemia and glucose intolerance (2).

Impairment of superoxide dismutase and catalase activity

Two major antioxidant enzymes are superoxide dismutase (SOD) and catalase. Three different forms of superoxide dismutase exist. Dismutation of superoxide to H_2O_2 is performed in the presence of Cu,Zn-SOD. It is found in cytosol. Extracellular SOD is found in plasma and extracellular space. Mn-SOD is located in mitochondria (2). Also, decomposition of H_2O_2 to water and oxygen is performed in the presence of catalase (19). Destruction of superoxide dismutase and catalase enhances free radical production and oxidative stress (17).

Lipid peroxidation in diabetes mellitus

Lipid peroxidation is a complex process in which a free radical initiates reaction and separates a hydrogen atom from polyunsaturated fatty acid and these reactions are continued (20). In this process, polyunsaturated fatty acid is the primary substance. This process is induced by radical and non-radical oxidants (16). Lipid structure and biological action of membrane are changed during lipid peroxidation process (21).

Susceptibility of Low-density lipoprotein (LDL) cholesterol to oxidation

Incubation of LDL cholesterol with glucose increases susceptibility of LDL to oxidation as measured by TBARS and conjugated diene formation (2,22,23). Diabetic patients were much more sensitive to LDL oxidation than normal subjects. LDL oxidation can be measured by conjugated diene formation after initiation of LDL oxidation by increment of copper (24).

Oxidative Phosphorylation

The mitochondrial respiratory chain is another source of non-enzymatic generation of reactive species. During the oxidative phosphorylation process, electrons are transferred from electron carriers NADH and FADH2, through four complexes in the inner mitochondrial membrane to oxygen, generating ATP in the process (14).

Antioxidants

Antioxidants are divided into enzymatic and non-enzymatic antioxidants groups.

Enzymatic antioxidants

- ***Superoxide dismutase (SOD)***

Superoxide dismutase eliminates free radicals and ROS. Therefore, it is called a primary enzyme. SOD is an enzyme that converts superoxide to H_2O_2 (7). There are several types of SOD in the cell. Mn-SOD is in mitochondria. It dismutates $O2^{-}$ which is produced by oxidative phosphorylation. Cu,Zn-SOD is mostly in cytosol and dismutates superoxide to H_2O_2 (2,13).

- ***Catalase***

Catalase is an enzyme that decomposes H_2O_2 to water. H_2O_2 in the presence of transition metals forms hydroxyl radical but it does not react with proteins and lipids. Catalase is mainly placed in peroxisomes or microperoxisomes (2,17). A study showed that catalase activity is decreased in liver and endothelial cell of diabetic rabbits. Also, the activity of this enzyme is decreased in NIDDM patients (13).

- ***Glutathione reductase***

Glutathione reductase regenerates glutathione Glutathione. It applies NADPH to reduce oxidized Glutathione. Decreased activity of Glutathione reductase will ruin the capability of cells to tackle with ROS. A study showed that the action of Glutathione reductase is reduced in erythrocytes of NIDDM patients (13).

- ***Glutathione peroxidase (GPX)***

Selenoproteins are proteins that have selenium group. A class of selenoproteins is GPX. This enzyme has multiple human isoforms. The commonplace isoform is GPX1. It is found in cytosol. GPX2 is found in the gastrointestinal tract and liver. GPX3 exists in plasma and milk. These enzymes act on H_2O_2 and fatty acid hydroperoxide. GPX4 exists in testis. It can reduce phospholipid hydroperoxides. Also it has a vital role in spermatogenesis (13,25,26).

Non-enzymatic antioxidants

These non-enzymatic antioxidants postpone or inhibit the oxidative proceeding. The increased lipid peroxidation enhances the need for lipid soluble antioxidants. Because free radicals are consumedly produced in diabetic patients, they need greater amounts of antioxidants. Antioxidants can postpone or bar free radical production and oxidative proceeding (15). In this section, the important non-enzymatic antioxidants are explained.

- ***Vitamin E***

A prominent lipophilic antioxidant is vitamin E. It is located in plasma and red blood cell and reduces lipid peroxidation. There is an inverse relation between the level of serum glucose and the level of vitamin E in plasma of NIDDM and IDDM patients. Also, there is an inverse correlation between vitamin E and complications as well as duration of diabetes. Consumption of vitamin E decreases lipid peroxidation induced by glucose in plasma of IDDM patients. Therefore, vitamin E is as an antioxidant, because it decreases lipid peroxidation (13).

- ***Vitamin C***

A major hydrophilic antioxidant is vitamin C that is found in plasma and cytosol of many cells. Vitamin C can counteract free radical and in conjugation with vitamin E winds up lipid peroxidation. The level of vitamin C is decreased in diabetic patients. Vitamin C levels are inversely associated with duration of diabetes (13). Also, another study shows that the levels of antioxidants such as α-lipoic acid can be effective in preserving vitamin C in plasma, liver and kidney (13).

- ***α- Lipoic acid (LA)***

α-Lipoic acid (LA) is a component derived from potato extracts. LA has a disulfide bond due to two sulfur atoms (at C6 and C8) and can be oxidized in higher oxidation situation (27). LA can pass the blood-brain barrier. It is reduced in cells to active dihydrolipoate, which potently regenerates other antioxidants such as vitamin C, vitamin E, and Glutathione through redox cycling (9). LA acts as an antioxidant and postpones oxidative stress in multiple tissues. It prevents lipid peroxidation and preserves energy status (9). A study showed that the oxidative stress and lipid peroxidation is decreased in the presence of LA in diabetes (9).

- ***Coenzyme Q10***

Transfer of electron in the mitochondrial oxidative respiratory chain performs in the presence of coenzyme Q10. It is a lipid-soluble compound. Coenzyme Q10 acts as an antioxidant and prevents lipid peroxidation. Free radical and oxidative stress can cause neurodegenerative diseases and coenzyme Q10 can exert beneficial therapeutic effects (28).

- ***L-carnitine***

Carnitine (C7H15NO3) is another antioxidant which is biosynthesized from lysine and methionine. Carnitine synthesis occurs in liver and kidney. Carnitine transports fatty acids from cytosol to mitochondria for β-oxidation. It suppresses lipid peroxidation and oxidative stress induced in myocardial cell (29).

- ***Albumin***

Albumin is an antioxidant in the plasma and reduces oxidative stress. It destroys free radicals. Among the proteins, albumin is an abundant circulating plasma protein (30).

- ***Uric acid***

Uric acid is a compound with $C_5H_4N_4O_3$ formula. During the breakdown of purine nucleotides, uric acid is produced. One of the most important antioxidants in blood plasma is uric acid. It protects erythrocyte against

oxidative stress; so, it decreases the formation of oxo-heme (31).

- ***Glutathione***

A tripeptide which is formed from cysteine, glutamate and glycine is glutathione. It reduces radicals and reactive oxygen compounds. It acts such as vitamin C and E (18).

- ***Carotenoids***

Carotenoids are components that exist in chloroplasts and chromoplasts of plants. They are responsible for the colors of various fruits and vegetables (14,32). Carotenoids protect cells from cancer. Associations of carotenoids with other antioxidants can reduce oxidative stress. Furthermore, one study showed an inverse relationship between the levels of blood carotenoids and cancer (14,32,33). Also, other non-enzymatic antioxidants include trace elements like copper, zinc, selenium and cofactors like folic acid, and vitamins B1, B2, B6 and B12.

Biomarker of lipid peroxidation

Malondialdehyde (MDA)

A byproduct of lipid oxidation is malondialdehyde (MDA). It is a byproduct of cyclooxygenase activity. Moreover, it can be formed non-enzymatically. Free amine groups of protein, lipid, and DNA can react with MDA by schiff base. In addition, aggregation of MDA alters membrane organization by increasing phosphatidylserine externalization. Aggregation of MDA and its adducts are correlated with many diseases (13).

4-Hydroxy-nonenal (4-HNE)

Another lipid oxidation byproduct which can be formed non-enzymatically is 4-Hydroxy-nonenal (4-HNE). Oxidation of n-6 polyunsaturated fatty acids (mainly linoleic acid and arachidonic acid) leads to the formation of 4-HNE. 4-HNE is more reactive with proteins and can react with histidine, lysine and cystein residues of protein, leading to formation of stable Michael adducts with hemiacetal structure (34).

Lipid hydroperoxides/Eicosanoids

Middle lipid peroxidation byproducts are lipid hydroproxides. These components are formed under action of lipoxygenases. These forms can be changed by lipoxygenases and glutathione peroxidase to hydroxy fatty acids, leukotrienes and lipoxins (13).

Conclusion

Diabetes mellitus is a group of metabolic diseases caused by a combination of insulin resistance and impaired insulin secretion by pancreatic β cells. There has been currently great interest in the potential contribution of increased oxidative stress to the development of diabetes complications.

Several mechanisms seem to be involved in the pathogenesis of the oxidative stress. Since oxidative stress may be a contributing factor in diabetes complications, antioxidants supplementation could be of interest, by preventing or delaying the development of diabetic complications.

Reference

1. Sheikhpour R, Jalali B, Afkhami Ardekani M. The effect of zinc on lipid oxidizability in diabetic patients in Yazd city. Feyz. Medical Science of Kashan University.2009;13(2):103-10. (in Persian)
2. Sheikhpour R. Incretin, dipeptid peptidase 4 and inhibitors and diabetes. Lambert. 2012;1-13
3. Sheikhpour R. Evaluation of lipid profile in diabetic patient. Clinical Biochemistry. 2011;44(13):160
4. Sheikhpour R, Yaghmaei P. A Survey on Herbal Medicines for Hypoglycemia in Diabetic Patients. Iranian Journal of Diabetes and Obesity. 2012;4(1):40-50
5. Kangralkar VA, Patil SD, Bandivadekar RM. Oxidative stress and diabetes: a review. Int J Pharm Appl 2010;1(1):38-45.
6. Tripathi T. Rasshed Z. The oxidative by product, hydroxyl radical, damaged immunoglubolin-G in patients with non insulin dependent diabetes mellitus. Bratisl Lek Lisy. 2010;111(9):477-84
7. Moussa S. Oxidative stress in diabetes mellitus. Romanian J biophys. 2008;18(3):225-36

8. Uttara B, Singh AV, Zamboni P, Mahajan RT. Oxidative stress and neurodegenerative diseases: a review of upstream and downstream antioxidant therapeutic options. Current neuropharmacology 2009;7(1):65-74.
9. Andrea M. Vincent T, James W. Oxidative Stress in the pathogenesis of Diabetic Neuropathy. Endocrine Reviews.2004;25(4):612-28
10. Muller FL, Lustgarten MS, Jang Y, Richardson A, Van Remmen H. Trends in oxidative aging theories. Free Radical Biology and Medicine 2007;43(4):477-503.
11. Pieper GM, Langenstroer P, Siebeneich W. Diabetic-induced endothelial dysfunction in rat aorta: role of hydroxyl radicals. Cardiovascular research 1997;34(1):145-56.
12. Marshall MV, Cancro LP, Fischman SL. Hydrogen peroxide: a review of its use in dentistry. Journal of periodontology 1995;66(9):786-96.
13. Dana M. The Role of Oxidative Stress in Diabetic Complications. Cell Biochemistry and Biophysics. 2005;43:289-330
14. 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.
15. Ramakrishna V, Jailkhani R. Evaluation of oxidative stress in Insulin Dependent Diabetes Mellitus (IDDM) patients. Diagnostic Pathology. 2007;2(22):1-6
16. Ahmed RG. The physiological and biochemical effects of diabetes on the balance between oxidative stress and antioxidant defense system. Medical Journal of Islamic World Academy of Sciences .2005;15:31-42
17. -Sheikhpour R, Jalali B, Yaghmaei P, Afkhami-Ardekani M. Comparison of two supplementary zinc doses on lipid peroxidation in diabetic patients. Iranian Journal of oF diabetes and obesity. 2010;2(2):17-24
18. Chad Kerksick1, Darryn Willoughby. The Antioxidant Role of Glutathione and N-Acetyl-Cysteine Supplements and exercise-induced oxidative stress. Journal of the International Society of Sports Nutrition. 2005;2(2):38-44
19. Lee HY, Eum WS, Kim DW, Lee BR, Yoon CS, Jang SH, et al. Isolation and identification of an antioxidant enzyme catalase stimulatory compound from Garnoderma lucidum. Journal of Biochemistry and Molecular Biology 2003;36(5):450-5.
20. Palmer B, Sblendrio V. Oxidative stress tests: overview on reliability and use European Review for Medical and Pharmacological Sciences 2007;11:309-342
21. Marjani A. Lipid peroxidation alterations in type 2 diabetic patients. Pakistan Journal of Medical Science.2010;13(15):723-30
22. Yoshida H, Kisugi R. Mechanisms of LDL oxidation. Clinica Chimica Acta 2010;411(23):1875-82.
23. Safari M.R. Effects of Lycopene on the Susceptibility of Low-Density Lipoproteins to Oxidative Modification. Iranian Journal of Pharmaceutical Research. 2007;6(3):173-7
24. Atalay M, Laaksonen D.E. Diabetes, Oxidative stress and physical exercise. Journal of Sports Science and Medicine 2002;1,1-14
25. Schneider M, Fo¨rster H, Boersma A, Seiler A, Wehnes H, Sinowatz F, et al. Mitochondrial glutathione peroxidase 4 disruption causes male infertility. FASEB. 2009;23:3233-44
26. Conrad M, Moreno S.G, Sinowatz F, Ursini F. The Nuclear Form of Phospholipid Hydroperoxide Glutathione Peroxidase Is a Protein Thiol Peroxidase Contributing to Sperm Chromatin Stability. Molecular and cellular biology. 2005;7637-44
27. Evans JL, Goldfine ID. α-Lipoic acid: a multifunctional antioxidant that improves insulin sensitivity in patients with type 2 diabetes. Diabetes technology & therapeutics 2000;2(3):401-13.
28. Matthews RT, Yang L, Browne S, Baik M ,Beal MF. Coenzyme Q10 administration increases brain mitochondrial concentrations and exerts neuroprotective effects. Proceedings of the National Academy of Sciences 1998;95(15):8892-7.
29. Dayanand CD, Krishnamurthy N, Ashakiran S, Shashidhar KN. Carnitine: A novel health factor-An overview. Int J Pharm Biomed Res 2011;2(2):79-89
30. Roche M, Rondeau P, Singh NR, Tarnus E, Bourdon E. The antioxidant properties of serum albumin. FEBS letters 2008;582(13):1783-7.
31. Ames BN, Cathcart R, Schwiers E, Hochstein P. Uric acid provides an antioxidant defense in humans against oxidant-and radical-caused aging and cancer: a hypothesis. Proceedings of the National Academy of Sciences 1981;78(11):6858-62
32. Paiva SA, Russell RM. β-carotene and other carotenoids as antioxidants. Journal of the American College of Nutrition 1999;18(5):426-33.
33. Gramza-Michałowska A, Stachowiak B. The Antioxidant potential of carotenoid extract from phaffia rhodozyma. Acta Sci. Pol., Technol. Aliment 2010;9(2):171-88
34. .Negre-Salvayre A, Coatrieux C, Ingueneau C, Salvayre R. Advanced lipid peroxidation end products in oxidative damage to proteins. Potential role in diseases and therapeutic prospects for the inhibitors. Br J Pharmacol. 2008;153,6-20.