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Role of antioxidant in oxidative stress and diabetes mellitus

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Abstract

Diabetes mellitus is a group of metabolic disorder characterized by abnormally elevated levels of blood glucose due to complete or relative insufficiency of insulin secretion as well as disturbances in carbohydrate, fat and protein metabolism. Increasing evidence revealed that oxidative stress plays a main role in the pathogenesis of diabetes mellitus. Free radicals are formed excessively in diabetes by glucose oxidation and non-enzymatic protein glycation. Abnormally high levels of free radicals and the simultaneous decline of antioxidant defense mechanisms can lead to damage of cellular organelles and enzymes increased lipid peroxidation, and development of insulin resistance. These consequences of oxidative stress can promote the development of complications of diabetes mellitus. Antioxidants obtained from nature helps in neutralization of reactive oxygen species and significantly reduce the probability of progression of diabetic complications. A variety of nutritionally important vitamins, supplements and some constituents of natural food sources, including cappers, broccoli, tomatoes, berries, grapes, spinach, carrots, nuts, etc. naturally reduce the injury caused by oxidative stress in diabetes mellitus. The review describes the oxidative stress, antioxidants and their role in diabetes mellitus.

Keywords: Diabetes Mellitus, Antioxidants, Food sources, Free Radicals

1. Introduction

Diabetes mellitus characterized by elevated blood glucose level is basically a metabolic disorder in which the beta cells of the pancreas produce insufficient insulin [1]. Diabetes mellitus problems vary from one individual to another, but are being determined by on health and patient diet [2]. Globally, about 190 million population having different age groups are affected by diabetes mellitus and is one of the most prominent cause of impairment and death in world [3]. The metabolic theory of diabetes mellitus proposes that complications such as endothelial damage and cellular damage belongs to long term hyperglycemia, while genetic theory propose that diabetes complications are genetically predetermined. In 1983-1993 practices are carried for diabetes control and complications which determine that maintained blood glucose can be very effective [4]. Diabetes mellitus symptoms include polyphagia (increased hunger), polydipsia (increased thirst), polyuria (increase urination). Due to hyperglycemia malfunctioning and dysfunction of various organs such as heart (mainly myocardial infraction), kidneys (diabetic nephropathy), nerves (diabetic neuropathy), eyes (diabetic retinopathy) usually occur [5, 6].

2. Diabetes Mellitus and Oxidative Stress

Various mitochondrial, enzymatic and non-enzymatic pathways mainly comprise oxidative stress in diabetes mellitus. The imbalance in an antioxidant - prooxidant is due to auto oxidation of glucose level in diabetes usually leads to high energy particle generation. In cells, there usually exists a balance between antioxidants elimination and free radical development. The gradual increase in free radicals and diminishing antioxidant defense mechanism potential is also the fact linking diabetes mellitus with oxidative stress [7].

In the oxidative stress initiated by non-enzymatic sources, free radicals/reactive oxygen species generation is directly increased by hyperglycemic condition. Auto-oxidation of glucose generates hydroxyl radicals. In the non-enzymatic path glucose reacts with proteins which causes improvement in advanced glycation end products and changes protein and cellular/immune function, advanced glycation products bind with their receptor and causes improved cell signaling pathways and reactive oxygen species production during the biological

process at multiple steps. Xanthine oxidase, Nitric oxide synthetases and NAD (P) H are enzymes associated with membrane and is importantly played role in the enzyme source of reactive oxygen species in diabetes mellitus. In polyol (sorbitol) pathway the increase glucose metabolism leads to improved production of superoxide radicals.

In diabetic patients there occurs association between lipid peroxidation and impaired glucose level. In diabetic patients elevate level of some pro-oxidants a protein such as ferritin containing 20% of iron usually found in homocysteine and intestine are the probable sources of oxidative stress. By the peroxidation of arachidonic acid the prostaglandin like compounds F-2 isoprostanes are formed mediated by free radicals. In type 2 diabetic patients levels of F2-isoprostane have been augmented in plasma and urine^[8, 9].

The mitochondrial respiratory chain also acts as a resource of reactive species through the non enzymatic mechanism. The process involves the transfer of electrons from electron carriers NADH to FADH₂, during oxidative phosphorylation through complex formation in the inner mitochondrial membrane. Research studies also devised that in diabetic patients during hyperglycemic condition superoxide is the 1st step of oxidative stress. Normally superoxide molecules are removed immediately by endogenous mechanism. In hyperglycemia condition the endothelial cell triggers increased amount of reactive oxygen species usually superoxide which tends to the development of diabetes disorders^[10].

3. Antioxidants

Antioxidants are chemical or biological agents able to neutralize the potentially damaging action of free radicals such as unstable molecules as peroxy radical, hydroxyl radical, and singlet oxygen and peroxy nitrate radicals. The oxidation process of other macromolecules is avoided or slows down by antioxidants. The destructive effect of free radicals in cells is minimized or terminated by antioxidants. The tissues or cell damage by toxic metabolites is minimized by antioxidants. In humans everyday activities oxidation plays important role as there is antioxidant defense mechanism present such as lycopene, beta carotene, glutathione, flavonoid, selenium natural vitamin such as vitamin E, vitamin A antioxidant enzymes such as catalase peroxidase, glutathione-S-transferase finish the accessibility of peroxidase as heme protein, iron, copper ions. In recent studies there is strong relation found between oxidative stress and reactive oxygen species for human disorders/diseases. So antioxidants and free radicals studies are very important in today's research for understanding the relationships of diseases such as cancer, neurodegenerative diseases, diabetes mellitus and cardiac arrest^[11].

4. Antioxidants Classification

Antioxidants may be Synthetic or Natural.

Synthetic Antioxidants;

The phenolic group compounds are included in synthetic antioxidants and these finish the oxidative stress, free radicals and various biological reactions associated with the free radical negative effect. e.g.; Nordihydroguaiaretic acid (NDGA), esters of gallic acid (propyl gallate), tertiary butyl hydroquinone (TBHQ), butylated hydroxytoluene (BHT) and butylated hydroxytoluene (BHT).

5. Natural Antioxidants

These act on lipid free radicals and break the chain. e.g.: Mineral antioxidants, Vitamins, Phytochemicals^[12].

6. Origin and Sources of Antioxidants

In colored fruits Beta carotene is the most biologically active antioxidants like squash, potatoes, apricots, pumpkin, mangoes and orange. Natural food, leafy vegetables and fruit sources are the richest source of antioxidants. Besides this lemon, amla, ashwagandha also contains antioxidants. Beta carotene is also found in green leafy vegetables such as spinach, kale, and coloured greens. For healthy eyes Lutein is best green leafy vegetable.

In most of developing countries wheat and rice are the main dietary source of selenium having major antioxidant enzymes. Carrots, milk, sweet potatoes, mozzarella and egg yolks consist retinol, 3 hydroxyretinol and dihydroretinol. Poultry, beef, cereals and fish contains vitamin C.

Flavonoids, diterpenes, cinnamic acid, phenylpropanoids contains phytoconstituents with antioxidants. In wheat germ oil, corn oil, mangoes, almonds, nuts contains vitamin E. Higher plants contain natural antioxidants in leaves, pods, roots, seeds, pollen, wood and bark. Treatment of severe diseases with oxidative stress is possibly cured by plants antioxidants including diabetic mellitus^[13-16].

7. Plasma Antioxidant Potential

In humans Plasma contains antioxidants and use as a marker to measure oxidative stress. There are many compounds present in plasma, which protect cell and cellular biomolecules from oxidative stress. So the combined action of all molecules in plasma represents the antioxidant capacity of plasma^[29, 30]. The plasma glycemic level will be low in diabetic patients than healthy ones because the antioxidants are present in low amount in diabetic patient plasma^[31, 32].

The increase in oxidative stress while the decrease of antioxidant capacity is correlated with complications of diabetes mellitus as insulin resistance and DNA damage^[31]. Due to low antioxidant defence in plasma the problems like blindness, nerve damage, cardiovascular disease and nephropathy occurs^[34].

8. Role of antioxidants in diabetes mellitus

Antioxidants could be obtained from different dietary sources and is used for maintaining free radicals stable and not to develop oxidative stress thus improving our defence mechanism.

In nature, there are various non-enzymatic and enzymatic mechanisms for removal of reactive oxygen species. In non-enzymatic antioxidant system includes ascorbic acid, retinol, glutathione, carotenoids, tocopherols, and trace elements like selenium, copper, zinc, coenzyme Q10, uric acid, factors of folic acid, riboflavin and thiamine. Vitamin E is the fat soluble responsible for prevention of lipid peroxidation. Glutathione acts as a scavenger as well as a substrate for glutathione peroxidase. There are eight different forms in vitamin E exist in the fat soluble form in which A tocopherol is found in sunflower and wheat germ oil and the safflower oil is most active in biological form in humans. Lipid peroxidation is prevented through fat soluble vitamin E. Researchers recently suggested that nitric oxide production in epithelial cells is increased through vitamin C.

In chronic cardiac complications of diabetes patient the important enzymes goes into smooth muscles. So the major organs such heart, kidneys are directly affected by diabetes. In the enzymatic antioxidant defence mechanism SOD and Glutathione reductase is important. Glutathione reductase regenerates glutathione, which can be used as hydrogen donor

by glutathione peroxidase through elimination of hydrogen peroxide. SOD converts superoxide to hydrogen peroxide [17-19].

There are various mechanisms in which antioxidant differs in their action mechanism. These are free radicals scavenging mechanism, inhibition of enzymes that humiliate free radical reactions, degradation of proteins, including transferring that can bind metals which eventually stimulate free radicals.

9. Human health and oxidative stress

Oxidative stress is a pathological condition triggered by the damaging action on cells and tissues of the body. Oxidative is the direct consequence of an increased generation of free radicals and or reduced physiological activity of antioxidant defenses against free radicals and reactive nitrogen species. Non radical species are hydrochlorous acid and hydrogen peroxide molecules. Free radical species are superoxide molecules, hydroperoxyl molecules, hydroxyl molecules. Reactive nitrogen species are having free radicals are nitrogen dioxide and nitric oxide while non-radical are peroxy nitrates and peroxy nitrites. By the physical, physiological and chemical factors the reactive radicals, nitric oxide peroxy nitrite and superoxide molecules cause tissue damage. There are a variety of different defense mechanisms by which human body works against oxidative stress induced by free radicals as tissue repair, anticipatory mechanism, physical resistance and antioxidant defense. Reactive oxygen species of various free radicals are involved in cardiovascular diseases, renal disorders, autoimmune disorders, neurodegenerative disorders, peptic ulcer, cataract, lung cancer [20, 21].

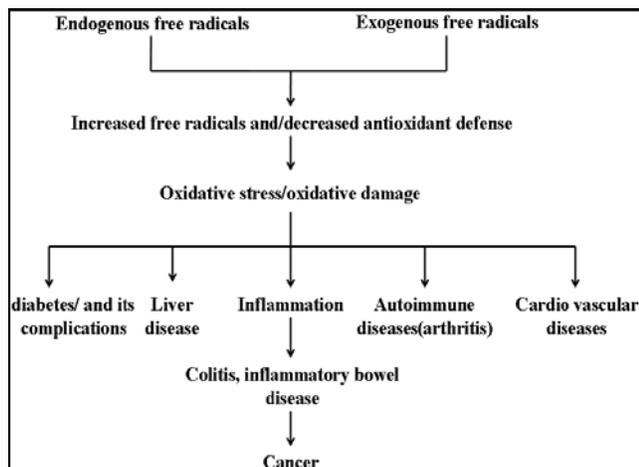


Fig 1.

10. Newer therapeutic/preventive approaches through natural antioxidants

Diabetes mellitus management with no side effect is still a challenge in 21 century for doctors and researchers. In the treatment of diabetes mellitus herbal drugs is of great interest due to low cost, efficiency and less side effects and so a variety of plants are being used as an herbal treatment. In the WHO report about 80% of the global population are dependent on traditional medicines because of poverty. In herbal treatment phytoconstituents derived from plants are important and includes glycosides, alkaloids, glycopeptides, steroids, hypoglycans, guanidine, carbohydrates, gums, various amino acids and peptidoglycans. The phytoconstituents greatly influence metabolic activities which directly affect glucose level in the body.

For the management of some diseases such as Alzheimer disease, stroke, cardiac arrest, cancer, atherosclerosis and Parkinson disease antioxidant formulation is of great study and effort. Diabetic complications can be reduced by dietary antioxidants and is one of promising therapeutic approach. For the treatment of some diseases such as stroke, atherosclerosis, cancer, neurodegenerative diseases, diabetes mellitus and human ailments [22-24].

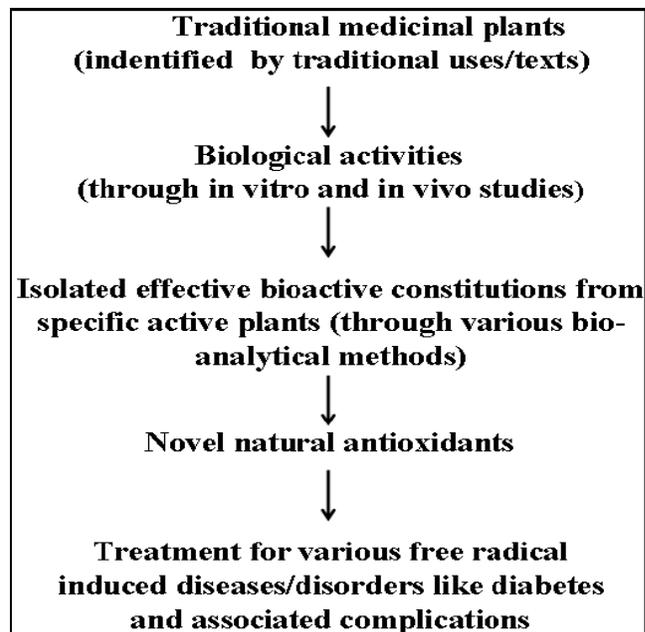


Fig 2.

11. Conclusion

In recent studies, it is stated that if a traditional system of medicines like Siddha and Ayurveda is used with modern science medicines will be very effective. Diabetic complications associated with oxidative stress can be minimized to some extent by natural antioxidants. But there is no perfect mechanism developed till to date in which the diabetic complications are known exactly. In various there are various clinical, epidemiological and experimental antioxidants are developed to cure of diabetes and other diseases.

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