A REVIEW ON ANTIOXIDANTS AND OXIDATIVE STRESS IN TYPE-2 DIABETES MELLITUS

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ABSTRACT

Strikingly the developments in both therapeutic and nutritional circuits have punctuated with some success and some spectacular failures in treating Type-2 Diabetes mellitus (T2-DM). It is advocated that antioxidants should be given only if pre-existing deficiency is present. Selection of antioxidant is another important aspect. Type-2 Diabetes mellitus (T2-DM) is measured to be one of the most frequent chronic diseases global. There is a increasing scientific and public awareness in connecting oxidative stress with a variety of pathological conditions including Type-2 Diabetes mellitus (T-2DM), cardio vascular diseases (CVD), coronary artery diseases with Type-2 Diabetes mellitus (CADT2-DM) as well as other human diseases. Pre-existing experimental and clinical studies report that oxidative stress plays a major role in the pathogenesis and development of complications in T2-DM. Conversely, the exact mechanism by which oxidative stress could contribute to and accelerate the development of complications in T2-DM is only to some extent known and remains to be clarified. On the one hand, hyperglycemia induces free radicals; on the other hand, it impairs the endogenous antioxidant defense system in patients with diabetes. Endogenous antioxidant defense mechanisms include both enzymatic and non-enzymatic pathways. Common antioxidants include the vitamins A, C, and E, glutathione (GSH), and the enzymes superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and glutathione reductase (GRx). This review describes role of oxidative stress in micro and macro vascular complications of T2-DM. Lastly but most importantly the impact of OS is not obligatory but facultative. As such only those diabetic patients will be benefited by antioxidant therapies that have impelling punch of pro-oxidants.

KEYWORDS: Antioxidant enzymes, Dietary antioxidant, Oxidative stress, Diabetic mellitus, Free radicals, Lipid peroxidation

INTRODUCTION

"Just few years ago, antioxidant pills were rising stars in the fight against heart disease but now they appear heading for the dustbin of history" (Health & Nutrition, October 2001, P-63). Only last month in Nature Ulrich Theopold has appropriately said "Few concepts have been embraced by popular science as enthusiastically as the idea that the reactive oxygen species (ROS) are harmful and their levels should be controlled by including antioxidants in the diet or as supplements". (1) He is therefore right to point out that this concept accepted so hurriedly without proper scientific verification was expected to change. It is therefore not surprising that it has gone through radical changes in last two decades. Initially antioxidants were projected as miracle species with an inherent quality just short of elixirs. Even now some scanty reports favour their liberal use. In second phase, with many disappointing clinical outcomes, the wisdom of calling them as miracle molecules was questioned. In the recent phase, growing clinical and experimental evidence suggests that the excess intake of antioxidants may not only harmful effects but may cause increased mortality as well. (2) Free radicals are continuously produced during aerobic metabolism. These unstable species may cause oxidative damage to DNA, carbohydrates, proteins and lipids that are normally counteracted by protective antioxidants. These biochemical defences have been named as ANTIOXIDANTS. Antioxidants get their name because they combat oxidation. They are substances that protect other chemicals of the body from damaging oxidation reaction by reacting with free radicals and other reactive oxygen species within the body, hence hindering the process of oxidation. During this reaction the antioxidant sacrifices itself by becoming oxidized. However, antioxidant supply is not intimated as one antioxidant molecule can only react with a single free radical. Therefore, there is a constant need to replenish antioxidant resources, whether endogenously or through supplementation. (3)

WHAT ARE ANTIOXIDANTS?

1. Antioxidants are substances that prevent neutralize, or kill free radical.
2. Antioxidants can also be defined as any substance that delays or inhibits oxidative damage to a target molecule.

3. More specifically antioxidants are enzymes, vitamins, minerals, coenzymes and herbs that help our body against fight and prevent damage from toxins and free radicals.

MODE OF ACTION OF ANTIOXIDANTS

Broadly the possible mechanisms by which antioxidants work are:

1. Reducing the concentration of reactive oxygen species e.g. glutathione.
2. Scavenging initiating radicals e.g. superoxide dismutase which acts in aqueous phase to trap superoxide free radicals.
3. Facilitating the repair of damage caused by free radicals.
4. Providing (e.g. as a cofactor or by acting to maintain as suitable redox status) a favorable environment for the effective functioning of other antioxidants. (4)

TYPES OF ANTIOXIDANTS

A. **Antioxidant enzymes**

Main antioxidant enzymes (cellular origin are as follows)

(a) Glutathione peroxidase (Gpx)
(b) Glutathione reductase (GR)
(c) Glutathione-S-transferase (GST)
(d) Glucose-6-phosphate dehydragenase (G6PD)
(e) Superoxide dismutase (SOD)
(f) Catalase (CAT)

B. **Dietary antioxidants**

i. Nutrient antioxidants – Vit. A, E, C and betacarotine.

ii. Other dietary oxidants – Caroteinoids, Flavonoids

C. **Synthetic Antioxidants**

(a) 3-Hydroxy pyridine (3hp)
(b) 1,4 dihydroxy pyridine (1,4-dhp)
(c) Ambunol (A-1)
(d) Silane (Si-1)

D. **Antioxidant Compounds**

(a) Glutathione (GSH)
(b) Uric Acid
(c) Melatonin

WHAT IS OXIDATIVE STRESS?

Oxidative stress (OS) is general term used to describe a state of damage caused by reactive oxygen species or oxygen free radicals in biological system. Oxidative stress is an imbalance between the generation of reactive oxygen species (ROS) and antioxidant defence capacity of the body. (5)

OXIDATIVE STRESS AND MACRO VASCULAR COMPLICATIONS OF DIABETES

Depletion of cellular antioxidant defence mechanism and the generation of oxygen free radicals by advanced glycation end products plays a major role in the pathogenesis of diabetic vascular complication. Oxygen derived free radicals inactivate endothelium derived releasing factors and selectively attenuate endothelium dependent relaxation. Endothelium dependent relaxation has been found to be impaired in diabetic hypertensive subjects moreover the frequency of endothelial cell death and associated endothelial permeability is significantly increased in the aorta of spontaneously hypertensive rats. (6-18)

Cardiovascular disease is the major cause of mortality in patients with diabetes. 8 Oxidation of LDL cholesterol is a key step in the formation of atheroma and is thought to be a major factor in the development of cardiovascular disease. (19)

OXIDATIVE STRESS AND MICROVASCULAR COMPLICATIONS OF DIABETES

The equilibrium between peroxidation and antioxidants disturb the metabolic status of body and leads to the development of microvascular (retinopathy, nephropathy, neuropathy) complications of diabetes mellitus. (20-22)

The retina experiences increased oxidative stress and antioxidant inhibits these retinal abnormalities and the development of retinopathy. Possible source of oxidative stress in diabetes include increase generation of ROS by auto-oxidation of glucose, and impaired activities of antioxidant enzymes. Superoxides and nitric oxide can react and form peroxynitrite, a highly reactive intermediate, which can increase DNA damage, deplete intracellular reduced glutathione (GSH) levels and initiate lipid peroxidation. (23)

BIOMARKER OF OXIDATIVE STRESS IN DIABETES LIPID PEROXIDATION

Marker of lipid peroxidation is used to evaluate oxidative stress. The lipids within the membrane of cells from higher organism contain large number of polyunsaturated fatty acids side chains. Such fatty acids are prone to undergo a process known as **"Lipid peroxidation"**, which involves the generation of carbon radicals followed by production of peroxide radicals.

MECHANISM OF PEROXIDATION OF POLYUNSATURATED FATTY ACIDS

Oxidizability of plasma as measured by lipid hydroperoxides was greater in DM group, although baseline levels were similar in subject with normal glucose tolerance, impaired glucose tolerance and type-II DM. Furthermore, plasma TBARS level was significantly increased in type-II DM with the duration of disease and development of complications.

Liposomes constructed from red cell membranes of DM patients were highly sensitive to superoxide induced lipid peroxidation. (24, 25)

CATALASE (CAT)

Catalase was first isolated and obtained in cystaline form from ox-liver by Summer and Dounce, 1937 and later from blood and other sources. It is large enzyme containing harm-bound iron at its active sites. The enzyme contains four ferripro to porphyrin groups per molecules (Mol. wt. 240000) which corresponds to a protohaem content of 1.1% and an iron content of 0.09% catalase is present in all body organs being especially, concentrated in liver and erythrocytes. The brain, heart and skeletal muscle contains only low amounts. In most mammalian tissues catalase is located in small organelles called peroxisomes.

Mechanism of Action

Catalase removes H_2O_2 by breaking it down directly in to O_2. Affinity of catalase for H_2O_2 is low thus needs high H_2O_2 concentration to work fast.

Catalase, located in peroxysomes, decomposes hydrogen peroxide to water and oxygen Winter bourn. (26-28)

NCV - Nerve conduction velocity,

VSMC - Vascular smooth muscle cell.

SUPEROXIDE DISMUTASE (SOD)

It was the discovery of the superoxide dismutase (SOD) enzymes, first described in 1968 by McCord and Fridovich in the USA that converted the free radical theory of the oxygen toxicity; it's a superoxide theory of O_2 toxicity. SOD is an endogenously produced intracellular enzyme present essentially in the every cell of the body. Cellular SOD is actually represented by a group of metaloenzyms with various prosthetic groups. The prevalent enzyme is Cupro-zinc (CuZn) SOD, which is stable dimeric protein (32,000 D) SOD appears in three forms:

1. Cu-Zn SOD in the cytoplasm with two subunits.
2. Mn-SOD in the mitochondria.
3. A third extra cellular SOD has recently been described contains copper (Cu-SOD).

MECHANISM OF ACTION

Most prevalent of all forms is Cu-Zn SOD. In this 'Cu' is the catalytic metal while 'Zn' helps to maintain the enzyme structure.

The metals bound to SOD catalyze the reaction of two superoxide [O_2^-] molecules with H^+ ions to form H_2O_2 and O_2. This reaction occurs slowly at pH 7.4.

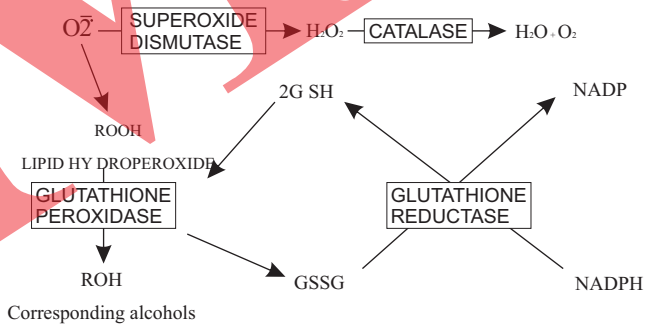
but SOD accelerate it by 10,000 times, catalase and

$$2O\dot{2}+2H^{+} \xrightarrow{SOD} H2O2+O2$$

selenium dependent glutathione peroxidase are responsible for reducing H_2O_2 to H_2O.

Excessive superoxide inhibits glutathione peroxidase and catalase to modulate the equation from H_2O_2 to H_2O. Likewise, increased H_2O_2 slowly in activates Cu-Zn-SOD. Meanwhile, catalase and glutathione peroxidase, by reducing H_2O_2, conserve SOD, and SOD by reducing superoxide conserves catalases and glutathione peroxidase. Through this feedback system steady low levels of SOD, gluthione peroxidase, and catalase as well as superoxide and H_2O_2 are maintained, which keep the entire system in a fully functional state. SOD also exhibits antioxidant activity by reducing O_2^- that would otherwise lead to the reduction of Fe^{3+} to Fe^{2+} and there by promote OH^- (hydroxyl) ions formation.

When catalase activity is in sufficient to metabolize the H_2O_2 produced SOD will increase the tissue oxidant activities. Hence, it was found that the antioxidant enzymes function as tightly balanced system, any disruption of this system would lead to promotion of oxidation. (29-35)



CONCLUSION

Thus the results of clinical trials on T-2DMpatients and for that matter in other diseases such as CVD cancer, aging etc can broadly be divided into four categories: I) beneficial effects II) no effects III) harmful effects and IV) increased mortality. A long drawn study of 23 yr follow up in a cohort in Finland consisting of 2285 men and 2019 women for 4 tocopherols, 4 tocotrienols, 6 carotenoids and ascorbic acid showed that dietary intake of these of antioxidants reduced the risk of T-2DM. Ascorbic acid (500 mg) slightly but non-significantly decreased the risk whereas beta-carotene had no effect. In their final conclusion, they said that neither of these nutrients had any positive or negative effect on the risk of the development of T-2DM. Therefore, despite all the loaded evidence for the involvement of reactive species in the diabetes, the debate continues on three

points: a) is it selective in patients or present in all patients but not detectable by available methods, b) is it facultative, that is, it is capable of causing disease but does not necessarily do so in all patients and c) is it obligatory, that is, it universally participates in the genesis of diabetes. Antioxidants have so for not received putative pat in the medicine though FR involvement has lately been given recognition. We would only like to post a caution "Those who fail to read the history are destined to suffer from repetition of the mistakes". We must therefore tread carefully with accuracy in future.

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