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Diabetes, Oxidative Stress, Antioxidants and Saliva: A Review

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1. Introduction

Diabetes mellitus is a devastating disease throughout the world. It has been estimated that the number of peoples affected with diabetes in the world will increase to 300 million by 2025 (1). Diabetes is associated with several mechanisms, one of which is oxidative stress. Increased oxidative stress is a widely accepted participant in the development and progression of diabetes and its complications (2,3). Oxidative stress is a general term used to describe the imbalance between the production and manifestation of reactive oxygen species and a biological system's ability to ready detoxify the reactive intermediates or to repair the resulting damage (4). Oxidative stress occurs when free radical production exceeds the body's ability to neutralize them. The imbalance may be due to either: decrease production of antioxidants; or excessive production of free radicals. In diabetes, free radicals are formed disproportionately by glucose oxidation, non-enzymatic glycation of proteins and the subsequent oxidative degradation of glycated proteins (5). 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 (6). These consequences of oxidative stress can promote the development of complications of diabetes mellitus.

2. Sources of oxidative stress in diabetes

There are multiple sources of oxidative stress in diabetes including non enzymatic, enzymatic and mitochondrial pathway.

Non enzymatic sources of oxidative stress originate from the oxidative biochemistry of glucose. Hyperglycemia can directly cause increased Reactive Oxygen Species (ROS) generation. Glucose can undergo autooxidation and generate hydroxyl *OH^- radicals (7). In addition, glucose reacts with proteins in a non enzymatic manner leading to the formation of advanced glycation end products (AGEs). ROS is generated at multiple steps during this process. In hyperglycemia, there is enhanced metabolism of glucose through the polyol (sorbitol) pathway, which also results in enhanced production of superoxides (*O2-) .

Enzymatic sources of augmented generation of reactive species in diabetes include Nitrous Oxide Species (NOS), NAD(P)H oxidase and xanthine oxidase (8-10). The mitochondrial

respiratory chain is another source of non enzymatic generation of reactive species. Hyperglycemia-induced generation of $*O_2^-$ at the mitochondrial level is the initial trigger of vicious cycle of oxidative stress in diabetes (11,12).

3. Saliva as diagnostic fluid

Saliva in humans is a mouth fluid possessing several functions involved in oral health and homeostasis, with an active protective role in maintaining oral health. It plays a role in the preliminary digestion of food, fascilitates taste perception, maintains teeth enamel mineralization, buffers the acid components of food, and antimicrobial functions. The assay of saliva is an increasing area of research with implications of basic and clinical purposes. Recently, the use of saliva has provided a substantial addition to the diagnostic armamentarium as an investigative tool for disease processes and disorders. In addition to its oral indications, the analysis of saliva provides important information about the functioning of various organs within the body. Saliva analyses have been used mainly in dentistry and for studies in oral disease to help assess the risk of caries, by measuring buffering capacity and bacterial contents (13). Oral fluid is mainly utilized for research and diagnostic purposes concerning systemic diseases such as diabetes.

The determination of the oxidative stress and antioxidants require sometimes invasive techniques such as venepuncture. Whole saliva is an important physiologic fluid that contains a highly complex mixture of substances. Variable amounts of blood, serum markers that accurately reflect the redox status of the body can be determined in saliva and may have great clinical interest. The assay of salivary oxidative stress parameters has brought substantial insight into the pathogenesis and evolution of many systemic diseases including diabetes.

4. Mechanisms for increased oxidative stress in diabetes

1. Advanced glycation end products (AGEs):

AGEs are products of glycation and oxidation (glycol-oxidation), which are increased with age, and at accelerated rate in diabetes (14,15). The formation of AGEs is an important biochemical abnormality that accompanies diabetes mellitus. AGEs initiate oxidative reactions that promote the formation of oxidized LDL. Interaction of AGEs with endothelial cells as well as other cells accumulating within the atherosclerotic plaque, such as mononuclear phagocytes and smooth muscle cells provides a mechanism to augment vascular dysfunction (16)

Nuclear magnetic resonance spectra of AGEs were determined in saliva of 52 consecutive patients with diabetes mellitus and 47 age-matched healthy control subjects. Resonance spectra showed specific peaks at 2.3, 7.3, and 8.4 ppm in saliva from patients with diabetes mellitus, indicating the presence of advanced glycation endproducts which was associated with approximal plaque index. (17).

In a study of Garay-Sevilla et al (18) who measured AGEs in skin, serum and saliva of diabetic patients with complications they concluded that the AGEs measurement in saliva is useful to evaluate diabetes complications.

2. Alteration in glutathione metabolism:

Reduced glutathione detoxify reactive oxygen species such as hydrogen peroxide and lipid peroxide directly or in a glutathione peroxidase (GPX) catalyzed mechanism. Glutathione reductase (GRD) catalyzes the NAD(P)H dependent reduction of oxidized glutathione, serving to maintain intercellular glutathione stores and a favorable redox status (19).

Blood GSH was significantly decreased in different phases of type 2 diabetes mellitus such as: glucose intolerance and early hyperglycemia (20) and poor glycemic control (21)

Measurement of salivary GPX and GRD activities and GSSG/GSH ratio, provide a non-invasive method to assess the degree of oxidative stress in pathophysiologic status, such as diabetes (22).

The decrease in salivary reduced-glutathione levels in patients with type 1 DM may have a role in periodontal tissue destruction by predisposing tissues to oxidative stress.(23). Our previous study (24) identified GSH activity in serum and saliva of patients with type 2 diabetes which was significantly low when compared with control group. This finding was explained on the basis that oxidative stress may consumes some naturally occurring local antioxidants such as reduced glutathione and this reflects the overwhelming adaptive response to the challenge of oxidative stress in the diabetic state with or without complications

3. Impairment of SOD and catalase activity:

SOD and catalase are also major antioxidant enzymes, SOD exists in 3 different isoforms; Cu,Zn-SOD is mostly in the cytosol and dismutate superoxide to hydrogen peroxide, Extracellular SOD is found in the plasma and extracellular space and Mn-SOD is located in mitochondria. Catalase is H_2O_2 decomposing enzyme mainly localized to peroxicomes or microperoxicomes. Superoxide may react with other reactive oxygen species such as Nitric Oxide to form highly toxic species such as peroxynitrite (25).

The major reason for the decreased SOD activity is the glycosylation of Cu,Zn-SOD which has been shown to lead to enzyme inactivation both in vivo and in vitro (26). Salivary SOD was measured in saliva (27) .Belce et al suggested that the main reason for the decrease of salivary SOD activity may be increased glycation of the enzyme and/or deleterious effect of increased free oxygen radicals by glycated proteins on SOD activity in diabetes which could lead to oral complications in diabetic patients.However; Al-Rawi study (24) demonstrated an increase in the level of SOD in serum and saliva of diabetic patients, this increase could be due to the existance or increased free radicals production which could enhance the antioxidant defense system that couter-balance the pro-oxidant environment.

4. Polyol Pathway:

The polyol pathway consists of two enzymes. The first enzyme, aldose reductase (AR), reduces glucose to sorbitol with the aid of its co-factor NADPH, and the second enzyme, sorbitol dehydrogenase (SDH), with its co-factor NAD^+, converts sorbitol to fructose. In animal models, treatment with AR inhibitors (ARI) was shown to be effective in preventing the development of various diabetic complications, including cataract, neuropathy, and nephropathy (28). The possibility of determination of sorbitol and fructosamine in saliva has been studied in healthy volunteers and patients with diabetes. It was concluded that saliva

sorbitol and fructosamine levels measurements may be used as diagnostic tests in diabetes and serve as indicators of efficacy of therapy in diabetes (29).

5. Lipid peroxidation and protein oxidation in diabetes

Lipid peroxidation: Lipid peroxidation end-products very commonly detected by the measurement of thiobarbituric acid reactive substance (TBARS). The use of TBARS as an index of lipid peroxidation has been increased in plasma of diabetic patients (30-35). Thiobarbituric acid reacting substances (TBARS) are produced during lipoperoxidation-oxidative stress-induced damage of lipids and are, thus, a widely used marker of oxidative stress (36,37). However, they represent a heterogeneous group of compounds – best known is malondialdehyde (MDA). TBARS is associated with parodontopathies when measured directly in the injured gingival tissue (38). In previous studies we have shown that TBARS can be found in measurable concentrations in saliva and that these levels are higher in patients with parodontopathies and their origin is unlikely to be plasma (39,40). Whether the difference in patients is caused by a rise of MDA or instead of and which other factors influence salivary TBARS levels is unknown.(40) thus, assume, that salivary TBARS may reflect the local oral oxidative stress, although the producer is still hidden (41). Salivary MDA levels are directly affected by sytemic oxidative stress, since MDA levels were also elevated in saliva of diabtetic patients without parodontopathies (24). Astaneie et al (42) have reported no difference in salivary versus serum MDA levels and presence of high Antioxidant activity (AOA) in type 1 diabetics. Studies conducted on diabetic rats have reported an increase in salivary and serum MDA with variable antioxidant activity (43). Celec et al (44) have found an increase in MDA levels in non diabetics which was attributed to age, altered periodontal status and smoking. Hodosy et al (45) suggest that MDA levels depend on the time of sampling and also are affected by factors like tooth brushing and antioxidative therapy received by the patients. Studies by Reznick et al (46)and Astaneie et al (42) have shown both salivary and serum antioxidants to increase depending on HbA1C levels and severity of diabetes. The AOA levels of both the groups did not show notable correlation with Fasting Plasma Glucosa (FPG) but a significant correlation existed between salivary MDA and FPG levels in the diabetic group.

6. Diabetes and antioxidants

Antioxidants are substances that inhibit the destructive eefects of oxidation. Some of the general antioxidants that are known are glutathione effects, glutathione peroxidase, vitamins A,C,E, catalase and SOD. The decreased efficiency of antioxidant defenses (both enzymatic and non-enzymatic) seems to correlate with the severity of pathological tissue changes in type 1 diabetes (47).

Administration of the antioxidants, for example, the vitamin C and free amino acids, get a better reaction to insulin and can supply extra benefit to the proposed reduction of oxidative stress in tissues (48,49). Experimental study on diabetic rats suggested that nutritional vitamin E supplementation helps fatty acids metabolism and lower lipid peroxidation in rat tissues (50). Oral vitamin C and vitamin E has the ability to lower the oxidative stress in eye (51) and the vascular endothelia function get better in type1 and not type 2 diabetes (52). Vitamin C and Vitamin E, probably have an important role in reducing the oxidative

damage produced by nitric oxide and other free radicals. The estimation of vitamin levels and other antioxidants in saliva could provide a good insight about the body function against oxidative stress and it can be used to monitor therapy.

7. Conclusion

The saliva matrix is an upcoming area of research for basic and clinical application purposes, with considerable potential for growth and progress. Nevertheless, to date salivary assays are still little used compared with plasma assays, even it is possible to have a quantitative estimate of oxidative stress markers and antioxidants in saliva.

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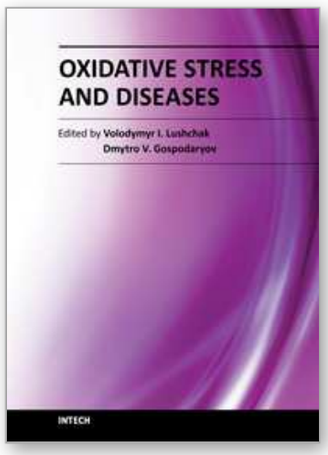

Oxidative Stress and Diseases

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The development of hypothesis of oxidative stress in the 1980s stimulated the interest of biological and biomedical sciences that extends to this day. The contributions in this book provide the reader with the knowledge accumulated to date on the involvement of reactive oxygen species in different pathologies in humans and animals. The chapters are organized into sections based on specific groups of pathologies such as cardiovascular diseases, diabetes, cancer, neuronal, hormonal, and systemic ones. A special section highlights potential of antioxidants to protect organisms against deleterious effects of reactive species. This book should appeal to many researchers, who should find its information useful for advancing their fields.

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