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Oxidative stress is a central factor in diabetes mellitus: an overview

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Diabetes mellitus is a disease having a characteristic symptom of high level of sugars in the blood (hyperglycemia), perceptible through the urine due to failure of metabolism, and thus, the name. Controversy exists about whether increased oxidative stress is merely associative rather than casual in diabetes mellitus. Several mechanisms may cause oxidative insult in diabetes mellitus, although their exact contributions are not entirely clear. Accumulating evidences point towards many interrelated mechanisms that increase the production of reactive oxygen and nitrogen species or decrease antioxidant protection in diabetic patients. Therefore, their role in diabetes mellitus needs critical examination. This review aims to summarize the role of oxidative stress in diabetes mellitus.

Key words: Antioxidant, B-cell, diabetes mellitus, oxidative stress, reactive oxygen species.

Introduction

Although oxygen is an essential molecule for animals and plants that produce their energy through the oxidation of biological molecules, it can also be potentially highly toxic resulting in oxidative stress. Oxidative stress is that set of intracellular or extracellular conditions that lead to the chemical or metabolic generation of the oxygen derived species, i.e., reactive oxygen species (ROS), among which are highly reactive intermediates free radicals such as superoxide anion ($O_2^{\cdot-}$), hydrogen peroxide (H_2O_2), hydroxyl free radical (OH^-) and lipid peroxides.[1] These free radicals are unpaired electron that alters the chemical reactivity of an atom or molecule, usually making it more reactive than the corresponding non-radical.[2] In the state of oxidative stress, there is an imbalance between the generation of ROS and the antioxidant defense of the body and is closely associated with aging and numbers of diseases including cardiovascular diseases, diabetes and diabetic complications, cancer, etc.

It is now well recognized that diabetes mellitus (DM) is a global epidemic disease and an estimated 150 million of people are affected by diabetes worldwide and this number is likely to reach 300 million by the year 2025 if successful strategies are not implemented for its prevention and control.[3] Diabetes is a syndrome characterized by hyperglycemia predisposing to markedly increased cardiovascular mortality and serious morbidity and mortality related to development of nephropathy, neuropathy and retinopathy.[4] Recently some evidences suggest that oxidative stress may play an important role in the etiology of diabetes and diabetic complications.[5] However, controversies still exist in the nature and

mechanism of oxidative stress in diabetes mellitus and its complications. Accordingly, the present review was taken up to study their role in diabetes mellitus.

Oxidative Stress in Dabetes Mellitus

Several mechanisms have been reported to cause oxidative insult in diabetes, although their exact contributions are not entirely clear. Although data are not yet conclusive, oxidative stress has been increasingly implicated in the pathogenesis of diabetic micro and macro vascular disease.[6] Oxidants or ROS have been implicated in the pathology insulin dependent diabetes mellitus (IDDM) and non-insulin dependent diabetes mellitus (NIDDM). Sato *et al.* in 1979 were first to report increased levels of plasma thiobarbutyric acids reactive substance (TBARS),[7] a putative measure of ROS-induced lipid peroxidative damage in IDDM and NIDDM patients. Subsequent studies have confirmed this observation of increased lipid peroxides in blood of NIDDM and IDDM patients,[8] and in various tissues from rats with streptozoctocin (STZ)- or alloxan-induced diabetes.[9] Further indications that the complications of diabetes associated with elevated level of apparently oxidative changes to proteins and lipids have been reviewed by Baynes in 1991.[10]

It has been suggested that increase generation of ROS may arise from transition metal catalyzed auto-oxidation of glucose and other small auto-oxidizables molecules or oxidation of glycated proteins.[11] On the other hand, a number of studies have suggested that oxidative stress is deeply involved in the pathogenesis of hypertension[12] and cardiovascular complications are considered as the leading causes of morbidity and mortality in patients with diabetes mellitus.

It has been therefore suggested that diabetes may be considered as cardiovascular disease. An evidence of implicating ROS in the development of diabetic vascular dysfunction has been expanding rapidly in the recent years. Hyperglycemia and increased free fatty acids in the blood stream, the chief characteristics of DM, can both lead to the leakage of superoxide anion ($O_2^{\cdot-}$) from the mitochondrial respiration process and NADPH oxidase activation.[13] This increased production of ROS in turn lead to the impaired endothelium dependent vaso-relaxation in models of both type-I and type-II DM.[14]

Furthermore, investigatory reports suggested that increased oxidative stress as measured by the indices of lipid peroxidation and protein oxidation has seen to increase in both IDDM and NIDDM even in patients without complications.[7] And the report was supported by strong experimental evidences that indicate that oxidative stress may determine the onset and progression of late diabetes complications.[10] In this, the structural change is clearly oxidative in nature and oxidation of lipid plasma lipoproteins and cellular membranes is associated with development of vascular disease in diabetes.

Proteins are an important target for oxidative challenge as elevated protein's carbonyl levels were detected both in type-I and type-II diabetes.[15] In addition to lipid and protein oxidation, oxidative damage of DNA has been reported in diabetic patients. Type-I and type-II DM patients have significantly higher levels of 8-hydroxydeoxy guanosine, an indicator of oxidative damage of DNA in mononuclear cells.[16]

Moreover, an increased oxidative stress based on increased peroxidation and reduced antioxidant status in diabetes mellitus has been shown by Godin *et al.*[17] It is noted that prolonged hyperglycemia due to its ability of non-enzymatic protein glycation may alter cellular functions and

may cause oxidative damage to the cellular membranes. This auto-oxidation process present in DM give rise to formation of free radicals which causes damage directly either affecting a specific molecule or indirectly by forming numerous toxic derivatives.[18] Recently, study in type-II diabetes animal models suggests that the progressive reduction of B-cells of pancreas is associated with excessive oxidative stress. In these animal models, when hyperglycemia is allowed to continue, the so called glucose toxicity to B-cells impairs insulin secretion and eventually causes fatal islet cell injury, accelerating B-cell loss.[19]

Consistently, Japanese type-2 diabetic patients show reduction of B-cell mass and evidence of increased oxidative stress related to the tissue damage that is correlated with the extent of the B-cell lesions.[20] Many more studies have also suggested that the B-cell dysfunction results from prolong exposure to high glucose, elevated FFA levels or combination of both.[21] B-cells are particularly sensitive to ROS because they are low in free radical quenching antioxidant enzymes such as catalase, glutathione peroxidase and superoxide dismuatase.[22]

Therefore the ability of oxidative stress to damage mitochondria and markedly blunt insulin secretion is not surprising.[23] Interestingly, it has also been reported that both the FFA and glucose may impair insulin secretion in B-cells by activating uncoupling of protein-2.[24] Therefore as glucose and FFA overload is presented during increased caloric disposal, it is possible that the combination with high glucose will maximize B-cell toxicity. On the other hand, many prospective studies have confirmed that the serum hemoglobin A1c (HbA1c) concentration is important predictor of both macro-vascular and micro-vascular complications of DM including coronary mortality and lower extremity amputations and is an outcome of the glycosylated hemoglobin due to increase oxidative stress in diabetic patients.[25]

Antioxidant Defense in Dabetes Mellitus

It has been speculated that the susceptibility of an organisms to oxidative damage is influenced by the antioxidant defense system's ability to cope with stress, which in turn can be influenced by the nutritional intervention with antioxidants.[26] Inherent antioxidant defense system consisting of enzymes such as catalases and superoxide dismutase etc. and nutrients (Vitamins E, C & A, etc.) may participate in coping oxidative stress.[27] There is evidence from molecular level studies that support the possibility that the oxidative stress alters the intracellular signaling pathway inducing insulin resistance.[21]

The recent finding that the insulin resistance is associated in humans with reduced intracellular antioxidant defense also supports this hypothesis.[28] Antioxidant enzymes dependent defenses play an important role in scavenging free radicals produced under oxidative stress. However, it has been reported that diabetic humans have shown increased lipid peroxidation and decreased level of reduced glutathione, glutathione reductase, glutathione peroxidase and glucose-6-phosphate dehydrogense.[29-30]

Acute administration of the antioxidants, vitamin C improves endothelium dependent vasodilatation in patients with NIDDM and this finding supports the hypothesis that oxygen derived free radicals contribute to abnormal vascular reactivity in diabetes, restoring endothelial function has important clinical implications of vascular disease in diabetic patients. Administration of vitamin E to diabetic animals decreases the rate of embryo malformations and increases their size and maturation, supporting a role of free radicals in terato-

genic effects of diabetes.[31]

Moreover supplementation with vitamin C, E and beta-carotene resulted in improvement of antioxidative status of rats with streptozoctocin induced diabetes.[32] These findings led us to the conclusion that the requirements of antioxidant is more on diabetic subjects than the non diabetic and the activities of body's inherent antioxidant enzymes and antioxidant nutrients are impaired due to presence of oxidative stress in them

Conclusion

This article has dealt with convergence and relationships presenting the hypothesis that oxidative stress may be a common pathway relating to diverse seemingly distinct mechanisms proposed for pathogenesis of diabetes mellitus and its complications. There are many possible causes of increased oxidative stress in diabetes and every source has their own impact in implicating the complications of diabetes mellitus.

However, at present it cannot be concluded whether or not this relevant dysfunction is the only key factor in development of diabetes mellitus. Further studies using standardize methodologies, molecular biological techniques, better defined diabetic models or subjects with better understood pathophysiology will be necessary to bring the concept closer to the understanding of the role of oxidative stress in diabetes mellitus. However, this review may eventually lead to the development of effective strategies for complementing therapeutic approaches to the treatments of diabetes.

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