Review on Malondialdehyde and Superoxide dismutase levels in patients of Type 2 Diabetes Mellitus with Retinopathy and without Retinopathy

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ABSTRACT- This review is based on the recent diagnostic and prognostic biomarkers for Diabetes and Diabetic complications. Diabetes mellitus (DM) is known to stimulate oxidative stress along with deranging different metabolisms; one of the Long term complications of diabetes mellitus is diabetic retinopathy, which is a leading cause of acquired blindness. Diabetic Retinopathy is a progressive disorder disease. It is the mainly frequently cause of blindness in people aged 35-75 years. Poor glycemic control and oxidative stress have been credited to the development of complications like diabetic retinopathy. The retina has high content of polyunsaturated fatty acid (PUFA) and glucose oxidation relative to any other tissue. Hyperglycemia and dyslipidemia in diabetes mellitus stimulate increased lipid peroxidation and reactive oxygen species formation, an important mechanism in the pathogenesis of diabetic retinopathy. The oxidative stress is altered between excess oxidative species formation and impaired exclusion of the reactive oxygen species via antioxidant defence system like superoxide dismutase. Hence the study over a period of 6 month from 1st Jan to 30 June 2015 with 54 diabetic retinopathy cases and 54 control cases without retinopathy was undertaken to evaluate the oxidative status and simultaneously decrease serum vitamin antioxidants levels in diabetic retinopathy cases and increase level of HbA1c. The aim of this study was to analyze and correlate oxidative stress marker, Malondialdehyde and superoxide dismutase along with glycosylated hemoglobin (HbA1c) in diabetic patients with and without retinopathy.

Key words- Diabetic retinopathy, Diabetes mellitus, Glycosylated hemoglobin, MDA and SOD

INTRODUCTION

Diabetes mellitus (DM) refers to a group of common metabolic disorders that share the phenotype of hyperglycemia¹. The relationship of diabetes and diabetic retinopathy is assuming clinical significance in the world scenario². Diabetes is one of the most common chronic hyperglycemic syndromes, affecting nearly 200 million people worldwide³⁻⁴. In future this disease has become one of the most difficult health evils of the 21st century. It affects more than 230 million people worldwide, and this number will be reach 350 million by 2025⁵. Retinopathy is characterized by increased vascular permeability, through vascular closure mediated by the formation of new blood vessels neo-vascularization, on the retina and posterior surface of the vitreous.⁶ Approximately 25% of patients with type- 1 DM have been shown to be affected through retinopathy, by the frequently rising to 60% after 5 yrs and 80% after 10-15 yrs of affli-ction. The type-2 DM accounts for a more quantity of patients with visual impairment ⁷.

The epidemiology of diabetic retinopathy and has been previously described, largely in the Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR).⁸ Glycosylated hemoglobin (HbA1c) level at baseline has been found to be strongly related to the incidence, progression, or both of Diabetic Retinopathy⁹. Diabetes increases oxidative stress in the retina: the levels of lipid perox-ide, thiobarbituric acid substances, and superoxide are increased in the retina¹⁰. Oxidative stress has been implicated in the pathogenesis of diabetic retinopathy ¹¹. This increase in oxidative stress can be the result of several diabetes-induced abnormalities, as well as auto-oxidation of glucose, the development of advanced glycation end products, and impairments in the antioxidant defense system¹¹-¹³. The activity of SOD, an enzyme recognized to scavenge superoxide, is reduced in the retina in diabetes, and its function is down regulated¹²,¹⁵. Hence the study was undertaken to evaluate the role of oxidative stress condition and its association with hyperglycemia and duration in patients of Non-insulin dependent diabetes mellitus (NIDDM) with and without retinopathy study. These highly reactive molecules affect bio-molecules such as lipids, proteins, nucleic acids and carbohydrates ¹⁴⁻¹⁵. Studies on patients with long duration and poorly controlled diabetes recommend that the free radicals of oxidant in diabetes mellitus and
Diabetic retinopathy is a vision-threatening disease characterized by neurodegenerative features associated with general vascular changes. It remains uncertain how these pathologies relate to each other and their net contribution to retinal damage. There are numerous biochemical pathways, which help in the development of the neurovascular injury in DR. As a result, biomarkers which reveal dissimilar pathways are released locally and into the circulation. Early identification of these biomarkers could be in favor of predicting and efficient management of DR. Among these biomarkers are the ones related to inflammatory response, oxidative stress and retinal cell death. Diabetes increases oxidative stress, which plays a key regulatory role in the development of its complications. Hyperglycemia induced reactive oxygen species (ROS) creation is measured a causal link between elevated glucose and the pathways of development of diabetic complications. Oxidative stress may lead to cell death via apoptotic means. Apoptosis of retinal neurons particularly ganglion cells has been demonstrated in diabetic retinopathy as demonstrated by profound retinal abnormalities, evaluated by electro-retinography, and potential visual changes evoked before the onset of the first vascular change is detectable in the diabetic retina. Retinal capillary cells also undergo accelerated apoptosis, which precedes the detection of any histopathological changes characteristic of diabetic retinopathy. The current review discusses the markers of oxidative stress and retinal cell death associated with DR.

### Table 1: International Classification of Diabetic Retinopathy Disease Severity Scale

<table>
<thead>
<tr>
<th>No.</th>
<th>International Classification of Diabetic Retinopathy Disease Severity Scale</th>
<th>Findings Observable on Dilated Ophthalmoscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Proposed Disease Severity Level</td>
<td>No abnormalities</td>
</tr>
<tr>
<td>2</td>
<td>Mild NPDR</td>
<td>Microaneurysms only</td>
</tr>
<tr>
<td>3</td>
<td>Moderate than severe NPDR</td>
<td>More than just microaneurysms, but less</td>
</tr>
<tr>
<td>4</td>
<td>Severe NPDR</td>
<td>Quadrants; definite venous beading in 2+</td>
</tr>
<tr>
<td>5</td>
<td>Proliferative diabetic retinopathy</td>
<td>Neovascularization and vitreous preretinal</td>
</tr>
</tbody>
</table>

NPDR = nonproliferative diabetic retinopathy; IRMA = intraretinal microvascular abnormalities.

Oxidative stress and diabetic retinopathy

Oxidative stress and diabetic retinopathy chronic hyperglycemia diseases plays a critical role in the pathogenesis of diabetic retinopathy (DR). The system of hyperglycemia-induced retinal damage is still to be evaluated. Still the oxidative stress which represents an imbalance between excess generation and impaired removal of reactive oxygen species has been suggested to be the key events in the pathogenesis of diabetic retinopathy. The high content of polyunsaturated fatty acids, oxygen uptake and glucose oxidation make the retina more susceptible to oxidative stress than other tissues. ROS are produced continuously in all cells to support normal cellular functions. However, excess production of ROS, or inefficient removal of ROS, could result in pathological conditions. In addition to ROS, reactive nitrogen species (RNS) are also a part of normal physiological function, and have great potential to contribute to oxidative stress. In the presence of superoxide, nitric oxide spontaneously forms peroxynitrite. Peroxynitrite is much more reactive than superoxide and nitric oxide and can exert direct oxidative modifications through one- or two-electron oxidation processes. Thus, excessive abundance of ROS and RNS with concurrent dysfunction of antioxidant defense systems, which includes reducing enzymes such as superoxide dismutase (SOD), catalase and glutathione peroxidase (GSH), contributes to oxidative stress in diabetic retina. Chronic oxidative stress causes spoil to DNA, carbohydrates, lipids, and proteins disruption in cellular homeostasis resulting in many disease processes of clinical interest. Accumulation of damaged molecules and ROS that are not easily removed contributes not only to the pathogenesis of DR but furthermore to the not sensitive of retinopathy to back even after good glycemic control is re-established the metabolic remembrance phenomenon.

Sources of ROS in diabetic retina Chronic express of retinal cells to hyperglycemia causes excess production of ROS by activation of unlike enzymatic pathways which extra likely interact to create the retinal damage seen in DR (Fig. 1). These sources consist of but not limited to NADPH oxidase, mitochondrial electron transport chain (ETC), development of advanced glycation end products (AGEs), aldose reductase/polyol pathway, protein.

Adapted with permission from the American Academy of Ophthalmology.
Fig 1: Oxidative stress mediated dysmetabolisms in diabetic retinopathy oxidative stress is a cytopathic consequence of excessive production of reactive oxygen species (ROS) and the suppression of ROS removed by antioxidant defense system. Hyperglycemia oxidative stress is considered a causal link between elevated glucose and other metabolic abnormalities important in the development of diabetic complications. Several diabetes-induced abnormalities in the retina that are postured in the development of retinopathy are influenced by oxidative stress, and are considered to be interrelated.

Hyperglycemia-Induced Pathogenic Mechanisms: Mitochondrial Superoxide Production

In endothelial cells improved MnSOD expression inhibits both hyperglycemia and fatty acid–induced inactivation of the antiatherosclerosis endothelial enzyme prostacyclin synthase by nitration in diabetes. Over expression of both MnSOD and UCP-1 also prevents inhibition of eNOS activity by these metabolites. This relationship is reliable with a central role for mitochondrial ROS formation in the pathogenesis of diabetic complications (Fig: 2).

Fig 2: Production of ROS by the mitochondria electron transport chain. In cultured endothelial cells, the electron donors NADH and FADH$_2$ are generated by the oxidation of glucose–derived pyruvate. The flow of the donated electrons (e–) through the electron transport chain in the inner mitochondrial membrane spaces. When the voltage gradient is the high because of increase flux of electron donors, more superoxide ids generated. H$^+$ ions can pass back across the inner membrane along their concentration gradient, either via ATP synthase (to produce ATP) or via proton gradient as heat. Cyt c indicates cyt c indicates cytochrome c. Adapted from Brownlee.

Metabolic Pathways Implicated in the Development of Diabetic Microvascular Complications

PROGNOSIS

Prognosis of DR depends on the stage of the disease and the availability of treatment. Around 5%–10% of diabetic patients among normal retinal exam will develop diabetic retinopathy within one year. Therefore, early dilated and comprehensive eye examinations should be done within 3–5 years after diagnosis of type 1 DM and among the diagnosis of type 2 DM. The examination helps to detect early DR where maintaining glucose level and blood pressure within the normal suggested ranges is measured the main available therapeutic modality for mild to moderate NPDR without macular edema. For example, the DCCT showed 75% and 50% reduction in the formation and development of DR after 3 years.
of intensive treatment to decrease blood glucoserespectively\(^{17}\). Early Treatment Diabetic Retinopathy Study (ETDRS) recommendations are considered the main gold standard practice for the management of advanced stages of DR. According to ETDRS recommendations, patients with severe NPDR, non-increase risk PDR, increase risk PDR should be treated with scatter photocoagulation also known as panretinal photocoagulation. Early treatment of severe NPDR and non-high risk PDR before the development to increase risk PDR – the sight-threatening retinopathy – was related with 50% decrease in the risk of blindness and vitrectomy comparing with treatment deferral until increase risk PDR is developed\(^ {38}\).

If the patient develops fractional retinal detachment or vitreous hemorrhage that hinder it is procedure, then vitrectomy should be considered. Currently a number of clinical trials are investigating drugs with dissimilar mechanism of actions for the treatment of DR. For instance, ruboxistaurin (RBX) is a new drug that inhibits the β-isof orm of protein kinase C (PKC) enzyme which is assumed to play an important role in the improvement of microvascular complications of diabetes.

**CONCLUSION**

The evo studies advise that oxidative stress is greatly elevated in patients suffering from diabetic retinopathy. When compared, oxidative stress is still increase in diabetic patients with retinopathy than patients without retinopathy. The retina has increase content of polyunsaturated fatty acids and has the elevated oxygen uptake and glucose oxidation relative to any different tissue. This phenomenon renders retina more sensitive to oxidative stress and is inversely associated to glycemic control. Hyperglycemia is a long period in retinopathy raise level of HbA1c. This may be due to dejected antioxidant enzyme levels and may also be dependable for further depletion of antioxidant enzyme SOD. This worsens the oxidative stress and creates a vicious cycle of unevenness of free radical production and debit of antioxidant status in these patients which may lead to nervous system damage causing diabetic retinopathy. Thus a best glycemic control is important for prevention of diabetic retinopathies and therapeutic approaches to the handling complications in diabetes. The study was concluded confirm whether these exists an involvement in between antioxidant nutrient intake and reduction in the improvement of diabetic complications particularly retinopathy.

**REFERENCES**


