

The Correlation Between Diabetic Retinopathy, Serum Antioxidants, and Intestinal Microbiome in Adult-Onset Diabetes Mellitus Individuals

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Abstract

The retina, a light-sensitive nerve layer at the back of the eye, creates images of objects and relies on small blood vessels to supply oxygen and nutrients. Retinopathy is a retinal condition that is more common in patients with Type 2 Diabetes Mellitus (T2DM). Diabetic retinopathy is a major cause of blindness as prolonged hyperglycemia weakens the retinal capillaries, causing blood leakage into the surrounding area. This bleeding can lead to the formation of scar tissue, potentially resulting in traction retinal detachment and maculopathy. Developing a set of blood biomarkers to monitor diabetic retinopathy is crucial for both diagnosis and prognosis. Proteomics, a powerful tool for analyzing complex protein mixtures and identifying biomarkers, is highly valuable in this context. As hyperglycemia and oxidative stress play key roles in the pathogenesis of diabetic retinopathy, this confirms that the progression of retinal damage can be slowed in well-controlled T2DM patients through treatments that reduce oxidative stress.

Keywords: Diabetic Retinopathy; Retinal Nerve Fiber Layer Thickness; Blood Antioxidants; Gut Microbiota**Abbreviations:** T2DM: Type 2 Diabetes Mellitus; OCT: Optical Coherence Tomography; ROS: Reactive Oxygen Species

Introduction

Diabetes Mellitus is an endocrine disorder characterized by elevated blood glucose levels due to disruptions in insulin production, function, or both. Over time, diabetes causes permanent damage to various organs, including the eyes, kidneys, and blood vessels [1]. It is classified as a metabolic disorder associated with chronic hyperglycemia and impaired macronutrient metabolism. Several mechanisms contribute to the development of diabetes, including autoimmune destruction of pancreatic β -cells, leading to insulin deficiency or resistance [2,3].

The clinical presentation of diabetes is linked to a high risk of long-term complications, which often emerge after a decade but can be the initial symptom in individuals who are otherwise asymptomatic. These complications primarily affect large blood vessels (macroangiopathy), increasing the risk of cardiovascular diseases, including coronary artery disease, which causes about 75% of deaths among diabetic patients. Other macrovascular complications include cerebrovascular accidents (strokes) and peripheral vascular diseases. The primary diabetic complications,

however, arise from microvascular damage (microangiopathy), particularly affecting the eyes, kidneys, and nerves [4].

Diabetic retinopathy is one of the leading causes of blindness globally. It can result in severe visual loss due to maculopathy and proliferative retinopathy, which may lead to vitreous hemorrhage, retinal detachment, and secondary glaucoma [5]. The incidence of diabetic retinopathy increases with the duration of diabetes, affecting about 50% of Type 1 and 30% of Type 2 diabetes patients. Regular monitoring, blood glucose control, and management of blood pressure and cholesterol can reduce the risk of retinopathy progression [6].

Diabetic retinopathy is often asymptomatic in the early stages, with vision deterioration occurring gradually as the condition worsens. Therefore, regular eye examinations are crucial for early detection [7]. The severity of diabetic retinopathy is typically classified into two types: non-proliferative and proliferative [8]. Optical coherence tomography (OCT) is a modern imaging technique that offers valuable insights into the retinal structure

and is useful in diagnosing diabetic retinopathy [9]. Treatment for diabetic retinopathy targets both the ocular and systemic aspects of the disease, including management of blood glucose, blood pressure, and cholesterol. Ocular treatments include therapies like laser surgery, vitreous surgery, and intravitreal injections [5].

Oxidative stress plays a significant role in the development of chronic diseases, including diabetes mellitus. The characteristic feature of diabetes is prolonged hyperglycemia, which increases the production of reactive oxygen species (ROS) and leads to oxidative stress in pancreatic β -cells. These β -cells exhibit reduced antioxidant enzyme activity, making them more susceptible to oxidative damage [10]. ROS contribute to the impairment of insulin production and cellular function by damaging mitochondria, and they are closely linked to both microvascular and macrovascular complications in diabetes. Elevated blood glucose and oxidative stress are major contributors to the development of diabetic complications, with ROS production being a key mechanism [11].

Increased oxidative stress in diabetes is linked to cell apoptosis and impaired mitochondrial energy function, contributing to complications such as retinopathy, nephropathy, and neuropathy. Oxidative stress results from the autooxidation of glucose, depletion of antioxidants like glutathione and vitamin E, and decreased activation of enzymes like superoxide dismutase and catalase. The retina, with its high concentration of polyunsaturated fatty acids, is especially vulnerable to oxidative stress, making it susceptible to damage from high glucose levels and oxidative stress, both of which play a crucial role in the pathogenesis of diabetic retinopathy [12].

The gut microbiota plays an essential role in maintaining the physical and biochemical integrity of the intestinal wall [13]. The human gut hosts more than 100 trillion bacteria from over 1,000 species, which perform various metabolic, trophic, and protective functions, effectively making the gut microbiome a "virtual organ" with a composition that outnumbers the human genome. The gut microbiota's composition is influenced by factors such as diet, genetics, and immune status, with certain bacterial communities linked to diseases like obesity and diabetes [14,15].

Alterations in the gut microbiota are associated with conditions like obesity and insulin resistance, which are common in Type 2 diabetes. Some studies have suggested that Type 2 diabetes is closely related to the gut microbiota, particularly regarding energy metabolism and chronic low-grade inflammation [16,17]. Obese individuals and those with insulin resistance tend to have an altered gut microbiota, with a higher Firmicutes-to-Bacteroidetes ratio compared to healthy individuals. This imbalance is believed to increase gut permeability, leading to the production of metabolic endotoxins that contribute to chronic inflammation, insulin resistance, and Type 2 diabetes [18,19].

Diabetic retinopathy affects approximately 60% of non-insulin-dependent diabetes patients [20]. Studies have shown

that the concentration of Gram-positive bacteria, including *Staphylococcus aureus*, is higher in diabetic patients, especially those with diabetic retinopathy. These findings align with research indicating that *Staphylococcus epidermidis* and *Staphylococcus aureus* are the most common pathogens in the eyes of Type 2 diabetes patients [21,22].

Clinical Modulation

Oxidative stress is integrated in pathogenesis and advancement of diabetic retinopathy in both types of diabetes. Recognizing efficacious modalities for retinopathy prevention and early intervention, is essential to maintain vision. Therefore, clinical treatment of oxidative stress can be implemented in preventing visual loss caused by diabetic retinopathy. Hyperglycemia is combined with many pathophysiological mechanisms that aggravate diabetic retinopathy. Different methods should be fixed on to manage diabetic retinopathy including oxidative stress-related medication that can stabilize the retinopathy stage in uncontrolled non-insulin diabetics.

Conclusion

Hyperglycemia and oxidative stress are implicated in the etiological pathogenesis of diabetic retinopathy and different treatment options that reduce oxidative stress can delay progressive damage in controlled type 2 diabetics.

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