ABSTRACT

The retina is a vascularized neural structure that is composed of blood vessels, neurons, glial cells, and microglia. Diabetes produces a number of well-known alterations to the vascular structure of the eye, but also causes significant retinal neurodegeneration. The response of the retina to visual stimulation has long been evaluated using the electroretinogram. This method assesses the summed electrical activity across the entire retina, and may fail to detect small regions of retinal dysfunction. More recently, retinal dysfunction in diabetes has been evaluated using the multifocal electrotetroretinogram (MF-ERG), which simultaneously records the electrical activity of dozens of discrete retinal regions. The MF-ERG is able to detect subtle retinal dysfunction in eyes that lack clinically evident retinopathy, and to identify retinal regions that subsequently develop significant retinopathy. Optical coherence tomography, which measures small differences in retinal thickness, is also increasingly used to evaluate retinal changes in diabetic macular edema (DME). The incidence of DME is significantly affected by a number of systemic factors, including glycemic control, hypertension, congestive heart failure, kidney failure, hypoalbuminuria, and anemia. Recent studies have identified numerous retinal growth factors and cytokines that may influence the development of diabetic retinopathy. Understanding the mechanisms of retinal neurovascular dysfunction and edema formation in diabetes should help to improve patient care by ensuring that modifiable risk factors are adequately addressed, and may also lead to the development of new and more effective therapies for diabetic retinopathy and DME.


The retina is not simply a set of blood vessels, but is a vascularized neural structure that develops from embryonic tissue of central nervous system origin. There are at least 4 major classes of cells in the retina: blood vessels, neurons, glia, and microglia. Visual processing is performed by several different types of neurons within the retina.1 Photoreceptors (rods and cones) capture photons and transduce light energy to chemical signals. The photoreceptors form synapses with bipolar and horizontal cells, which perform initial signal processing and relay signals to the ganglion cells, which perform higher-order processing within the retina. Amacrine cells convey signals from the rods to the ganglion cells, and also adjust retinal sensitivity.1,2 The function of the neurons and the blood vessels is integrated by the glial cells (astrocytes and Müller cells), which extend small projections that envelop the blood vessels in the inner nuclear layer and convey nutrients from the blood vessels to the

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neurons. The Müller cells span nearly the entire thickness of the retina and regulate the local ionic environment and the electrical properties of the neurons. Retinal microglia act as either antigen presenting cells or as macrophages.

Histological analyses and imaging studies using fluorescein angiography have demonstrated that diabetic retinopathy (DR) produces a number of well-known alterations in the vascular structure of the eye, including leakage of fluid from capillaries, hemorrhage, microaneurysms, loss of capillary pericytes, and acellular capillaries. However, recent research by numerous laboratories has shown that all of the retinal structures, including the blood vessels, glial cells, neurons, and the microglia, are affected in diabetes. Animal model and clinical studies have demonstrated that diabetes is associated with significant retinal neurodegeneration. Barber and colleagues described several features of retinal neural injury in a rat diabetes model, including a 14% reduction in the thickness of the inner nuclear layer, a 10% reduction in the number of ganglion cells, and a 10-fold increase in the number of neurons that displayed markers for apoptotic cell death. These investigators also found high levels of neuronal apoptosis in the retinas of patients with diabetes. More recently, Seki and colleagues found significant reduction in brain-derived neurotrophic factor, which promotes neuronal growth and survival, within the retinas of diabetic rats. These investigators also found that the number of retinal amacrine cells was reduced by 50% in diabetic animals. Thus, it may be more appropriate to view DR as a neurovascular disease rather than simply a disorder of the retinal vasculature. Recent improvements in understanding of the role of neurodegeneration of the retina in diabetes may allow the development of better treatments for DR.

The causes of vision impairment in DR may be classified as mechanical, optical, or cellular in nature. Mechanical causes are objects that obstruct sight, including hemorrhage or lipid in the fovea or distortion caused by epiretinal membranes. Optical factors include light scattering within the eye. Cellular effects include foveal ischemia and neuronal dysfunction or death. Some clinical conditions can produce vision loss as a result of all of the factors. For example, in cystoid macular edema the cysts create significant light scattering, resulting in degradation of the visual image. This optical effect is accompanied by neuronal and glial loss in the ganglion cell layer and the inner nuclear layer.

Evaluating Retinal Changes in Diabetes

The electrical response of the retina to visual stimulation has long been evaluated using the electroretinogram, which measures the summed electrical activity across the entire retina. The disadvantage of this method is that it can miss small regions of retinal dysfunction. Several recent studies have evaluated retinal function in patients with diabetes using a multifocal electroretinogram (MF-ERG), in which electrical recording is performed simultaneously for dozens of distinct regions across the retina. MF-ERG can be used to create a visual depiction of neuronal activity across the retinal surface that resembles a topographic map, with higher peaks showing regions of increased neuronal response to visual stimulation (Figure 1). MF-ERG measures electrical activity across the central 45 degrees of the retina, providing coverage of a portion of the retina that is similar to a midfundus photograph. It is able to identify discrete regions of retinal neuronal dysfunction in patients with diabetes. Using this method, Fortune and colleagues have
reported that even in relatively young patients with type 1 diabetes and clinically normal eye examinations, significant impairment of the electrical response to visual stimulation is detectable in small, discrete portions of the retina when compared with healthy normal subjects. In addition, Han and associates have reported that at 1-year follow-up of patients with clinically healthy eyes at baseline, retinal regions with abnormal MF-ERG findings were the most likely to subsequently develop retinopathy. These findings emphasize the importance of neuronal dysfunction in the progression of visual impairment in patients with diabetes, whether caused by macular edema, macular ischemia, or even a traction retinal detachment. Although MF-ERG is an important new method for understanding how diabetes affects vision, it is not primarily a clinical tool.

Another method that is becoming increasingly important in the analysis of diabetes-related vision loss is optical coherence tomography (OCT). In OCT, near-infrared beams are projected through the vitreous, the retina, and the choroid, creating interference patterns that allow detailed measurement of the retinal thickness. This method is useful for vitreoretinal traction and retinal thickening by cystoid macular edema (defined as a thickness of ≥250 mm in the fovea). It is more sensitive than a 78-diopter lens and fundus photography and even more sensitive than a fundus contact lens. It is sensitive enough to detect variation in the thickening during the course of the day. Although its direct correlation with changes in DR is still unclear, OCT is now included as a secondary endpoint in a number of important multicenter clinical trials. Studies have begun to examine subtle changes in retinal thickness in patients who do not yet have clinically significant diabetic macular edema (DME). This approach has been used to show that there is a thickening of the retina associated with a macular cyst during the early morning hours, which decreases within several hours of awakening. This finding corresponds with reports from many patients who say that they do not see well during the early morning hours.

**Mechanisms of DME**

In order to understand the causes and treatments of DME, it is helpful to first review the mechanisms by which edema develops. Starling’s law of the capillaries is the fundamental principle that describes the movement of fluid between the intravascular and interstitial spaces. According to Starling’s law, the amount of fluid resulting from edema formation in any tissue, including the retina, is the net difference between the pressure driving fluid from the capillary to the surrounding tissue (the hydrostatic pressure) and pressure driving fluid to enter the capillary (the oncotic pressure). Hydrostatic pressure is a function of blood pressure and fluid volume, and oncotic pressure is a function of plasma albumin concentration. Thus, edema formation is increased when the hydrostatic pressure is increased, and is very common among patients with diabetes as a result of hypertension. Hydrostatic pressure is also increased by intravascular fluid overload, which occurs in a number of conditions including congestive heart failure or renal failure. Edema formation is also increased under conditions of decreased colloid oncotic pressure, which occurs as a result of hypoproteinemia. The role of Starling’s law in edema formation in the retina was reviewed by Kristinsson and colleagues, who noted that retinal hypoxia, impaired retinal metabolism, or hypertension all cause the dilation of retinal arteries, resulting in

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**Figure 2. Pathophysiology of DME**

Hypoxia, metabolic alteration, or hypertension all produce arteriolar dilation. The resulting increases in capillary and venous pressure cause capillary and venous dilation and increased permeability of vascular tight junctions, resulting in increased edema formation in accordance with Starling’s law of the capillaries.

DME = diabetic macular edema.

increased capillary and venous pressure. This results in the dilation and elongation of the retinal veins, which is a characteristic feature of DR. These alterations are accompanied by an increased permeability of vascular tight junctions. All of these factors contribute to the formation of DME (Figure 2).

The most widely recognized systemic risk factor for DME is poor metabolic (glycemic) control. However, the formation of edema as a consequence of Starling’s law suggests that several other systemic factors are also important in the development of DME. Hypertension (which is defined by the American Diabetes Association as blood pressure >130/80 mm Hg) is a clearly significant risk factor for DME. Other potential risk factors include conditions that create intravascular fluid overload, such as congestive heart failure, renal failure, or hypoalbuminemia, although these factors have not been extensively studied in DME. In addition, as shown by Chew and colleagues in the Early Treatment Diabetic Retinopathy Study (ETDRS), hyperlipidemia (cholesterol ≥240 mg/dL) is a risk factor for development of clinically significant macular edema and vision loss. Anemia is another important systemic factor that contributes to the formation of DR and DME, but that often receives relatively little attention. Many patients with diabetes develop anemia as a result of kidney dysfunction, which is associated with decreased production of erythropoietin. The largest proportion of persons with significant kidney disease and anemia are patients with diabetes. A hemoglobin value below 12 g/dL is a significant independent risk factor for retinopathy in patients with diabetes, and treatment of anemia has been shown to reduce the occurrence of DR. Retinopathy may occur in anemia simply because there are not enough red blood cells to carry oxygen to the retinal tissues, although it has also been suggested that erythropoietin may have direct neuroprotective effects.

**PRINCIPLES OF DR TREATMENT**

Optimal treatment of DR requires consideration of both systemic and ocular factors. For example, effective management of systemic factors such as glucose and hypertension can significantly improve DME. These treatments are also beneficial for renal function, overall life span, and other features of diabetes as well. Ocular factors include improved retinal metabolism or oxygenation by laser therapy, and reducing retinal inflammation, perhaps with steroids. Although the basic principles of macular photocoagulation in diabetes have been well established for more than 20 years, the Diabetic Retinopathy Clinical Research Network is now comparing the relative merits of modified ETDRS laser treatment versus a modified macular grid pattern. The results may be published within the next 2 years.

Vitrectomy has been one of the major advances in the treatment of patients with DR. However, therapeutic outcomes and the procedures used have been fairly constant over the last several years. Vitrectomy has also provided a source for diagnostic samples for analysis of vitreous fluids. These analyses have suggested that the milieu of the retina and the vitreous fluid in patients with diabetes is very complex, and that numerous growth factors within the retina may be important in diseases of the eye, including DR. These growth factors include vascular endothelium growth factor and pigment endothelium-derived factor, ephrin B2, connective tissue growth factor, hepatocyte growth factor, and insulin-like growth factor 1 and 2. Vitreous samples have also identified abnormalities of several cytokines, such as tumor necrosis factor α and interleukin-1 (IL-1), IL-6, and IL-8; glutamate; and trace elements such as Fe, Cu, and Zn.

**SUMMARY AND CONCLUSIONS**

The goal of treatment of DR is to allow patients to continue to have good vision despite their diabetes. This requires that ophthalmologists continue to be experts in all the technical and surgical aspects of diabetes, but also to increasingly be experts in medical management. Ophthalmologists have a unique and very important opportunity to consider not only the macular features but also systemic factors, such as blood pressure, lipids, and hematocrit value; and also to ask patients about their symptoms. Ophthalmologists can be advocates with primary care physicians and endocrinologists to help ensure that blood pressure is well controlled and that other conditions, such as congestive heart failure, are adequately addressed. The emphasis must continually be on preventing the development of retinopathy in persons who have normal fundus findings. They represent the greatest therapeutic opportunity for the millions of people with diabetes.
REFERENCES


