An Integrated Approach to Diabetic Retinopathy Research

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This review discusses the pathophysiology of diabetic retinopathy related to direct effects of loss of insulin receptor action and metabolic dysregulation on the retina. The resulting sensory neuropathy can be diagnosed by structural and functional tests in patients with mild nonproliferative diabetic retinopathy. Research teams can collaborate to integrate ocular and systemic factors that impair vision and to design strategies to maintain retinal function in persons with diabetes mellitus. Evolving concepts may lead to inclusion of tests of retinal function in the detection of diabetic retinopathy and neuroprotective strategies to preserve vision for persons with diabetes.


WHAT IS DIABETIC RETINOPATHY?

Diabetic retinopathy is a prototypical microvascular disorder associated with microaneurysms, intraretinal hemorrhages, capillary nonperfusion, intraretinal microvascular abnormalities, and neovascularization. These features are readily apparent because blood vessels carry erythrocytes that are easily visualized in the fundus. In contrast, the impact of diabetes on the transparent retina is difficult to assess by clinical evaluation, although it has been known for 5 decades that diabetes disrupts the neurosensory retina.5,6 Clinicians see the retina primarily as blood vessels, optic nerve, and pigmented epithelium, whereas neuroscientists view it more broadly as a network of neurons and glia (astrocytes, Müller cells, and microglial cells) that comprise approximately 95% of the retina, with blood vessels representing less than 5% of the retinal mass. The neurons, glia, and microglia are metabolically linked, and the neurons (photoreceptors, bipolar cells, horizontal cells, amacrine cells, and ganglion cells) integrate and transmit visual signals to the brain.7,8 Thus, neuroglial cells are involved in vision, and blood vessels provide nutrients to facilitate the process. Just as the network of retinal neurons and glia are intimately linked, there is no doubt that the neural and vascular components of the retina are closely associated by metabolic synergy and paracrine communication. The functional integration of blood vessels with the neurosensory retina is clinically evident during autoregulation in which retinal arterioles and venules constrict in response to hypertension and hyperoxia and dilate in response to hypercapnia. Likewise, disorders of the neurosensory retina and retinal vasculature are integrally linked, and understanding...
the interactions between blood vessels and the neurosensory retina is key to understanding diabetic retinopathy.

Numerous laboratory- and clinic-based observations reveal preclinical changes in the retina. Patients with diabetes exhibit reduced electrical responses with full-field and multifocal electoretinography, lowered blue-yellow color sensitivity, and diminished contrast sensitivity before the appearance of microvascular lesions. In addition, spatially distinct neural defects detected by the multifocal electoretinogram precede and predict the development and location of vascular lesions in patients with type 1 diabetes. Histopathologic studies have confirmed degeneration of the neurosensory retina that is disproportionate to the observed vascular lesions.

Studies using diabetic rodents reveal changes in the neurosensory retina within several weeks of onset of insulin deficiency, including death of retinal neurons, morphologic alterations of astrocytes and microglial cells in the inner retina, impaired glutamate metabolism by Muller cells, and the development of axonal dystrophy and synaptic degeneration. Increased leukostasis and breakdown of the endothelial cell junctions develop concurrently, illustrating the functional and structural relationship of retinal vascular and neural cells.

So what is diabetic retinopathy? Diabetes affects the entire retinal parenchyma, so the term “microvascular disease” is insufficient to describe the full picture of diabetic retinopathy. A more inclusive definition, which was suggested at a 2007 Association for Research in Vision and Ophthalmology Summer Eye Research Conference, is “structural and functional changes in the retina due to diabetes.” Thus, diabetic retinopathy can be viewed as a sensory neuropathy similar to autonomic and peripheral neuropathies that are common features of diabetes and prediabetes, including corneal neuropathy.

This broader view of diabetic retinopathy provides a foundation to understand the mechanisms of visual impairment in persons with diabetes. Clinicians attribute visual impairment to macular edema, ischemia, epiretinal membranes, vitreous hemorrhages, and/or traction detachments. In contrast, the cellular changes within the neural retina are more subtle. For example, visual impairment associated with diabetic macular edema may result from ischemia, cystic compression of neurons, disruption of ionic concentrations required for neurotransmission, or light scattering through the cyst. In addition, loss of neurons or their synaptic connections may accompany the cystic changes and may be the final determinant of visual function.

WHAT IS DIABETES AND HOW DOES IT DAMAGE THE RETINA?

Diabetes mellitus is defined clinically on the basis of hyperglycemia because blood glucose concentrations correlate closely with patients’ symptoms, and the determination of blood glucose concentration is rapid and inexpensive. However, hyperglycemia is the consequence of impaired insulin action due to insulin deficiency and/or insulin resistance (diminished insulin effectiveness). The anabolic effects of insulin are achieved by insulin binding to its receptor in the plasma membrane, and by the activation of a cascade of enzymes and other intermediate proteins that allow nutrients to be oxidized for energy or incorporated into storage molecules depending on the metabolic needs of the person (Figure 1). That is, amino acids, glucose, and fatty acids are utilized to fulfill energy requirements or are incorporated into proteins, glycogen, and triglycerides, respectively. Both insulin deficiency and insulin resistance impair these metabolic processes and lead to accelerated breakdown of muscle protein, tissue glycogen, and fat, resulting in abnormal accumulation of amino acids, glucose, and fatty acids in the plasma of persons with diabetes. Therefore, hyperglycemia is but one aspect of the broad metabolic dysregulation that is diabetes.

Figure 1. Overview of anabolic insulin actions. A, Insulin binds to its receptor on the cell surface, leading to anabolic processes via activation of a cascade of intermediate proteins and enzymes that enable use of nutrients for energy or conversion to macromolecules. B, Insulin deficiency and/or insulin resistance creates a catabolic state with accelerated breakdown of macromolecules and accumulation of nutrients (glucose, amino acids, and free fatty acids) in the plasma. MAPK indicates mitogen-activated protein kinase.
The multiple catabolic effects of diabetes on various tissues are illustrated in Figure 2, which shows a child with type 1 diabetes mellitus prior to the availability of insulin, with marked loss of subcutaneous fat and skeletal muscle (Figure 2A) and the restoration of these tissues with insulin therapy (Figure 2B). This case demonstrates that diabetes is a multifaceted catabolic disorder due to impaired insulin action that results in impaired nutrient utilization and/or storage and accelerated tissue breakdown.

This concept of diabetes can be extended to diabetic retinopathy because the mammalian (rat and mouse) retina possesses a constitutively active insulin receptor signaling system, and diabetes causes similar impairment of this metabolic activity in retina as in skeletal muscle concomitant with the onset of the degenerative structural and functional changes, as shown in Figure 2. Systemic and ocular insulin administration restores defective retinal insulin receptor signaling. Similar alterations in insulin receptor signaling in tissues such as skeletal muscle, adipose, and liver account for the clinical signs and symptoms of diabetes, so it follows that defective retinal insulin receptor signaling might also contribute to the early preclinical metabolic and cellular changes in the retina. Recent studies in diabetic rats have shown that diabetes alters retinal metabolism of lipids in a manner that may contribute to retinal cell death and inflammation.

The most important insights into the development of diabetic retinopathy derive from the Diabetes Control and Complications Trial. This landmark study compared the effects of conventional insulin treatment (1-2 injections of insulin daily) with the effects of intensive therapy (3-4 injections of insulin or an insulin pump) in patients with type 1 diabetes. The patients were divided into 2 subgroups, those without retinopathy at baseline and those with mild to moderate retinopathy at baseline who were continuously treated with conventional or intensive insulin therapy and who were evaluated using a 3-step scale to measure progression of retinopathy. After 7 years, the intensively treated patients in the prevention and intervention arms exhibited 76% and 54% reductions in retinopathy, respectively, compared with the conventionally treated patients. Intensive treatment also reduced hemoglobin A1c and blood glucose levels more than conventional treatment did, leading to the conclusion that tight control of hyperglycemia led to less progression of retinopathy, peripheral neuropathy, and nephropathy. The study can also be interpreted as demonstrating that less insulin deficiency contributed to the improved outcomes.

Diabetes affects all organs, including skeletal muscle, liver, adipose tissue, kidney, retina, and even bone and skin. Diabetes affects these tissues over a continuum, depending on their relative responsiveness to metabolic and/or inflammatory insults. Complications such as retinopathy, nephropathy, and neuropathy are those organ changes that cause direct clinical impairment. Thus, understanding the pathogenesis of retinopathy in the context of the effects of impaired insulin action on other tissues may provide insight into how retinal damage may be ameliorated by systemic and/or local therapies to restore insulin receptor action or anti-inflammatory responses. Clearly, more studies are needed to define these pathways and identify optimal drug targets.

**Figure 2.** Insulin deficiency affects multiple tissues. A, A patient in 1922 with type 1 diabetes mellitus prior to insulin availability, exhibiting loss of subcutaneous fat and skeletal muscle. B, The same patient after insulin administration with restoration of subcutaneous fat depots and skeletal muscle.

**HOW DOES UNDERSTANDING DISEASE MECHANISMS HELP PATIENTS?**

Visual acuity is measured with high-contrast charts that assess the integrity of the central fovea. This function can remain unaffected even in eyes with advanced retinopathy. Numerous preclinical studies have shown physiologic and structural alterations of the inner and outer retina in diabetes, and psychophysical studies corroborate these changes in humans with and without vascular lesions. Therefore, it is possible to apply clinical tests to assay specific layers or cell types of the retina. For example, contrast sensitivity, standard automated visual fields, and frequency doubling technology evaluate the function of the inner retina, and dark adaptation measures the integrity of the photoreceptor-retinal pigmented epithelium complex. Numerous studies have described defects in these parameters, but it is still uncertain how defects in the inner and outer retina correlate with...
various degrees of retinopathy or diabetes metabolic control. Figure 3 illustrates reduced dark adaptation in a patient with nonproliferative diabetic retinopathy. Photoreceptors and pigmented epithelium do not rely on the inner retinal blood supply, so this defect may have a different basis than lesions in the inner retina. In comparison, frequency doubling technology measures primarily ganglion cell function, and Figure 4 shows that mild nonproliferative diabetic retinopathy severely reduces macular sensitivity, indicating ganglion cell defects despite excellent visual acuity. This observation is consistent with thinning of the inner retina and loss of retinal ganglion cells in patients with mild nonproliferative diabetic retinopathy.

These studies reveal that diabetic retinopathy includes features that ophthalmologists can see and features they cannot see. Full understanding of diabetic retinopathy requires a multifaceted strategy that embraces quantitative structural and functional analyses, including high-resolution imaging and functional analyses of specific retinal layers and regions to achieve a comprehensive picture of the effects of diabetes on the retina. These tests may reveal a variety of diabetic retinopathy phenotypes.

AN INTEGRATED APPROACH

Diabetic retinopathy is a diabetes complication of the eye, so it is best understood through integrated studies by laboratory- and clinic-based eye and diabetes researchers. For example, the cellular biological studies of neural retinal damage characterized in rodent eyes and confirmed in human postmortem eyes now guide the selection of clinical tests to characterize the full spectrum of diabetes-induced retinal pathophysiology. Additionally, the finding of reduced inner and outer retinal function in humans helps to further focus mechanistic studies in animals. Integrated approaches require the collaborative teamwork of groups of investigators working to-

Figure 3. Nonproliferative diabetic retinopathy impairs dark adaptation. A, A 57-year-old woman (hereinafter referred to as patient 73) with 21 years of type 2 diabetes mellitus, 20/25 visual acuity, and moderate nonproliferative diabetic retinopathy. The black circle represents the area of the retina that is assessed by the AdaptDx dark adaptometer. B, Dark adaptation curves of normal subjects (red circles) and patient 73 (blue squares) showing incomplete dark adaptation using AdaptDx dark adaptometer (Apeliotus Vision Sciences, Hershey, Pennsylvania), in spite of normal serum retinol, retinol binding protein, and retinyl ester levels. The dashed horizontal line is the 95% confidence interval for the upper limit of normal dark adaptation.

Figure 4. Mild nonproliferative diabetic retinopathy impairs visual fields. A, A 56-year-old male with 9 years of type 2 diabetes mellitus, mild nonproliferative diabetic retinopathy, and 20/16 visual acuity. B, 24-2 Humphrey fields. C, Matrix frequency doubling perimetry in the left eye of the same patient.
ward a common long-term goal to enable persons with diabetes to maintain good vision and to reduce the need for destructive, expensive, and uncomfortable treatments such as photocoagulation or intraocular injections. The predicted 3-fold increase in the risk of visual impairment and blindness caused by the diabetes epidemic is an unequivocal mandate to adopt new research strategies and resources proportional to the problem. Together, these studies will provide better means to develop strategies for early diagnosis and treatment of diabetic retinopathy to better predict patients at risk for vision loss, to preserve and restore vision, and to enable use of more robust clinical trial endpoints. Indeed, there is now widespread recognition of the need for improved endpoints for diabetic retinopathy research. Application of these tools will accelerate drug discovery and delivery strategies to improve the visual prognosis in persons with this disease (Figure 5). With greater understanding of the basic mechanisms of disease and a more intimate partnership between basic and clinical scientists, we can look forward to a time when diabetic retinopathy is preventable.

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Additional Information: Dr Jackson holds intellectual property related to the AdaptDX dark adaptometer. Dr Gardner is the Jack and Nancy Turner Professor.

REFERENCES


Archives Web Quiz Winner

Congratulations to the winner of our September quiz, Pawan Prasher, MD, Department of Ophthalmology, Sri Guru Ram Das Institute of Medical Sciences and Research, Amritsar, Punjab, India. The correct answer to our September challenge was subconjunctival pigmented fungus. For a complete discussion of this case, see the Research Letters section in the October Archives (Li EY, Yuen HK, Lung DC. Subconjunctival mycetoma as an unusual cause of tears with black deposits. Arch Ophthalmol. 2010;128[10]:1371-1372).

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