

---

# PREFACE

---

## INTRODUCTION

This monograph is intended to serve two functions: first, to help readers understand the impact of vision impairment in people living daily with diabetes rather than considering diabetic retinopathy solely as a medical problem; second, to explore what we know and what we do not know about the ways diabetes affect the eye. Even with the plethora of new information being generated, there are still a series of fundamental questions that must be addressed if we are to develop effective treatments for diabetic retinopathy.

In the first chapter of this volume, Stuckey relates her experiences with proliferative diabetic retinopathy (PDR) and associated laser treatment. She provides a perspective on the visual and emotional component of vision loss that can be explained only by someone who has experienced it firsthand. She describes not only the loss of vision from the vitreous hemorrhage, the pain of the laser treatments, but also the permanent consequence of reduced peripheral vision and ability to adapt to dark conditions and from dark to light. Thus, it is clear that ophthalmologists do not “cure” diabetic retinopathy with retinal photocoagulation, but merely keep people from really becoming blind. Stuckey provides powerful incentives for us to do a better job to understand the nature of the problems she and other people with diabetes face, or at least dread. She also provokes us to prevent diabetic retinopathy or at least maintain vision without the need for destructive treatment.

## HOW IS DIABETIC RETINOPATHY DETECTED?

For the detection and diagnosis of diabetic retinopathy in standard clinical practice, each patient is assessed individually with standard clinical tools including indirect ophthalmoscopy and slit lamp biomicroscopy following pupillary dilation. These methods of physical examination not only provide structural information about the ocular media and the status of the retinal blood vessels and optic nerve, but also provide little information regarding the structure or function of the neural retina, the part that is key to vision. So, the evaluation of large populations for the presence of retinopathy is usually done by photographic methods; the analysis of the resulting images has dramatically reduced vision impairment in communities of countries such as Iceland and Norway. However, the protocols for capturing and assessing the images continue to evolve because they require manual interpretation and are not quantitative.

Scanlon summarizes the progress in screening for diabetic retinopathy based on his extensive experience in the United Kingdom. Clearly, screening in European countries is much more widely implemented and successful than in the United States or elsewhere, revealing the distinct cultural and economic differences in response to a common problem across the oceans. Thus, there is no single solution to population screenings for diabetic retinopathy and multiple approaches may be needed to achieve optimal specificity and sensitivity.

Adams and Bearnse detail their extensive cross-sectional and longitudinal studies of patients with diabetes and no or mild nonproliferative retinopathy using multifocal ERGs and visual field tests. They find that prolonged implicit time on the mfERG, an indicator of bipolar cell and outer plexiform layer integrity, predicts the development of vascular lesions, with topographical correspondence. This technique has the advantage of being independent of patient responses and can assess nearly the entire retina. Their data clearly show the early impact of diabetes on the neurosensory retina prior to the loss of visual acuity, and illustrate the potential to diagnose retinal impairment early so that it can be slowed if treatments can be developed.

## HOW DOES DIABETES AFFECT THE EYE?

The clinical impact of diabetes on the eye is generally discussed in terms of diabetic retinopathy, but Midena reinforces the importance of corneal neuropathy which predisposes patients to epithelium breakdown, and is reflected by changes in the corneal structure as seen with confocal microscopy and by reduced corneal sensation. Diabetic corneal neuropathy has little direct impact on visual function but is further evidence of the widespread impact of diabetes in the eye. Furthermore, diabetes often frequently causes dysfunction of the autonomic nerves that regulate pupil size. Taken together with the impact of diabetes on sensory neurons in the retina, it is now evident that diabetes causes widespread neuropathic changes in the eye.

Cunha-Vaz and colleagues point out that there may be variable phenotypes of diabetic retinopathy based on clinical findings of microaneurysm turnover, vascular leakage, and macular thickening. In several longitudinal studies, they have quantified microaneurysm turnover on fundus photographs as well as vascular leakage and macular thickening to form a composite multimodal retinal analysis system that provides a more comprehensive assessment of retinopathy grade than any measure alone.

The clinical phenotype of diabetic retinopathy has generally been descriptive with little effort to provide quantitative parameters that predict the progress of diabetic retinopathy. The composite scoring system developed by Cunha-Vaz et al. is one of the first endeavors to account for consequences of increased vascular leakage and capillary closure. They found a greater rate of microaneurysm formation turnover in patients with more severe diabetes and worse visual acuity. This careful analysis of various patterns of vascular damage is an important step toward an improved understanding of diabetic retinopathy.

Medina and Vujosevic address the fundamental issue of the impact of diabetes on various aspects of vision. They trace a series of investigation into this question over the past 3 decades in which increasingly sensitive tests have been used to quantify defects in the inner vs. outer retina, and macular vs. mid-peripheral retinal in patients with various stages of diabetes. Most studies have evaluated a limited number of parameters in small cohorts of patients, so it remains difficult to have a comprehensive assessment of the impact of the range of diabetic retinopathy on vision over time. However, the net knowledge at this point that there is evidence of ganglion cell and inner retinal defects, as well as defects in the photoreceptor/pigmented epithelium with increased retinopathy grade, macular edema, and proliferative retinopathy. However, it remains uncertain

which cellular defects primarily give rise to loss of visual acuity or the relationship of functional defects to alterations in retinal structure.

Two chapters examine various aspects of blood–retinal barrier break down in diabetic retinopathy. First, Hafezi-Moghadam discusses the normal role of the blood–retinal barrier to protect the neural retina and the role of inflammation and BRB permeability in diabetic retinopathy. In particular, he summarizes the role of inflammatory leukocyte recruitment to capillary endothelium by adhesion molecules such as ICAM-1, integrins, and other molecules that allow leukocytes to migrate through extracellular matrix. One of the mechanisms by which leukocytes increase permeability is through the release of azurocidin, a protease that attracts other inflammatory cells and increases vascular permeability. The actions of azurocidin can be blocked by a protease inhibitor such as aprotinin in experimental models of diabetic retinopathy, and he points out that aprotinin is used clinically in patients undergoing cardiothoracic and orthopedic surgery to reduce vascular leakage. In sum, this model suggests that leukocyte recruitment and activation may play a critical role in retinal vascular leakage particularly media through azurocidin release and this strategy may provide a therapeutic target.

Runkle, Titchenell, and Antonetti detail the known cellular and molecular regulation of the blood–retinal barrier and its compromise by diabetes, notably VEGF. VEGF induces phosphorylation and ubiquitination of occludin, leading to its internalization and movement away from the plasma membrane, and increased endothelial cell permeability, as mediated by activation of protein kinase C (PKC) isoforms. Several of these steps may be targets for therapeutic regulation.

In addition to a change in the barrier function of the retinal vasculature, the vessels themselves undergo pathological changes. Kern describes the capillary nonperfusion and degeneration that are early hallmarks of diabetic retinopathy. These changes can lead to preretinal neovascularization, and many of the current therapeutic approaches are based on the premise that blocking the early vascular pathology will prevent this subsequent pathology.

Extracellular serine proteinases include urokinase plasminogen activator (uPA) and members of the family of zinc-dependent endopeptidases called matrix metalloproteinases (MMPs). These proteinases participate in the degradation of interstitial extracellular matrices and basement membranes, and help in the recruitment of progenitor cells into the extracellular matrix during tissue remodeling. Proteinases are expressed by normal cells in tissue remodeling events and also during pathological events such as tumor angiogenesis and metastasis. The roles of these proteinases in diabetic retinopathy are summarized in the chapter by Rangasamy, McGuire, and Das.

Urokinase activates its cognitive receptor, a member of the lymphocyte antigen receptor superfamily, and leads to MAPK activation. MMPs release extracellular matrix from angiogenic growth factors such as VEGF and bFGF. They are expressed in multiple retinal cell types and are potential targets for therapeutic manipulation, either directly or via tissue inhibitors of matrix proteinases (TIMPs). To date most of the work in the eye relates to the control of abnormal vascular leakage and macular edema or neovascularization.

One of the ways of gaining insight into the biochemical changes occurring in diabetic retinopathy is to examine the proteins in the vitreous. Feener describes the identification

of several hundred proteins in the human vitreous and the changes that occur in diabetes. Though many of the changes seen can be attributed a breakdown in the blood–retinal barrier, other may represent proteins secreted from the retina or attempts by the retina to counteract the deleterious effects of diabetes. As well as providing insights into the pathogenesis of the disease, these proteomic studies may give us sensitive biomarkers to indicate the stage and prognosis for patients.

Diabetic retinopathy is much more than a vascular disease and Barber, Robinson, and Jackson summarize the current knowledge of neurodegeneration in diabetic retinopathy. There are close similarities in structure in alterations and structure and function of the retina in animal models of diabetic retinopathy and humans. That is, there is delayed oscillatory potentials and reduction of the b-wave amplitude that corresponds with, but is not necessarily the direct result of increased death of retinal ganglion cells, amacrine neurons, bipolar neurons, and photoreceptors and/or reduced neurotransmission. Together, this extensive evidence clearly shows that there is neurodegeneration in early stages of diabetic retinopathy concomitant with the early detection of vascular changes. These findings are fundamental to our understanding of the nature of diabetic retinopathy and have a great impact on future efforts in diagnosis, prevention, and treatment.

Khan and Chakrabarti summarize the mechanisms by which hyperglycemia depresses the viability and function of retinal endothelial cells such that they have an increased rate of apoptosis, alters their participation in autoregulation, damages basement membranes matrix constituents, and contributes to neovascularization. Multiple biochemical changes have been described in animal models of diabetes and endothelial cells and cultural but the understanding of their roles in human diabetic retinopathy remains limited.

Stahl and coworkers discuss regarding insulin-like growth factor binding protein-3 (IGFBP-3) as a regulator of the growth hormone/insulin-like growth factor pathway in proliferative retinopathies. They summarize the relationship between VEGF-induced angiogenesis in retinopathy of prematurity (ROP) and PDR. Both conditions are characterized by peripheral retinal capillary closure, followed by peripheral retinal neovascularization, and treatments for both conditions are currently limited to growth factor inhibition and/or laser photocoagulation after the development of neovascularization. Their previous work in experimental models of ROP suggests that there are reduced insulin-like growth factor-1 (IGF-1) levels in the serum of premature infants associated with a loss of peripheral retinal vessels, and that systemic IGF-1 administration increases the risk of neovascularization. Likewise, patients with type 1 diabetes have reduced serum IGF-1 levels in the preproliferative stage, and systemic IGF treatment can accelerate the development of ocular neovascularization. Elevated serum IGF-1 levels are associated with accelerated proliferative retinopathy in pregnant diabetic women.

The authors describe the role of (IGFBP-3) which forms a molecular complex with insulin-like growth factors in the serum and retards their degradation. They propose that IGFBP-3 could be used as an adjunct to IGF-1 supplementation during the nonproliferative phase of retinopathy. In the proliferative phase IGF-1 may accelerate the involvement of neovascularization. Thus, titration of the levels of IGF and binding proteins may allow for improved regulation of proliferative retinopathies.

Murray and Ma summarize the panoply of proteins that exert prosurvival and differentiation features in retinal vascular and neuronal cells. They emphasize that despite

laboratory-based studies of the biological roles of these factors, most of them have not been studied sufficiently to enable clinical trials. Moreover, most of them are studied as single factors whereas they function in combination with others in vivo. Nevertheless, these naturally derived biological products have potential for clinical application.

The most severe forms of diabetic retinopathy occur due to vitreoretinal traction leading to epiretinal membranes with tangential or anterior traction, frequently resulting in retinal detachment and blindness.

For the past 15 years, the major emphasis in diabetic retinopathy research has been VEGF-induced neovascularization but the cause of fibrosis following treatment of neovascularization has remained unclear. van Geest et al. have pioneered the concept that connective tissue growth factor (CTGF) is increased during the fibrotic stage of diabetic retinopathy, or at least is expressed without the opposition of VEGF. In fact, they also show in strong evidence that CTGF expression increases in the blood vessels of diabetic rats shortly after diabetes induction suggesting that the fibrotic process actually starts in the preclinical stage of diabetic retinopathy, concomitant with basement lamina thickening, loss of pericytes, and capillary occlusion. Further studies will help to determine if CTGF inhibition can prevent fibrosis within the retina and the risk of tractional retinal detachment.

## HOW CAN VISION LOSS BE LIMITED: EXPERIMENTAL THERAPIES

The ultimate test of a proposed disease mechanism lies in its relevance as a therapeutic target. Since the initial discovery of increased VEGF levels in human diabetic retinopathy in 1994, numerous studies have demonstrated a relationship with DME and increasing severity of retinopathy. Kim, Do, and Nguyen review the literature on the effects of intravitreally administered VEGF antagonists on DME. The positive effects of repeated treatments have now been shown in several clinical trials, but the authors remind us that the mechanisms by which vision improves after VEGF inhibition remain uncertain. As they also point out, it is unknown precisely why and how vision is impaired by DME in the first place. The growing evidence of a key role of VEGF and its inhibition will stimulate further investigations into these important questions.

Simo and colleagues point out that the metabolic pathways leading to retinal neurodegeneration are poorly understood, but there is likely an imbalance of neuroprotective factors vs. neurotoxic metabolites such as glutamate. The authors also emphasize the use of the *db/db* mouse with a leptin receptor mutation as a model to study retinal neurodegeneration in diabetes because it eliminates any potential for confounding effects of streptozotocin on the findings.

The range of neuropeptides in the retina is extensive and includes pigment epithelial-derived factor (PEDF), somatostatin (SST), erythropoietin (Epo), neuroprotectin D1 (NPD1), brain-derived neurotrophic factor (BDNF), glial cell line-derived neurotrophic factor (GDNF), ciliary neurotrophic factor (CNTF), and adrenomedullin (AM). SST is potentially interesting in diabetes since its general function in the peripheral tissues is to mediate the effects of growth hormone and IGF-1. In the retina, SST is expressed by amacrine cells and pigmented epithelium, and is reduced in diabetic rats and in diabetic human vitreous. Retinal lipids are also important because docosahexaenoic acid is a precursor to NPD1.

One group of cells that serve as an important source of active peptides in the retina are the glial cells. Sawada and colleagues document the effects that cytokines released from glial cells can have on the blood–retinal barrier and discuss treatments that may show some benefit by altering the pattern of expression of these cytokines.

Begg and colleagues thoroughly reviewed the effects of improved diabetes control on the development and progression of diabetic retinopathy, detailing the results of the DCCT and EDIC studies. They also cite less known findings, such as the improved outcome in patients undergoing panretinal photocoagulation who have HBA1c < 8% at the time of treatment than those whose control is worse.

In addition, they summarize the studies that confirm strong beneficial effects of pancreas transplantation and islet cell transplantation, although the ocular benefits arise at the cost of more hypoglycemia and side effects of immunosuppression. In short, the prognosis for vision is markedly better with better metabolic control, irrespective of the means by which it is achieved.

From the chapters in this volume, it will be apparent that we have an overview of the timing and pathology of vascular lesions in the retinas of patients with diabetes. We also know that macular edema is a major factor in the loss of visual acuity and that laser photocoagulation and anti-VEGF therapies convey substantial benefit to many patients.

The list of what we do not know is much longer. We need to know whether metabolic factors beyond glucose contribute to vision-threatening diabetic retinopathy and how these lead to vision impairment. Is diabetic retinopathy a response to systemic metabolic abnormalities or are there unique ocular problems related to insulin resistance? Perhaps, the most fundamental gap in our knowledge is the relationship between the neural, vascular, and inflammatory abnormalities in diabetic retinopathy. Do they represent a pathological cascade induced sequentially or simultaneous responses to one or more metabolic perturbations? If we do not address these questions, it is possible that the long process of developing new therapeutics will target only one arm of the pathology and leave the retina open to damaging consequences of the others. Although we think of the changes detected in diabetes as being pathological, many of them may be an attempt by the tissue to restore normal function. This is certainly true in inflammatory responses, and we need to distinguish protective from damaging inflammatory responses.

Although there is much about the biology of the normal and diabetic eye that still needs to be learned, we also have an urgent need to develop tools that will help in the testing and application of new therapeutics. We clearly need to define optimal indices of retinal structure and function that predict development of diabetic retinopathy and vision impairment; indices that can be used as dynamic parameters for clinical trials of therapeutics.

While the list of outstanding questions is long, the tools to address them are now available and we can look forward to rapid progress in knowledge and, more importantly, new scientific approaches that lessen the vision impairment associated with diabetes.

*Joyce Tombran-Tink  
Colin J. Barnstable  
Thomas W. Gardner*

Visual Dysfunction in Diabetes

The Science of Patient Impairment and Health Care

Tombran-Tink, J.; Barnstable, C.J.; Gardner, Th.W. (Eds.)

2012, XV, 379 p., Hardcover

ISBN: 978-1-60761-149-3

A product of Humana Press