

## Glaucoma and Diabetic Eye Disease: Neuroprotection and Preserving Sight

BY NEERU GUPTA, MD, PHD, FRCSC, AND EFREM MANDELCORN, MD

Glaucoma and diabetic retinopathy are major causes of irreversible blindness worldwide. Treatment of glaucoma involves the medical and surgical reduction of pressure within the eye, while treatments for diabetic retinopathy relate to the effects of blood vessel pathology and proliferation in the eye. Ocular neuroprotection is a rapidly evolving field of study and application that refers to therapy to prevent retinal neuron death in the eye, irrespective of the original injury. Recent major progress in our understanding of glaucoma suggests that, in addition to the eye, glaucomatous disease spreads to vision centres in the brain. Furthermore, novel neuroprotective strategies directed at protecting neurons in the eye and brain in glaucomatous disease may be critical to prevent progressive disease. These findings present a new paradigm in the treatment of eye diseases and may be highly relevant to the treatment of diabetic retinopathy to prevent vision loss.

### Glaucoma

Glaucoma is the leading cause of irreversible blindness worldwide and is projected to affect almost 80 million people by 2020.<sup>1</sup> It is characterized by the death of retinal ganglion cells in the eye. Because it affects peripheral vision first, vision loss is slow, progressive, and without symptoms. Glaucoma may be associated with elevated pressure in the eye. Other risk factors include increasing age, family history, black race, diabetes, and vascular disease. Treatments are aimed at lowering intraocular pressure (IOP) by medical and surgical approaches; however, although this helps to slow vision loss, the disease may continue to progress despite these interventions. There is intense investigation into how this occurs and recent evidence indicates that glaucoma may involve more than the eye, affecting visual pathways within the brain.<sup>2-3</sup> Optic disc changes in the eye that are observed by clinicians may be only a glimpse of the injury extending behind the eye to central visual pathways in the brain (Figure 1).

Understanding that disease in glaucoma can spread from the eye to the brain may provide clues about how it progresses despite strategies directed at lowering IOP. Additional neuroprotective strategies aimed at the retinal ganglion cells (RGCs), their axons, and targets in the brain, may help to prevent or slow the progressive vision loss associated with glaucoma.<sup>4</sup>

### Connecting the eye to the brain

Axons of RGCs travel outside the globe and can be traced to the major vision target in the brain — the lateral geniculate nucleus (LGN). Ninety percent of RGCs terminate in the LGN, a 6-layered structure (Figure 2). Neurons in the LGN are functionally and anatomically segregated into magnocellular, parvocellular, and koniocellular pathways:

- magnocellular neurons responsible for motion vision are found in LGN layers 1 and 2
- parvocellular neurons participate in red-green colour processing and are located in LGN layers 3 to 6
- koniocellular neurons are responsible for blue-yellow processing and are sandwiched between the principal layers of the LGN.



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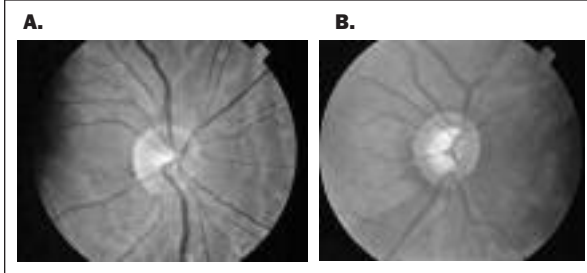
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**Figure 1: A. Normal optic nerve;  
B. Glaucomatous optic nerve**



### What happens to the brain in glaucoma?

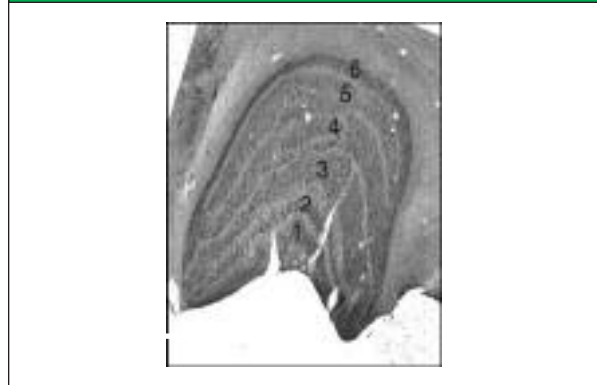
In the primate model of glaucoma, changes in the optic nerve head mimic those observed in human glaucoma. When pressure is raised in the primate eye, optic nerve fibers degenerate just as they do in human glaucoma. Changes include myelin loss and shrunken optic nerve fibers.<sup>5</sup> In glaucoma, major degenerative changes also occur in the LGN of the brain following elevated IOP.<sup>6-9</sup> The LGN has been shown to shrink in size, the loss and shrinkage of neurons affect the magno- and parvocellular layers of the LGN, and major neurochemical changes have been observed in koniocellular neurons. Using 3-dimensional morphometric techniques, cell numbers in the magno- and parvocellular layers were shown to be reduced in experimental primate glaucoma.<sup>6</sup> Measurements in these pathways also revealed reduced neuron size, consistent with observed histological changes.<sup>8</sup> The reduced cell size may be relevant to our understanding of glaucomatous injury, since scientists have demonstrated a link between cell size and cell function.

Neurons from the 3 major visual pathways – namely the magnocellular, parvocellular, and koniocellular neurons – may be affected in glaucoma and project to the visual cortex for further processing. As suspected, the visual cortex undergoes striking metabolic changes in glaucoma.<sup>9</sup> Normal visual cortex stains positively and homogeneously for cytochrome oxidase, a marker for metabolic activity. This is in contrast to glaucoma, where alternating light and dark ocular dominance bands are observed in the visual cortex and correspond to reduced activity driven by the glaucomatous eye. Other neurochemical changes have also been described in the visual cortex in primate glaucoma.<sup>10</sup>

### Are brain changes in glaucoma relevant to human disease?

The LGN and visual cortex were studied in a post-mortem patient with advanced glaucomatous optic neuropathy that was consistent with visual field loss.<sup>11</sup> Compared with age-matched controls, the size of the

**Figure 2: Lateral geniculate nucleus (LGN) of the brain: the first major target of retinal ganglion cells (RGCs) in the eye**



intracranial optic nerve just before the optic chiasm was reduced in this post-mortem case. Additionally, the overall size of the LGN appeared to be reduced as compared with normal LGN size and shrinkage of the LGN neurons was observed.<sup>11</sup> In the visual cortex of this index glaucoma case, cortical ribbon thinning, as compared with age-matched controls, was suggestive of the degenerative visual cortex changes in glaucoma and corresponded to the visual field defect. Thus, it appears from this case of human glaucoma with moderate vision loss, that degeneration of the retina and intracranial visual structures, including the LGN and visual cortex, can also occur.<sup>11-12</sup>

### Neuroprotective strategies in glaucoma

Neural degeneration in the central visual system observed in glaucoma may involve several mechanisms, such as those proposed for other neurological diseases (eg, Alzheimer's and Parkinson's diseases). These mechanisms – including glutamate toxicity, nerve growth factor deprivation, oxidative injury, ischemia, and autoimmunity – have been implicated in cell death in glaucomatous disease.

There is considerable interest in blocking glutamate toxicity as a strategy to protect neurons from injury in disease. Glutamate is the most abundant neurotransmitter in the brain. Excessive levels of glutamate can lead to excessive stimulation of glutamate receptors on neurons, inducing toxicity and cell death.

Blockade of excessive glutamate stimulation has been used as a treatment for Parkinson's disease for >25 years and more recently for Alzheimer's disease. Memantine is an *N*-methyl-D-aspartate (NMDA) open-channel blocker prescribed for this use, with Food & Drug Administration (FDA) approval for the treatment of cognitive impairment in Alzheimer's disease.<sup>13</sup> Memantine has been proposed as a candidate neuroprotective agent in glaucoma. By blocking the NMDA receptor in the presence of excessive glutamate, neurons

may be somewhat shielded from the magnitude of insult.

The effects of memantine have been studied in the central visual system in experimental primate glaucoma. One group with glaucoma was treated with memantine (4 mg/kg) each day for 14 months and compared with a vehicle-treated glaucoma group.<sup>14</sup> As measured by 3-dimensional morphometry, visual neurons in the magno- and parvocellular layers of the memantine-treated group were protected from shrinkage. Measurements of neuron size in these pathways revealed increased neuron size in the memantine-treated group that was consistent with observed histological changes. Thus, memantine was able to protect the neurons in the LGN from shrinkage in experimental primates with glaucoma.<sup>14</sup>

A multicentre, randomized, prospective, double-blind clinical trial to evaluate the possible role of memantine in protecting patients with glaucoma has been completed and is currently under analysis.<sup>15</sup> It will be interesting to see if memantine helps to protect against neural degeneration and vision loss in patients with glaucoma. This is an active area of research and lessons learned from neuroprotective treatments under investigation for eye diseases such as glaucoma may be highly relevant to the prevention of blindness from diabetic eye disease.<sup>16</sup>

### Diabetic eye disease

Diabetic eye disease is the leading cause of blindness in North America in patients aged <40 years and the second leading cause of blindness overall. Diabetic retinopathy (DR) occurs in both type I and type II diabetes and is detectable in at least 50% of patients with type I diabetes of 7 years duration and in 90% of patients with type I diabetes for >25 years. Although the most important risk factor in the development of diabetic retinopathy is poor blood sugar control, severe degrees of diabetic retinopathy requiring retinal treatment still occur in up to 25% of patients. Blindness afflicts 5% of all patients with diabetes.<sup>17-19</sup>

From the ophthalmologists' perspective, DR constitutes a complex of several well-defined retinal abnormalities that may or may not progress from one form – nonproliferative diabetic retinopathy (NPDR) – to a more advanced form, namely proliferative diabetic retinopathy (PDR). Blindness can occur in both forms.

### Diagnosis of diabetic retinopathy

The earliest pathologic change in the retina is the disappearance of pericytes around endothelial cells. Capillary basement membranes become thickened, increased protein synthesis occurs in endothelial cell walls, and dysfunctional diffusion gradients develop

### Figure 3: Non-proliferative diabetic retinopathy

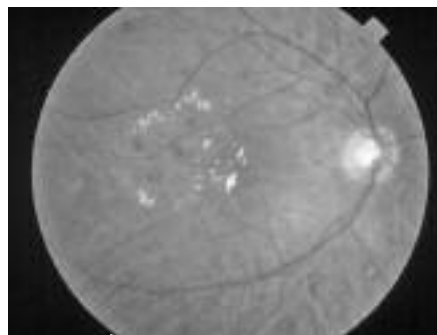
Cytoid bodies (focal segments of swollen ganglion cell axons) evident as cotton wool spots are clinical markers for retinal ischemia. Hard exudates and a few small retinal hemorrhages can also be observed.



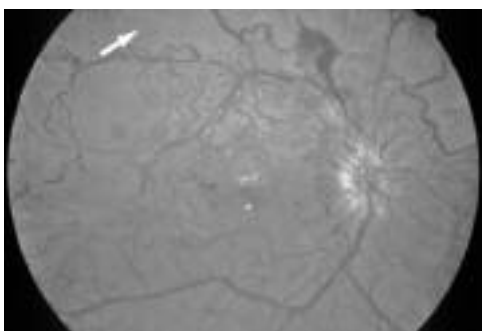
within the retinal capillary bed. People with diabetes can also develop erythrocyte abnormalities, including increased plasminogen and macroglobulins, leading to increased clumping and poor capillary circulation. Clinically, these cellular changes manifest as intraretinal hemorrhages, hard exudates (lipoprotein), and intraretinal microvascular abnormalities (IRMA), since the capillaries are not able to prevent blood and protein from leaking out of the intravascular space (Figure 3). Ultimately, there is leakage of blood and plasma into the retinal extracellular space. When this occurs in the centre of the retina, known as the macula, the condition of clinically-significant diabetic macular edema (CSDME) is present (Figure 4). Visual acuity becomes reduced and this is the mechanism that may lead to blindness in patients with NPDR.

As retinal disease progresses, areas where there are damaged capillaries undergo cell death or *capillary dropout*, leading to nonperfusion of the retina and retinal ischemia. The response of retinal cells to ischemia is increased expression of growth factors,

### Figure 4: Non-proliferative diabetic retinopathy (NPDR) with macular edema



**Figure 5: Proliferative diabetic retinopathy (PDR) with neovascularization**



predominantly vascular endothelial growth factor (VEGF), whose expression is enhanced by both hypoxia and high glucose. VEGF has 2 functions, namely, angiogenesis and increased permeability of the blood-retinal barrier. Low levels of VEGF are present in normal retina and vitreous; however, increased VEGF expression in conditions of hypoxia and high glucose can result in abnormal angiogenesis, known as “neovascularization,” and a marked increase in vascular permeability. The diagnosis of PDR is confirmed when neovascularization is clinically detected (Figure 5). Progression of PDR leads to vitreous hemorrhage (Figure 6), tractional retinal detachment, and/or neovascular glaucoma that may be the mechanisms leading to blindness in PDR.

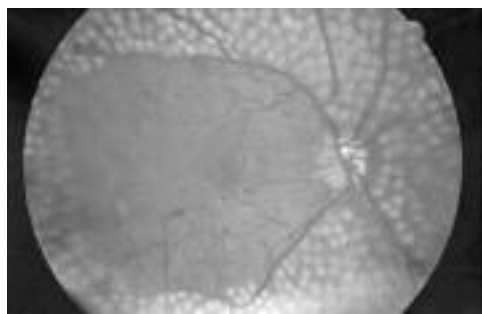
### *Management of diabetic retinopathy*

Management options depend upon the stage of DR. In all cases, control of all medical abnormalities, including blood glucose, blood pressure, and lipids, constitutes the first step.<sup>20</sup> With respect to direct

**Figure 6: Proliferative diabetic retinopathy**  
New blood vessels form a fibrovascular membrane on the inner retinal surface. There is focal microcystoid degeneration of the inner retinal layers.



**Figure 7: Laser treatment for PDR**



retinal intervention, the findings in a number of landmark, randomized, control trials constitute the basis for standardized evidence-based treatment.

It has been known for many years that people with diabetes and untreated PDR have at least a 50% chance of becoming blind within 5 years if they remain untreated. Until the early 1970s, many treatment approaches were described for this group of high-risk patients, but there was no universal agreement regarding whether or not any treatment was efficacious. For this reason, various studies were launched to study the effects of various treatments for DR.

**The Diabetic Retinopathy Study (DRS):** The DRS was the first prospective, multicentre, randomized, clinical control trial, organized and sponsored by the National Eye Institute of the National Institutes of Health in 1976. In this study, one eye of each patient with PDR was randomized to receive a specific laser treatment protocol, while the fellow eye served as a control. The DRS demonstrated a 50% reduction in severe visual loss in eyes that received laser treatment compared with untreated eyes. The study also identified which patients with PDR had the highest risk of severe visual loss and which ones received the greatest benefit from prompt laser treatment.<sup>21-23</sup> These findings – now >30 years old – still constitute the gold standard of prophylactic treatment for patients with PDR (Figure 7).

**The Early Treatment Diabetic Retinopathy Study (ETDRS)** was a multicentre, randomized, clinical trial that studied patients with CSDME associated with a high risk of severe visual loss. It revealed that a specific laser treatment protocol, different from that used in PDR patients, reduced the risk of moderate visual loss by 50% (12% risk of moderate visual loss for treated eyes versus 24% for untreated eyes at 3 years).<sup>24-26</sup> To this day, this treatment protocol remains the gold standard in the treatment of CSDME.

**The Diabetic Retinopathy Vitrectomy Study (DRVS):** For patients with PDR who have already become blind from complications of retinal neovascularization, the DRVS demonstrated that early vitrectomy was beneficial in eyes with non-clearing vitreous hemorrhage or severe fibrovascular proliferation.<sup>27</sup>

### **New approaches**

Recent developments in our understanding of the role of growth factors in the evolution of disease have led to the consideration of a number of new approaches to the treatment of DR. Many of these new therapies are currently being evaluated in randomized clinical trials.

Intraocular corticosteroids injected directly into the vitreous cavity can prevent or reduce the degree of breakdown in the blood–retinal barrier, suppress inflammation, and downregulate the production of VEGF. Intravitreal triamcinolone injection, for example, has been shown to improve visual acuity and reduce macular edema, although the effect is short-lived and serious side effects can occur.<sup>28-29</sup> Delivery of steroids through intravitreal sustained-release devices that provide prolonged medication delivery (eg, fluocinolone acetonide [Retisert<sup>®</sup>] and dexamethasone [Posurdex<sup>®</sup>]) are currently being evaluated.

Medications that directly target VEGF are becoming widely used clinically in the treatment of DR and are also the subject of a number of clinical trials. These include pegaptanib (Macugen<sup>®</sup>), ranibizumab (Lucentis<sup>®</sup>), and bevacizumab (Avastin<sup>®</sup>). Pegaptanib is an aptamer that selectively inhibits the 165-isoform of VEGF, the isoform most associated with pathologic ocular neovascularization and increased retinal vascular permeability. In a prospective, randomized, placebo-controlled, multicentre trial in eyes with CSDME, patients who received pegaptanib demonstrated better visual outcomes, showed reductions in retinal thickness, and were less likely to need additional laser treatment during the 36-week trial period.<sup>30-31</sup>

Ranibizumab has been approved in the USA and elsewhere for use in patients with age-related macular degeneration and is currently under study in the treatment of DR because of its ability to reduce VEGF-stimulated retinal neovascularization. A related compound, bevacizumab is approved for intravenous use in patients with colon cancer and is currently used off-label for intravitreal injection in selected patients with DR for treatment of CSDME, blindness due to complications of PDR and, in some cases, as pre-

operative adjunctive therapy in patients undergoing vitrectomy surgery for blindness due to DR.

A number of newer pharmacologic compounds are currently being tested to determine if there might be clinical benefit in using drug therapy to interfere with cell signaling to prevent the upregulation of VEGF production. It is known that chronic elevation of blood glucose causes increased cellular levels of diacylglycerol and other enhanced glucose moieties. These activate the beta-isoform of protein kinase C (PKC), an intracellular enzyme that, when activated, leads to increased synthesis of VEGF. In some clinical studies, ruboxistaurin mesylate (Arxxant<sup>®</sup>), a potent PKC-beta inhibitor, has provided significant benefit in DR. It is currently undergoing Phase 3 studies.<sup>32</sup> New approaches in the treatment of diabetic retinopathy continue to be developed based on an increased understanding of the disease at the molecular level.

### **Conclusion**

Novel neuroprotective treatments to target and protect retinal neurons and their connections from injury are well underway to prevent blindness from glaucoma. This approach to prevent and treat injury to the retina in diabetic eye disease – separate from treatments directed at vascular pathology – is a new and promising paradigm.<sup>33</sup>

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**Neeru Gupta, MD, PhD, FRCSC, DABO**, is Associate Professor of Ophthalmology and Vision Sciences and Laboratory Medicine and Pathobiology at the University of Toronto: Director of the Glaucoma & Nerve Protection Unit, St. Michael's Hospital; Keenan Research Centre at the Li Ka Shing Knowledge Institute of St. Michael's Hospital.

**Efrem Mandelcorn, MD**, is a senior resident in training, Department of Ophthalmology and Vision Sciences, University of Toronto.

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