ABSTRACT

Diabetic retinopathy is the leading cause of blindness in adults of working age in industrialized countries and a common cause of blindness in all age groups combined. With the global prevalence of diabetes increasing, the number of patients with diabetic retinopathy is expected to also increase. The challenge is to prevent the development and progression of diabetic retinopathy and preserve vision.

The mainstays of treatment are glycemic control, blood pressure control, and the use of panretinal photocoagulation for proliferative retinopathy and focal and/or grid photocoagulation for macular edema. However, these treatments are not enough; additional therapies are needed.

Numerous factors are involved in the progression of diabetic retinopathy, and several are logical targets for therapeutic intervention. Some of the factors involved in progression are pericyte loss, retinal ischemia and occlusion, and the formation of new fragile vessels that bleed easily and do little to perfuse the peripheral retina. Increased capillary permeability due to protein kinase C (PKC)-mediated release of vascular endothelial growth factor (VEGF) and other processes may be involved.

Several new therapies have been developed and are now in various stages of investigation. These therapies include somatostatin analogues, statins, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), PKC inhibitors, and growth hormone-, VEGF-, and advanced glycation end product-receptor blockers. Intraocular delivery of triamcinolone is also a currently available option.

The statins, which have had a major effect on reducing the risk of cardiovascular disease and mortality from cardiovascular causes in patients with diabetes and in nondiabetic individuals alike, are now being re-evaluated in at least one large clinical trial for their effects on diabetic retinopathy. Similarly, the ACE inhibitors and ARBs, which have been effective in controlling blood pressure, are being re-evaluated in primary and secondary prevention trials for their effects on retinopathy in patients with type 1 and type 2 diabetes mellitus.

Ruboxistaurin, a PKC inhibitor that specifically inhibits the PKC-β isoform, is currently being evaluated in phase III trials involving patients with diabetic retinopathy, diabetic macular edema, and diabetic peripheral neuropathy.

The results of all of these trials are expected to provide valuable data and lead to effective therapies to prevent the development and progression of diabetic retinopathy.

With the global prevalence of diabetes projected to increase from nearly 200 million today to 300 million by 2025, an increase in the number of persons with diabetic retinopathy can also be expected. The increasing prevalence of diabetes parallels the rise in obesity seen in recent years, and the high prevalence of obesity reflects human evolution. Whereas early man had a lean body build as a result of having to expend a great deal of effort to obtain scarce food, modern man, at least in industrialized countries, can obtain plenty of food with little effort; hence, the rise in obesity and the higher prevalence of diabetes.

**Effects of Diabetes on the Eyes**

Although the retina is the most common site of microvascular damage from diabetes, other eye structures are also affected adversely. Diabetes affects the corneas and is associated with an increased prevalence of keratitis. It also affects the lenses, hastening the development and increasing the severity of cataracts. The optic nerves can be affected, leading to optic neuritis that can result in loss of sight.

Diabetic retinopathy accounts for approximately 90% of blindness in patients with type 1 diabetes and approximately 33% of blindness in patients with type 2 diabetes. In addition to blindness caused by diabetic retinopathy in patients with type 2 diabetes, a significant percentage of blindness is caused by age-related macular degeneration and other age-related eye disorders in older patients with type 2 disease.

One particular area of the retina that is vulnerable to damage from diabetes is the macula, where central vision, detailed vision, and color vision are based. Here, damage results in maculopathy, which can be diabetic macular edema or ischemic maculopathy.

**Natural History of Diabetic Retinopathy**

The natural history of diabetic retinopathy is outlined schematically in Figure 1. The earliest stage of the disease is preclinical diabetic retinopathy, in which no lesions are observed on funduscopy or fluorescein angiography, but retinal blood flow is altered and histologic changes in the retinal vessels such as basement membrane thickening and loss of pericytes may already be occurring. Preclinical diabetic retinopathy is followed by mild nonproliferative diabetic retinopathy, moderate nonproliferative diabetic retinopathy, and severe nonproliferative diabetic retinopathy, which is also known as preproliferative diabetic retinopathy.

Macular involvement, as macular edema or ischemia, may coexist with nonproliferative and proliferative diabetic retinopathy. If proliferative retinopathy is not treated, or if it is not treated soon enough, it may progress to advanced diabetic eye disease and loss of sight.

The progression from preclinical diabetic retinopathy to advanced diabetic eye disease may take from approximately 10 years in the most rapidly progressing
and unchecked cases to 30 years or more in cases that progress slowly. However, in many instances, retinopathy does not reach the final stages.

**Nonproliferative Diabetic Retinopathy**

Mild nonproliferative diabetic retinopathy is characterized by red dots and blots on funduscopic examination (Figure 2). The red dots are microaneurysms or microhemorrhages. Microaneurysms are simply small dilatations of the retinal capillaries and are the earliest visible signs of retinopathy.

Moderate nonproliferative diabetic retinopathy is characterized by microaneurysms, larger hemorrhages, red lesions, and cotton-wool spots or hard exudates, which are lipoproteins that have transudated rather than exudated through the vessel wall and have accumulated within the retina (Figure 3).

Severe nonproliferative or preproliferative diabetic retinopathy is characterized by the coexistence of a number of lesions (Figure 4). Examination of the fundus reveals venous irregularities such as beading, loop formation or reduplication, numerous cotton-wool spots, numerous hemorrhages and capillary dilatations, and intraretinal microvascular abnormalities. When 2 or more of these lesions coexist in the fundus, the chance of progressing to proliferative retinopathy within the next 6 to 12 months is 50%.

**Maculopathy**

Maculopathy encompasses macular edema and ischemic maculopathy. In macular edema, fluid accumulates within the retinal tissue in and around the macula and is often indicated by the presence of hard exudates.

In the case of incipient maculopathy, there is no loss of sight and probably no significant edema even in the center of the macula. However, as maculopathy progresses, there are larger exudates and then massive macular edema, with involvement of the entire macula and pronounced swelling in the center. When this develops (Figure 5), severe and almost completely irreversible loss of vision already has occurred.

**Proliferative Retinopathy and Retinal Detachment**

New vessel formation is the hallmark of proliferative retinopathy. New vessels may form at the center of the optic disc and grow outward, or they may grow from the periphery of the retina. New vessels bleed easily and give rise to preretinal hemorrhages (Figure 6) and eventually to the formation of fibrous tissue, which may cause traction on the retina and retinal detachment, the hallmarks of advanced diabetic eye disease. As shown in Figure 7, a massive hemorrhage causing sudden loss of vision and fibrous

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*Figure 3. Moderate Proliferative Diabetic Retinopathy with Red Lesions and Hard Exudates*

*Figure 4. Severe Nonproliferative (Preproliferative) Diabetic Retinopathy*

*Figure 5. Macular Edema and Hard Exudates*

*Figure 6. Proliferative Retinopathy with New Vessels and Hemorrhages*

*Figure 7. Retinal Detachment with Fibrous Tissue*
tissue pulling on the retina resulted in retinal detachment and eventually led to permanent loss of vision.

**PROGRESSION OF DIABETIC RETINOPATHY**

Among the factors that may be involved in the progression of diabetic retinopathy are pericyte loss, increased capillary permeability, retinal ischemia and new vessel formation, and endothelial cell death and capillary occlusion. Protein kinase C (PKC)-mediated release of vascular endothelial growth factor (VEGF) may be an underlying mechanism.

**PERICYTE LOSS**

In normal healthy retinal capillaries, there is a 1:1 ratio of endothelial cells to pericytes in the capillary wall, with the pericytes embedded within the basement membrane. As a smooth muscle cell equivalent, the pericyte may play a role in regulating vessel diameter, definitely participates in the synthesis and degradation of the basement membrane, and may be involved in controlling endothelial cell proliferation.

However, in established peripheral diabetic retinopathy, there is a selective loss of pericytes whereby some pericytes in the basement membrane disappear; they become “ghost” pericytes, leaving empty cavities in the basement membrane in their place. When pericytes are lost, there is an initial proliferation of endothelial cells within microaneurysms and within capillaries that then become hypercellular. Later, when the capillaries become blocked, all the cells are lost altogether.

Several mechanisms have been suggested as causes of pericyte loss, including the particularly high sensitivity of these cells to excess glucose, selective expression of genes related to apoptosis, and basement membrane alterations that make the microenvironment less hospitable to pericyte survival. One mechanism that definitely causes pericyte loss is the cell’s susceptibility to oxidative stress.

**INCREASED CAPILLARY PERMEABILITY**

Retinal capillaries in patients with diabetic retinopathy leak fluid and lipoproteins into the retina because of increased capillary permeability. It has not yet been fully established why these vessels become more permeable in diabetes. However, several causes have been identified, including PKC-mediated release of VEGF, which plays an important role in the pathogenesis of diabetic macular edema; the endothelial
expression of the PAL-E antigen, which is associated with plasmalemmal vesicles; and abnormal endothelial expression of occludin, which results in altered tight junctions of the blood-retinal barrier. Altered contribution from macroglial cells has also been suggested as a cause of increased capillary permeability.

The effect of PKC-mediated release of VEGF on vascular permeability is shown in Figure 8, in which an injection of VEGF into the eye of a research model results in massive leakage of fluorescein (left panel). By comparison, there was no leakage of fluorescein in the control model (right panel).

Protein kinase C-mediated release of VEGF is a target mechanism for the action of some drugs, including a PKC inhibitor that is currently in phase III clinical trials involving patients with diabetic retinopathy, diabetic macular edema, diabetic peripheral neuropathy, and diabetic nephropathy.

**RETINAL ISCHEMIA AND NEW VESSEL FORMATION**

Many possible reasons to explain why retinal ischemia leads to the formation of new vessels and contributes to the progression of diabetic retinopathy have been offered over the years. A recently reported explanation is that glucose induces endothelial alterations that lead to a pro-inflammatory and procoagulant capillary surface, which leads to endothelial apoptosis. This development initiates a vicious circle in that apoptosis can induce a pro-inflammatory and procoagulant capillary surface that leads to microthromboses, which lead to capillary occlusion and the development of ghost capillaries.

The progressive reduction in perfusion to the retina resulting from endothelial apoptosis and capillary occlusion leads to the formation of angiogenic factors and the growth of new vessels. These new vessels are particularly inept at perfusing the retina, are venous in origin, grow inside the surface of the retina, and certainly do not reach the peripheral areas of the retina. They are also fragile and tend to bleed easily, causing a host of problems.

Angiogenesis is probably triggered by this widespread ischemia and mediated by VEGF. In addition, there are several permissive factors, including activation of the renin-angiotensin system, hepatocyte growth factor, and insulin-like growth factor-1, that allow angiogenesis to occur more easily. Several inhibitory factors, such as pigment epithelium-derived factor, have also been isolated. An important inhibitory factor, angioatin, is released immediately after photocoagulation, the mainstay of treatment for proliferative diabetic retinopathy.

**CURRENT TREATMENT OF DIABETIC RETINOPATHY**

The most important medical approaches to the treatment of diabetic retinopathy are metabolic control of diabetes and control of blood pressure.

**GLYCEMIC CONTROL**

The Diabetes Control and Complications Trial (DCCT) demonstrated that intensive insulin treatment is as effective as primary prevention, reducing the risk of developing new retinopathy by 76%. The DCCT also showed that intensive treatment versus conventional treatment is also as effective as secondary prevention, reducing the risk of progression of mild retinopathy by 54% over an 8-year to 9-year period, the risk of developing severe nonproliferative diabetic retinopathy or proliferative diabetic retinopathy by 47%, and the need for laser treatment by 56%.

In a separate cost/benefit analysis, the DCCT investigators found that intensive therapy over a patient’s lifetime conferred global overall cumulative benefits, with 15 years of freedom from proliferative diabetic retinopathy, 8 years of freedom from diabetic macular edema, and 7.7 years of freedom from blindness. These results are encouraging, but they are not good enough. As such, they underscore the need for additional therapies.
Diabetes Control and Complications Trial data confirm that optimized metabolic control of diabetes prevents retinopathy but does not induce regression of existing retinopathy, may cause rapid progression of existing retinopathy if it is implemented suddenly (“early worsening”), and is expensive, costing approximately $20,000 per quality-adjusted life-year gained for patients with type 1 diabetes mellitus.\(^{12}\) According to the United Kingdom Prospective Diabetes Study (UKPDS), the equivalent amount is $40,000 per quality-adjusted life-year gained for patients with type 2 diabetes.\(^{13}\)

However, the benefits of optimized metabolic control are indisputable. As demonstrated in the UKPDS, every 1% reduction in glycated hemoglobin translates into a 37% reduction in microvascular endpoints.\(^{13}\)

**Blood Pressure Control**

Tight control of blood pressure is also crucial in treating diabetic retinopathy and preventing its progression. As demonstrated in UKPDS 38, reducing a patient’s blood pressure from 154/87 mm Hg to 144/82 mm Hg resulted in a 34% reduction in the risk of worsening diabetic retinopathy and a 47% reduction in the risk of worsening visual acuity.\(^{14}\)

A finding from the UKPDS 36 emphasizes the importance of tight blood pressure control: for every 10-mm Hg reduction in systolic blood pressure, there is a 13% reduction in cumulative microvascular risk.\(^{15}\)

**Photocoagulation**

The most effective treatment for diabetic retinopathy is laser photocoagulation. Panretinal photocoagulation is used to treat proliferative retinopathy; for maculopathy, focal and/or grid photocoagulation; and vitrectomy for vitreous hemorrhage and advanced diabetic eye disease.

Before the introduction of laser photocoagulation, blindness developed within 5 years in 50% of patients diagnosed with proliferative retinopathy.\(^{16}\) This statistic was reduced to 20% when laser photocoagulation was introduced\(^{16}\) and has remained at approximately 5% since 1991.\(^{17}\)

As demonstrated in the Early Treatment of Diabetic Retinopathy Study (ETDRS), laser photocoagulation reduces blindness at 5 years by more than 90% if the treatment is applied appropriately and in a timely manner to developing high-risk diabetic retinopathy.\(^{17}\) The ETDRS also demonstrated that focal/grid photocoagulation reduces moderate visual loss (doubling of visual angle) by 50% at 3 years in patients with macular edema.

Although photocoagulation is effective in preventing blindness, with laser photocoagulation considered by many to be as important to ophthalmology as antibiotics are to infectious disease, there are drawbacks. For instance, photocoagulation destroys photoreceptors, does not restore lost vision, has unknown mechanism(s) of action, and has potential severe adverse effects. Furthermore, focal/grid photocoagulation is not nearly as effective in treating macular edema as laser photocoagulation is in treating proliferative retinopathy.

**Newer Therapies**

Newer therapies for diabetic retinopathy that are currently being investigated include PKC inhibitors, somatostatin analogues, statins, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), growth hormone-receptor blockers, VEGF-receptor blockers, advanced glycation end product-receptor blockers, steroids such as triamcinolone, and thiamine.

**Somatostatin Analogues**

The rationale for treatment with somatostatin analogues is rooted in case reports of reversal of proliferative diabetic retinopathy with pituitary ablation and based on research findings that growth hormone levels are increased in diabetes, insulin-like growth factor-1 levels are increased in the vitreous of eyes with proliferative retinopathy, and somatostatin may slow florid proliferative retinopathy.

Several phase II clinical studies have been performed; one study reported that somatostatin effectively slowed the occurrence of vitreous hemorrhage.\(^{18}\) At present, 2 phase III studies evaluating the somatostatin analogue octreotide are under way, one in Europe and the other in the United States. Recruitment for another phase III study was completed recently.

**Statins, ACE Inhibitors, and ARBs**

Statins, known for reducing cardiovascular risk and mortality in patients with and without diabetes, are now being re-evaluated for their effects on diabetic retinopathy.

Angiotensin-converting enzyme inhibitors, along with ARBs, continue to be studied for their effects on diabetic retinopathy. The actions of both classes of agents
provide the rationale for pursuing a blockade of the renin-angiotensin system (RAS) as a therapeutic approach to retinopathy. For example, angiotensin promotes proliferation of vascular cells, an intraocular RAS is present in the human eye, and ACE inhibition reduces the retinal expression of VEGF. Furthermore, the ACE inhibitor captopril may reduce pericyte uptake of D-glucose, and ACE inhibitors and the ARB losartan prevent neovascularization in rodent models of retinopathy of prematurity.

The ACE inhibitor lisinopril has been studied in a large clinical trial involving patients with diabetic retinopathy. The study found that a decrease in systolic blood pressure of 3 mm Hg reduced the risk of 1-step progression of retinopathy on the EURODIAB scale by 50% and the risk of progression to proliferative retinopathy by 80%.19

Recruitment was completed recently for a 2 x 2, randomized, controlled trial comparing perindopril-indapamide with a placebo and intensive versus conventional glucose control by gliclazide in patients with type 2 diabetes mellitus, with the outcomes being composite microvascular and macrovascular events.20

Similarly, an ongoing randomized controlled clinical trial is evaluating the ARB candesartan in primary and secondary prevention of diabetic retinopathy in patients with type 1 diabetes mellitus and in secondary prevention of retinopathy in patients with type 2 diabetes mellitus.

**PROTEIN KINASE C INHIBITION**

The PKC inhibitors have generated a great deal of interest in recent years. When activated by hyperglycemia, PKC (particularly PKCβ) is linked to hyperglycemia-induced microvascular dysfunction that may result in the development of diabetic macular edema and other microvascular complications. Ruboxistaurin, a PKC inhibitor that specifically inhibits the β isofrom of PKC, is being investigated in phase III trials involving patients with diabetic retinopathy, diabetic macular edema, and diabetic peripheral neuropathy.

Animal studies have demonstrated that ruboxistaurin is a strong inhibitor of PKC-mediated VEGF release. Results of a phase IIB clinical study reported that ruboxistaurin was safe and well tolerated by patients with type 1 or type 2 diabetes mellitus when administered in doses of 16 mg or less twice daily for 30 days, was not associated with a significant increase in adverse events, had no adverse effect on immune function, and produced no change in glycemic control.22 The study also demonstrated that the agent ameliorated diabetes-associated abnormalities in retinal vascular function.

In a controlled study in which the primary endpoint was the development of diabetic macular edema involving or imminent threat to the center of the macula or the application of focal/grid photocoagulation, ruboxistaurin dosages of 4 mg, 16 mg, and 32 mg were compared with a placebo. Although none of the dosages reached statistical significance when compared with a placebo, a subgroup analysis revealed that patients who had already received photocoagulation benefited most (Figure 9), with a dosage of 32 mg being significantly better than a placebo (P < .05).

When dosages of 8 mg, 16 mg, and 32 mg were compared with a placebo for their effect on progression of diabetic retinopathy or photocoagulation and moderate visual loss (defined as a decrease of 15 or more letters), there was no statistically significant difference between ruboxistaurin and the placebo, although there was a favorable trend for 32 mg. Although the primary endpoint was not reached, the secondary endpoints did suggest that larger study samples and differently defined primary endpoints could demonstrate greater drug efficacy.

![Figure 9. Effect of Ruboxistaurin versus Placebo on Progression of Diabetic Macular Edema in Patients Who Received Photocoagulation](image)

*P < .05 vs placebo

**Progression of DME to ≤100 microns of the center of the macula.**

DME = diabetic macular edema; RBX = ruboxistaurin.

IN ADDITION to current animal and clinical research on various receptor blockers and intravitreal steroid injections and implants, experimental work has been done on the effects of thiamine on carbohydrate metabolism and its role in diabetic retinopathy. One study in particular is worth noting, as it showed that benfotiamine, a thiamine analogue, blocked 3 major pathways of hyperglycemic damage and inhibited experimental retinopathy in diabetic rat models.24

CONCLUSIONS

Diabetic retinopathy accounts for approximately 90% of blindness in patients with type 1 diabetes mellitus and approximately 33% of blindness in patients with type 2 diabetes mellitus. With the increasing prevalence of diabetes worldwide, the number of people with diabetic retinopathy will also increase.

Although improved control of glycemia and blood pressure and the use of photocoagulation are the mainstays of treatment, additional therapies are needed to prevent the development and progression of diabetic retinopathy.

Suspected factors involved in the progression of diabetic retinopathy include pericyte loss, increased capillary permeability due to PKC-mediated release of VEGF, retinal ischemia, and new vessel formation. Therefore, therapies directed at blocking or attenuating these factors may be effective.

Newer therapies that are being investigated include PKC inhibitors, somatostatin analogues, ACE inhibitors, ARBs, statins, and various receptor blockers. PKC inhibitors have generated a great deal of interest in recent years. Ruboxistaurin, a PKC inhibitor with specific inhibition of the β isoform of PKC, is being evaluated in phase III clinical trials in patients with diabetic retinopathy and diabetic peripheral neuropathy. Statins, ACE inhibitors, and ARBs are also being investigated in ongoing or recently completed primary and secondary prevention trials in patients with diabetic retinopathy. Results of these trials and those evaluating ruboxistaurin and other therapies are eagerly awaited.

Q & A HIGHLIGHTS

Member of the audience: The DCCT/EDIC (Epidemiology of Diabetes Interventions and Complications) study has shown the phenomenon of metabolic memory. That is, patients with good glucose control in the DCCT, but not particularly good glucose control for the past 8 to 10 years, were still relatively resistant to the development of neuropathy and macrovascular complications. Do you see that in retinopathy? Are those data available for retinopathy? Could you speculate on a mechanism whereby very early control can help prevent complications 20 years later?

Dr Porta: The data confirm that the phenomenon applies to retinopathy. In fact, when the first EDIC results were published, there was still a 50% reduction in the onset and progression of retinopathy in patients with tight glucose control before the study was completed. It definitely works on retinopathy.

As for mechanisms, I think it’s anybody’s guess. My personal view is that perhaps advanced glycation end products or other substances accumulate in the basement membranes of capillaries, but are not easily metabolized or removed from the tissues. This suggests that if we can slow down the early accumulation of these compounds, we could slow the progression of retinopathy; however, there is not much experimental evidence.

There is some evidence for metabolic memory in cell cultures that were kept in low glucose and then in high glucose for half the time; there was less evidence of cell damage. However, what happens in cell cultures happens within days, whereas metabolic memory and complications take years to occur in humans.

Dr Saudek: There were some older studies in dogs before the DCCT that found that poor glycemic control followed by very good glycemic control did not protect against retinopathy. In other words, damage was already done, and secondary prevention by good glycemic control was ineffective. That observation in a sense mandated that the DCCT include a secondary prevention arm, in which patients with mild but definite established retinopathy were randomized to tight or “conventional” control. In fact, the DCCT did not confirm the earlier findings in dogs, showing instead that tight control was effective even when retinopathy was already established.

Now I’d like to ask quite simply how laser photocoagulation works. Those of us who are not ophthalmologists tend to think that it is simply by photocoagulating, essentially cauterizing leaky vessels, but we are told that this is not the case.

Dr Porta: Actually, we don’t hit the vessels because if we did, they would rupture and bleed. What we do is burn the peripheral ischemic retina.
There are 3 hypotheses: obliterate the ischemic tissue, so there is no longer any production of angiogenic factors; drill holes in the pigment epithelium to increase oxygenation from the choroid circulation, which is much more developed than the retinal circulation; and use photocoagulation possibly to stimulate the pigment epithelium and release pigment epitheli-um-derived factor, which is antiangiogenic. It may be that all 3 of these mechanisms work together, but no one has provided conclusive evidence that one of them prevails over the other.

Member of the audience: Could you comment on the deeper layers of the retina such as the inner and outer nuclear layers and the internal limiting membranes? Because Müller’s glial cells form tight junctions with photoreceptor cells, in addition to connections with the blood vessels, perhaps there are some changes that precede the visible changes in the superficial vessels.

Dr Porta: I did not address the neuroretina and the glia because of time constraints, but you raise an interesting point. There are data suggesting that glial cells may interact with vascular cells, and they may help tighten the junctions and keep the blood-retinal barrier intact. The data are very preliminary at this time, but the possible interaction between glial and vascular cells is something that should be considered.

REFERENCES