# Diabetic Retinopathy

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This is the ninth in a series of articles based on presentations at the American Diabetes Association's 67th Scientific Sessions, 22–26 June 2007, Chicago, Illinois, that discuss aspects of diabetic retinopathy.

A number of studies presented at the ADA meeting addressed aspects of the clinical epidemiology of diabetic eye disease. Saaddine et al. (abstract 819) used National Health Interview Survey and census data to project that the prevalence of diabetic retinopathy in the U.S. will increase from 5.8 to 17.7 million people from 2005 to 2050, with retinopathy threatening vision projected to increase from 1.3 to 3.7 million over this time. (Abstract numbers refer to the American Diabetes Association Scientific Sessions, *Diabetes* 56 [Suppl. 1], 2007.) Cataracts, Saaddine reported, will likely more than double in prevalence, and there will be a 12-fold increase in the number of Hispanics with diabetes ≥65 years old who have glaucoma.

Emanuele et al. (abstract 95) reported the presence of clinically significant macular edema in 11% of 536 diabetic individuals, with prevalence more than twice as great in Hispanic and African-American as that in non-Hispanic White patients. In multivariate analysis, diastolic blood pressure, duration of diabetes, and the urine albumin-to-creatinine ratio were additional contributory factors. Sibal and Home (abstract 832) studied 404 type 1 diabetic patients followed for 9 years, finding retinopathy to be associated with higher diastolic blood pressure, LDL cholesterol and triglyceride, and A1C levels.

A study by Tapp et al. (abstract 1,020) further suggested the complexity of the relationship between diabetes and retinal abnormalities. Tapp et al. studied 1,196 individuals having retinal examination in 2000 and in 2005. Of those who progressed to diabetes, evidence of diabetic retinopathy was present at baseline in 12.7%, while among those who did not develop diabetes, 5.7% had retinal abnormality at baseline, suggesting that mild background retinopathy might be a marker of future diabetes risk.

At a symposium on aspects of diabetic retinopathy, Massimo Porta (Turin, Italy) reviewed approaches to control of the disorder's onset and progression. Two of every 100,000 individuals in the population become blind because of diabetic retinopathy every year, he noted. He pointed out that the Diabetes Control and Complications Trial (DCCT) and the UK Prospective Diabetes Study (UKPDS) both showed benefit of glycemic treatment, in type 1 and type 2 diabetes, respectively, in reducing both the development and progression of diabetic retinopathy. There was a decrease of approximately one-third in these complications for every 1% reduction in A1C, with additional benefit shown with blood pressure–lowering treatment. "But what happens, really," he asked, in attainment of targets? Less than half of people receiving oral agents and only approximately one-quarter of individuals receiving insulin achieve glycemic goals, with similar low attainment of blood pressure goals, and "very, very few patients" are able to reach both of these targets. Porta stated that "the situation is bleak" for good metabolic control, and that efforts to improve control are "easier to preach than to practice" (1) despite increasing expenditures on glucose- and blood pressure–lowering pharmacotherapy.

There may be genetic components to complications; 43% of the DCCT patients in the worst A1C quintile did not develop retinopathy, whereas 10% of those in the best quintile did develop retinopathy. "Metabolic control is not the answer," he concluded, with both DCCT and UKPDS data suggesting that even with excellent glycemic control, the development of complications is simply delayed rather than prevented. Careful screening is important (2); dilated eye examinations are crucial to identifying patients with diabetic retinopathy. "We sorely need some more specific approaches," Porta concluded, "to preventing the onset and progression of retinopathy." Asked about adjunctive treatment approaches, he was cautious as to whether existing agents such as aspirin, angiotensin inhibition, and fibrates would have benefit for retinopathy, "although the results are intriguing."

Thomas Gardner (Hershey, PA) discussed the neural and glial cell changes occurring in the diabetic retina, addressing the question of how diabetes impairs vision and what diabetic retinopathy actually represents. "The concept that this is a microvascular disease is incomplete," he said, suggesting that it "ignores the forest for the trees" (3,4). In addition to blood vessels, the retina is composed of glial cells, the photoreceptor and retinal ganglion cells involved in vision, including astrocytes surrounding blood vessels and playing roles in nutrition and removal of waste products; microglial cells, the resident macrophages protecting nerve cells; and retinal pigment epithelial cells. In diabetes, this entire network of cell-cell interactions is disrupted, leading to disease. Diabetes alters the function and structure of retinal glia, with astrocyte regulation of the blood-retinal barrier impaired. The normal astrocyte metabolism of glutamate and glutamine as neurotransmitter and as energy source is altered. Retinal neurons now are known to die by apoptosis fairly early in the course of diabetes, changing prior concepts that neuronal death occurred late in the course of diabetic retinopathy. Retinal ganglion cell numbers are decreased, particularly in the peripheral retina of diabetic retinopathy. Microglia are more prominent in the diabetic retina and presumably

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**Abbreviations:** DCCT, Diabetes Control and Complications Trial; UKPDS, UK Prospective Diabetes Study.

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## NEWS FROM THE FOOD AND DRUG ADMINISTRATION

*From time to time, new announcements by the FDA pertaining to aspects of diabetes treatment will be highlighted in this section.*

The Winter 2008 edition of the FDA drug safety newsletter describes potential adverse effects of three medications relevant to the treatment of diabetes. Three phophodiesterase type 5 inhibitors used for treatment of erectile dysfunction, sildenafil citrate (Viagra), vardenafil hydrochloride (Levitra), and tadalafil (Cialis), have been reported in 113 cases to be associated with sudden hearing loss, with 29 cases more closely analyzed showing that tinnitus may accompany this effect. Two patients took the agent twice and experienced hearing loss on the second occasion as well, suggesting an almost certain causal relationship.

Thirty reports of acute pancreatitis in patients who received exenatide were described, occurring, on average, 34 days (range 4-300) after starting treatment but occurring in six patients soon after the dose of exenatide was increased from 5 to 10 μg twice daily. Many patients had contributory factors (other than diabetes itself), including obesity, gallstones, severe hypertriglyceridemia, alcohol use, and use of other medications reported to be associated with pancreatitis. However, in 22 cases, symptoms improved after exenatide was discontinued, and in 3 cases symptoms recurred with reinitiation of treatment. Finally, duloxetine, used for painful diabetic neuropathy, was reported to be associated with cases of hyponatremia, gastrointestinal bleeding, and urinary retention; none of these are new findings.

While recognizing that both the frequency of these adverse effects and whether there definitely is a causal relationship between them and given medications are not fully known, it remains important to be aware of all the potential effects of a given agent when giving it to a diabetic patient.

The complex full document is available at http://www.fda.gov/OHRMS/DOCKETS/98fr/2008-D-0118-gdl.pdf.

release cytokines, playing a role in retinal inflammation and damage, and potentially offering a therapeutic target.

The concept of neurodegeneration of the diabetic retina has been shown in all species studied, Gardner said, with clinical studies showing that even with mild diabetic retinopathy there is loss of nerve fibers. This leads to reduced color vision, impaired dark adaptation, impaired contrast sensitivity, and visual field defects. Macular edema can, in fact, be thought of as a form of neurovascular degeneration. Thus, although the vascular changes are prominent, this does not represent the full explanation of diabetic retinopathy. Furthermore, even patients with minimal evidence of vascular abnormality and relatively normal visual acuity often show significant abnormalities with more subtle measurements of retinal and visual function. The cysts present in macular edema also may scatter light, interfering with vision perception. "The retina is neural tissue," Gardner said, "and ultimately visual impairment must result" from damage to this tissue.

An unanswered question is of the relationships between the neural retina and vascular tissue. In proliferative retinopathy, new vessels regress when laser treatment is administered to the neural retina, and abnormalities of neural function predict the development of diabetic retinal vascular lesions, suggesting a close association between neural and vascular elements of the disease. The blood retina barrier appears to be disrupted in diabetic retinopathy, with both neural and vascular causes. Better quantification of retinal function and structure may be useful in clinical assessment of diabetic retinopathy, and the multifocal electroretinogram already has been shown useful as a research tool. There is a need to maintain the viability and function of viewer cells, blood vessels, glial cells, and neural elements. Furthermore, animal models have a number of limitations, and more accurate assessment of the abnormalities of the retina in clinical diabetic retinopathy may allow improved approaches to treatment. Gardner suggested that treatments that reduce the effects of vascular endothelial growth factor (VEGF) might be considered "a probe, if you will, to understand the physiology of the retina," noting that VEGF inhibition could damage the neural retina; therefore, great care is needed in pursuing this approach.

In a study presented at the ADA meeting addressing the relationship between vascular factors and retinopathy, Schernthaner et al. (abstract 98) noted that while endothelial progenitor cell levels are decreased in people with macrovascular disease, there is evidence that their levels are increased in states of pathologic neoangiogenesis, as seen in proliferative diabetic retinopathy. They studied 60 diabetic individuals with and 60 without retinopathy; half of each group had macrovascular disease. Among those without retinopathy, endothelial progenitor cells were reduced by 37%, and among those with macrovascular disease, the number of endothelial progenitor cells decreased progressively with worsening levels of retinopathy. Among those not having macrovascular disease, however, the group with severe proliferative diabetic retinopathy showed an increased level of endothelial progenitor cells. A clinical study similarly suggested discrepancy between risk factors for retinopathy and nephropathy, with Conway et al. (abstract 823) reporting findings from a 16-year prospective study of 448 people with childhood-onset type 1 diabetes with a mean diabetes duration of 19 years. The likelihood of proliferative retinopathy more than doubled in women and in men whose hemoglobin exceeded 16.1 and 16.5 g/dl, respectively, contrasting with evidence that progression of diabetic kidney disease is associated with anemia. In a study that suggests a potential approach to treatment, Haurigot et al. (abstract 97) addressed the question of whether insulin-like growth factor (IGF)-1 plays a role in diabetic retinopathy. Nondiabetic mice overexpressing IGF-1 in the retina showed increased vascular leakage of both low–molecular weight compounds and of proteins, with altered expression of tight junction complex proteins, so that increased intraocular IGF-1 may in part mediate breakdown of the blood-retinal barrier.

Rakesh Chibber (Kings College, London, U.K.) discussed the role of leukocytes and inflammation in retinopathy. Capillary occlusion is an early clinical feature of diabetic retinopathy that leads to retinal nonperfusion and subsequent damage, with this form of nonperfusion

potentially being reversible. Leukocytes of individuals with diabetic retinopathy show decreased deformability and increased adhesion to retinal capillaries leading to leukostasis, which appears to play a role in retinopathy, both in animal studies and, based on studies with laser ophthalmoscopy, in patients with diabetes as well. Leukocytes are present within microaneurisms and may play roles in the development of these abnormal vessels. Diabetes leads to increased leukocyte adhesion molecule expression, and leukocytes isolated from diabetic people, when incubated with retinal epithelial cells, show increased adhesion. Chibber suggested that in diabetes modified leukocyte glycoproteins may mediate this effect.

Increased galactose formation in diabetes may alter these leukocyte glycoproteins. Galactose feeding in animal models mimics features of diabetic retinopathy. Plasma glucose levels modify a key leukocyte intracellular glycosylating enzyme, core 2 GlcNAc ($\beta$1,6) transferase (5), contributing to increased leukocyte adhesion, with additional regulatory factors mediating these effects, in particular inflammatory cytokines such as tumor necrosis factor (TNF)-$\alpha$ (6). The mechanisms of effect of high glucose and TNF-$\alpha$ may involve activation of PKC$\beta$ (7), perhaps involving oxidative stress, activation of which can be inhibited with agents such as ruboxistaurin. Animals overexpressing PKC$\beta$2 demonstrate increased phosphorylation of the core 2 transferase, with activation of the transferase leading to increased glycosylation of leukocyte molecules in turn associated with increased adhesion levels. Potential interventions to address this process include control of blood glucose, antagonists to TNF-$\alpha$, antioxidants, and PKC$\beta$ inhibition. Chibber pointed out that these data suggest that ruboxistaurin might be better used early in the prevention of diabetic retinopathy, rather than later in the natural history of the disorder. A natural plant steroid that inhibits core 2 transferase has been discovered, and appears to offer promise as a potential treatment of the increased leukostasis mediating capillary occlusion in diabetes. Importantly, leukostasis may be associated with other diabetic complications, with evidence of a worsening effect on diabetic cardiomyopathy (8), so that this approach may have a variety of benefits in treatment of diabetic patients.

Several studies presented at the ADA meeting addressed aspects of inflammation in diabetic retinopathy, which may include abnormalities of leukocyte function. Singh et al. (abstract 476) injected insulin-loaded hydrogels subconjunctivally in diabetic rats, which resulted in normalization of retinal synaptic protein and c-Jun N-terminal kinase expression, suggesting that insulin itself has potential as a pharmacologic approach to ameliorating the degenerative and inflammatory responses in diabetic retinopathy. Navaratna et al. (abstract 99) reported that the extracellular protease urokinase plasminogen activator is upregulated in a diabetic rat model, and that an inhibitor of this protease reduced retinal vascular permeability, suggesting a potential therapeutic target.

Michael Ip (Madison, WI) discussed steroids, VEGF, and other novel intravitreal approaches for diabetic macular edema. Diabetic retinopathy accounts for 12% of blindness in the U.S., with macular edema as the major cause of vision loss. Laser photocoagulation has been the mainstay of treatment, based on the concept that intervention is appropriate for clinically significant macular edema, which is defined based on the area of involved macula and its proximity to the fovea. The Early Treatment Diabetic Retinopathy Study of this approach showed a 50% reduction in vision loss; however, 12% of treated eyes still lost three or more letters of vision on the eye chart, and <15% of treated eyes improved three or more letters, with multiple treatments needed, potentially causing the adverse consequences of leaking microaneurisms near the fovea, accidental burns, and scar expansion.

In individuals failing to respond to photocoagulation, a variety of different approaches have been attempted, with intravitreal corticosteroids and anti-VEGF agents most widely studied. Steroids decrease inflammation, as well as retinal capillary permeability and macular edema, with intravitreal injection appearing to be a safe and effective approach. Injection of 4 mg triamcinolone in a 0.1-ml volume has been used over the past 8 years, with ocular tomographic measurement showing rapid and persistent improvement in macular edema to a degree not previously attainable. Potential adverse consequences, however, include retinal detachment, hemorrhage, infection, cataract, and glaucoma. A clinical trial has been performed by the Diabetic Retinopathy Clinical Research Network (DRCR Net), with results pending. A surgically implanted steroid-releasing device has also been studied, with a trend to improvement in visual acuity in a 3-year randomized controlled trial, but safety issues include high rates of development of glaucoma and cataract, with infections occurring at increased frequency.

The use of intravitreal administration of VEGF inhibitors is based on evidence of the role of this growth factor in diabetic retinopathy. VEGF has been identified as having a major role in the genesis of diabetic retinopathy, with increased levels in experimental diabetes and in the vitreous and aqueous of people with diabetic retinopathy (9). Intravitreal VEGF administration in experimental animals duplicates many features of diabetic retinopathy. Hence, agents to attenuate VEGF action "appear to be a very attractive target," as they both reduce permeability, contributing to macular edema, and decrease the vascular proliferation of neovascularization. Pegaptanib is FDA-approved for age-related macular degeneration. It is an oligoribonucleotide enantiomer binding isoform 165 of VEGF in the extracellular space, and does not exhibit the immunogenicity that would accompany administration of an antibody having this effect. In a phase-2 30-week study of 172 individuals with diabetic macular edema receiving pegaptanib versus placebo, vision improved on average to 20/50 vs. 20/63, with 34% of treated patients vs. 10% of control subjects gaining 10 letters on the eye chart. Central retinal thickness decreased by 68 $\mu$m versus increasing by 4 $\mu$m, and laser photocoagulation was required in 25% vs. 48% of treated people. Improvement occurred in neovascularization as well (10). A number of additional anti-VEGF compounds are being studied. Ip concluded that although laser photocoagulation is safe and effective, there are many circumstances in which it fails to optimally improve diabetic retinopathy, with these new approaches offering new ways of improving outcome in diabetic patients. Combination approaches using photocoagulation after administration of anti-VEGF agents may be of particular benefit in complex cases.

A number of studies presented at the ADA meeting suggested additional approaches for the treatment of diabetic retinopathy. Gonzalez et al. (abstract 100) compared effects of panretinal photocoagulation with those of intravitreal administration of pegaptanib in high-risk proliferative diabetic retinopathy. Complete regression was seen in 1 of 10 eyes

receiving photocoagulation at 3 and 6 weeks, but in 9 and 8 of 10 eyes receiving pegaptinib at the respective times; there was an increase versus a decrease in mean foveal thickness and macular volume in the photocoagulation versus pegaptanib groups, which is suggestive of an effect on macular edema. Sheetz et al. (abstract 481) analyzed the effect of the PKCβ inhibitor ruboxistaurin (32 mg daily) versus placebo on 685 diabetic individuals who had not had prior photocoagulation and who had moderately severe to very severe nonproliferative diabetic retinopathy with visual acuity at least 20/125. The results showed a greater improvement in visual acuity as well as a reduction in macular edema. Rask-Madsen and King (abstract 96), recognizing that the PKCβ-selective inhibitor ruboxistaurin did not stop progression of proliferative retinopathy in clinical trials, examined whether VEGF action is mediated by the α, δ, or ε isoform of PKC, which also are activated in the retina with diabetes. Decreased expression of the ε isoform of PKC with small interfering RNA reduced VEGF effect, while PKCα appeared to increase it, suggesting that specific PKCε inhibitors may have benefit in the treatment of diabetic proliferative retinopathy

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