# Diabetic Retinopathy and Diabetic Neuropathy

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This is the sixth in a series of articles on presentations at the American Diabetes Association's 66th Scientific Sessions, Washington, DC, 9–13 June 2006, reviewing aspects of diabetic retinopathy and neuropathy and lower extremity vascular disease.

Maria Grant (Gainesville, FL) discussed the treatment of diabetic retinopathy with insulin-like growth factor (IGF)-1 antagonists, reviewing a number of lines of evidence. There is evidence of hypersecretion of growth hormone in diabetes. Furthermore, diabetic retinopathy has been seen following administration of growth hormone to individuals without diabetes (1); there is evidence of reduction in diabetic retinopathy in growth hormone–deficient individuals (2), and pituitary ablation has been shown to have a benefit in reducing diabetic retinopathy progression (3). A number of studies have addressed the potential benefit of somatostatin and its analogs in the treatment of diabetic retinopathy (4). IGF-1 causes a phosphatidylinositol 3-kinase–mediated increase in vascular endothelial growth factor (VEGF) expression by retinal pigment epithelial cells leading to effects on retinal endothelial cells. Somatostatin reduces circulating IGF-1, as well as acting directly in the retina to reduce VEGF production and to decrease retinal neovascularization, with three of the five somatostatin receptor subtypes having been identified in the retina.

Octreotide is an eight–amino acid synthetic peptide acting at somatostatin receptors. In a 15-month study of the effect of administration of octreotide to diabetic individuals with severe nonproliferative (NPDR) or early proliferative (PDR) diabetic retinopathy, 11 patients receiving treatment were compared with 12 control subjects, with 5 vs. 40% requiring panretinal photocoagulation over 15 months (5). In a similar study, among nine patients with persistent high-risk PDR after panretinal photocoagulation treated with 100 mcg octreotide three times daily for 36 months, there was one small vitreous hemorrhage, while nine control subjects experienced five dense hemorrhages requiring surgery, with evidence that octreotide led to preserved visual acuity (6).

The long-acting acetate of octreotide is an injectable depot formulation maintaining circulating levels for 1 month, used clinically in treatment of acromegaly at typical doses of 10–20 mg monthly. There is case-report evidence of a clinical benefit in diabetic retinopathy (7). Grant reviewed two phase III randomized controlled clinical trials, in individuals with moderate and severe NPDR not requiring laser therapy treated with 30 mg octreotide monthly: Study 804 of 313 patients carried out in the U.S., Brazil, and Canada comparing 30 mg versus placebo and Study 802 of 585 patients carried out in Europe comparing 30 mg, 20 mg, and placebo. The majority of enrolled individuals had type 2 diabetes, most had microalbuminuria, and the mean A1C was 8–8.4%. In Study 804, there was a delay in the time to progression and a 40% reduction in the likelihood of developing PDR but no difference in macular edema. Serum IGF-1 levels were suppressed by ~50%, although they appeared to increase during the period of observation. In Study 802, however, although IGF-1 levels were suppressed, there was no significant delay in time to progression to PDR at either dose and no difference in macular edema, with the 30-mg dose associated with improvement in visual acuity at a level of significance of 0.03; although given the multiple comparisons, their statistical criterion was $P < 0.025$. There was no difference in albuminuria in either study. Adverse effects of treatment included 70 vs. 33% incidence of diarrhea, 44 vs. 19% of cholelithiasis, 43 vs. 38% of hypoglycemia, and 20 vs. 12% of abdominal pain. A1C levels tended to be stable and were not influenced by treatment with octreotide. At this point, then, there is a suggestion of benefit in some individuals with diabetic retinopathy, but octreotide cannot be recommended for general use in the condition.

Paul Dodson (Birmingham, U.K.) discussed the complex relationship between dyslipidemia and diabetic retinopathy and the question of whether lipid-lowering treatment improves diabetic retinopathy. Combined hyperlipidemia is associated with peripheral ischemia, cotton wool spots, and exudates. Familial hypercholesterolemia is not directly associated with retinopathy, although it is a risk factor for retinal vein and arterial occlusion, with individuals having high degrees of carotid stenosis sometimes developing an ocular ischemic syndrome. The combination of both hyperlipidemia and diabetes is associated with retinal abnormality. In the Atherosclerosis Risk In Community (ARIC) Study, carotid intima-media thickness was associated with diabetic retinopathy. There is a significant increase in LDL cholesterol with worsening grades of retinopathy (8). As cholesterol quartile increases, there is increased risk of maculopathy and proliferative retinopathy. In the Diabetes Control and Complications Trial, the highest quintile of LDL cholesterol showed a doubling in likelihood of clinically significant macular edema and hard exudates (9). LDL, par-

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**Abbreviations:** AGE, advanced glycation end product; ARIC, Atherosclerosis Risk In Community; CVD, cardiovascular disease; ICAM, intracellular adhesion molecule; IGF, insulin-like growth factor; NFκB, nuclear factor-κB; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; PKC, protein kinase C; STZ, streptozotocin; VEGF, vascular endothelial growth factor.

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ticularly if glycated or oxidized, may be associated with decreased cell growth, potentially mediating some aspects of diabetic retinopathy. An association has been reported between statin use and lower risk of development of vitreous hemorrhage (10), and several small studies have suggested that pravastatin (11) and atorvastatin (12) improve some aspects of diabetic retinopathy.

Statins may lower intraocular pressure, and some studies have shown that fibrates decrease retinal exudates. Results of two large clinical trials are of interest. In CARDS (Collaborative Atorvastatin Diabetes Study), 2,838 individuals with diabetes with 30% diabetic retinopathy prevalence at baseline were randomized to atorvastatin versus placebo, with a nonsignificant trend to decrease in requirement for laser treatment in 17.9 vs. 20.5% at a mean 3.9-year follow-up (13). In the FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) Study, 9,795 participants aged 50–75 years with type 2 diabetes not taking statin therapy were randomized to placebo versus fenofibrate. At baseline, 8% had diabetic retinopathy; at 5 years of follow-up, 253 control subjects (5.2%) versus 178 (3.6%) individuals allocated fenofibrate needed one or more laser treatments for retinopathy, a highly significant reduction, concordant with the reduction in albuminuria reported in the study (14). Thus, there is intriguing evidence of a benefit of lipid-lowering therapies on diabetic retinopathy, suggesting an additional rationale to the well-established benefit in cardiovascular disease (CVD) prevention.

Gabriella Tikellis (Melbourne, Australia) discussed the concept of the eye as a risk marker for CVD. The association of retinal microvascular abnormality was first reported more than a century ago (15), with studies in the 1930s showing that the severity of retinal microvascular abnormality was predictive of 3-year mortality in individuals with hypertension (16). Tikellis described the retinal circulation as a "window to the systemic circulation," with retinal vessels sharing many characteristics with those of other organs. Focal or localized retinal vascular findings may include focal arteriolar narrowing, arteriovenous nicking, arteriolar wall thickening, and diabetic retinopathy–like lesions, including hemorrhages, microaneurisms, and cotton-wool spots, while macular edema may be regarded as a sign of generalized abnormality of vascular permeability. Fundoscopic exam is, however, imprecise (17), and easily detectable but more severe changes such as hemorrhages are infrequent in individuals with hypertension, leading to the use of systematic retinal vascular grading performed by ophthalmologists, using subjective assessment of retinal photographs, or, more recently, the development of computer techniques to allow rapid and objective assessment of retinal vascular characteristics, such as the degree of arteriolar branching, bifurcation angles, and venous tortuosity. Large datasets from population-based studies including the ARIC Study, the Beaver Dam Eye Study, the Blue Mountains Eye Study, the Wisconsin Epidemiological Study of diabetic retinopathy, the Multi-Ethnic Study of Atherosclerosis, and the Rotterdam Study have shown up to a 14% prevalence of retinal abnormality, having strong association with blood pressure (18), with a linear relationship between blood pressure and the degree of retinal arteriolar narrowing (19). There is also an association of smaller arteriolar-venous ratio with increased likelihood of diabetes (20) and of retinal vessel caliber to the likelihood of progression of diabetic retinopathy (21). More specific abnormalities, such as cotton wool spots, were associated with a ninefold greater increase in stroke in the ARIC Study (22). Further analysis of this study showed that risk of heart failure was markedly increased in individuals with retinal abnormality, with the presence of hypertension not adding further risk in multivariate analysis of individuals with diabetic retinopathy (23). Finally, in the Beaver Dam Study, retinal microvascular abnormality was associated with coronary mortality (24). Tikellis concluded that there is strong and consistent correlation of blood pressure with a number of retinal findings and some evidence of association with CVD; thus, the retinal exam, particularly when making use of detailed assessment of retinal photographs, may add independent information about risk and prognosis.

A number of research presentations at the American Diabetes Association Scientific Sessions addressed aspects of diabetic retinopathy. Zhang et al. (abstract 992) analyzed the NHANES (National Health and Nutrition Examination Survey) 1999−2002, finding visual acuity better than 20/200 but <20/40 among 5% of individuals with and 2.3% of those without diabetes, while 1.3 and 0.6%, respectively, were blind (visual acuity ≤20/200) (abstract numbers refer to the American Diabetes Association Scientific Sessions, *Diabetes* 55 [Suppl. 1], 2006). Further information from this survey shows that, among individuals with diabetes aged ≥65 years, 16 and 9% had visual acuity <20/40 with and without correction (25). Coleman et al. (abstract 229) analyzed the risk of developing diabetic retinopathy among 1,949 individuals enrolled in the UK Prospective Diabetes Study who did not have diabetic retinopathy at baseline, finding association with A1C, blood pressure, and urine albumin >300 mg/l, while smoking and increased age were associated with lower risk. Rubino et al. (abstract 823) reviewed medical records from clinics in France, Italy, Spain, and the U.K. (mean of 41 clinics/country), finding respective prevalences of diagnosed diabetic retinopathy of 11, 18, 10, and 20% in general practices. Of 752 patients with diabetic retinopathy, ~40% had mild, 16–28% moderate, and 2–4% severe NPDR, and 20–30% had PDR. Skrivarhaug et al. (abstract 967) studied 294 individuals developing type 1 diabetes before age 15 in Norway between 1973–1982, with retinal imaging in 1989–1990 showing no diabetic retinopathy in 194 individuals, 163 of whom had diabetic retinopathy in 2002–2003. PDR was found in the second set of photographs in 31 individuals, with significant predictors the presence of retinopathy at the initial exam, A1C >9.9%, and triglyceride >141 mg/dl. The authors pointed out the importance of modifiable risk factors. Sun et al. (abstract 825) studied diabetic retinopathy among 98 individuals who received the Joslin Clinic 50-year Medal for living ≥50 years with type 1 diabetes, finding that 7% had no diabetic retinopathy, 39% had mild, 8% moderate, and 1% severe NPDR, while 42% had PDR. In addition, 63% had visual acuity 20/20 or better. Neither diabetic retinopathy severity nor visual acuity correlated with duration, age of onset, A1C, lipids, BMI, C-peptide, GAD antibodies, or HLA DQB1, DQA1, and DRB1 genotypes, suggesting that a large minority of individuals with type 1 diabetes are protected against complications by factors yet to be characterized.

Several studies addressed potential mechanisms of diabetic retinopathy. Al-Shabrawey et al. (abstract 15-LB) studied streptozotocin (STZ)-induced diabetic mice, finding increased albumin extravasation from retinal vessels, suggesting abnormality of the blood-retinal barrier and

increased retinal vascular leukocyte adhesion and intracellular adhesion molecule (ICAM)-1 expression, in conjunction with increased retinal reactive oxygen species production determined in sections using dichlorofluroscein imaging. Diabetic mice either with deletion of the NAD(P)H oxidase subunit gp91 phox gene or treated with the NAD(P)H oxidase inhibitor; apocynin, however, had normal reactive oxygen species formation, ICAM-1 expression, leukostasis, and blood-retinal barrier. The retrovirus-associated DNA sequence (*ras*) originally isolated from Harvey murine sarcoma viruses (H-*ras*) encodes phosphohydrolase G-proteins that hydrolyze GTP to GDP, acting to regulate aspects of cellular growth and differentiation. Kowluru et al. (abstract 227) reported that H-*ras* expression increases after exposure of bovine retinal endothelial cells to high glucose and that overexpression of H-*ras* increases the effect of glucose exposure on nitric oxide, nuclear factor-κB (NFκB), and apoptosis, while retinal endothelial cells overexpressing an inactive *ras* mutant have reduced effect of high glucose on these processes. Mu et al. (abstract 822) found that PDR was associated with increased vitreous and serum levels of angiopoietin-2, which appears to downregulate new blood vessel branching and sprouting, antagonizing the effect of angiopoietin-1 at the TIE-2 endothelial cell receptor. Angiopoeitin-2 levels may correlate with the degree of angiogenic activity in PDR, suggesting an additional pathway to that of VEGF, which may play a role in diabetic retinopathy.

Several studies in animal models suggest potential new therapies for diabetic retinopathy. Chen et al. (abstract 16-LB) studied the effect of erythropoietin on oxygen-induced retinal vascular degeneration in a neonatal mouse model, showing that hyperoxia suppressed retinal erythropoietin mRNA more than fivefold, with a rebound >10-fold increase after subsequent room air exposure, with systemic erythropoietin administration before and during hyperoxia reducing retinal vasoobliteration and subsequent neovascularization, although administration of erythropoietin after oxygen exposure failed to have a protective effect. Mogami et al. (abstract 226) studied retinal abnormality in the spontaneously diabetic Torii (SDT) rat model of type 2 diabetes, finding that the angiotensin II receptor blocker candesartan reduced cataract formation and vascular permeability assessed by retinal fluorescein angiography, with decreased lens and vitreous levels of the advanced glycation end product (AGE) pentosidine and decreased retinal VEGF mRNA expression, all in a dose-dependent manner, with the authors speculating the AGE-reducing effect to be primary. Lee et al. (abstract 504) reported that magnolol, a polyphenolic compound derived from the bark of Houpu magnolia used in Chinese traditional medicine, decreases AGE formation and lens aldose reductase activity, with reduced lens opacity and reduced sciatic nerve sorbitol in STZ-induced diabetic rats. Gubitosi-Klug and Kern (abstract 225) studied STZ-induced diabetes in animals with and without expression of 5-lipoxygenase, an enzyme essential to synthesis of eicosanoids, finding decreased numbers of acellular retinal capillaries and reduced retinal adhesion of leukocytes, suggesting a potential proinflammatory target for prevention of diabetic retinopathy. Small interfering antisense RNA sequences serve as guides for the cleavage of homologous mRNA in the RNA-induced silencing complex. Chen et al. (abstract 818) found that diabetes increased retinal levels of the transcriptional coactivator p300, as well as of fibronectin and NFκB, and found that intravitreal small interfering antisense RNA targeted toward p300 reduced p300, fibronectin, and NFκB, suggesting a potential treatment approach. Hu et al. (abstract 820) found increased retinal levels of the adhesion molecules vascular cell adhesion molecule-1 and ICAM-1 in STZ-diabetic rats and found that the phosphordiesterase III inhibitor cilostazol reduced both mRNA expression and protein levels of ICAM-1, vascular cell adhesion molecule-1, as well as decreasing PPARα and PPARγ, suggesting another potential treatment.

There has been interest in the use of inhibitors of protein kinase C (PKC)-β in the treatment of diabetic retinopathy. Aiello et al. (abstract 230) analyzed the combined data from two 3-year randomized controlled trials (26,27) comparing 401 individuals receiving placebo and 412 treated with the PKC-β inhibitor ruboxistaurin, 32 mg daily, in individuals with moderate to very severe NPDR. Moderate visual loss, defined as loss of ≥15 letters (three lines) on the Early Treatment Diabetic Retinopathy Study visual acuity chart, sustained for the last 6 months on study, occurred in 10% of those receiving placebo and in 6% of those receiving ruboxistaurin, with 2 vs. 5% gaining ≥15 letters on the chart. Of those with clinically significant macular edema >100 μm from the center of the macula, 67 vs. 50% progressed to the high-risk state of having this degree of macular edema ≤100 μm from the center of the macula. The authors concluded that ruboxistaurin showed evidence of protection against macula edema and against loss of visual acuity in patients with moderately severe to very severe NPDR. Tuttle et al. (abstract 436) reported renal safety data in the two ruboxistaurin trials, showing neither protective nor adverse effect on the glomerular filtration rate or the likelihood of progression to glomerular filtration rate <30 ml/min per 1.73 $m^2$. Albuminuria was not discussed in this presentation, but the author has previously reported reduction in albuminuria with ruboxistaurin administration to individuals with established nephropathy (28). Casellini et al. (abstract 791) reported a 39% improvement in the neuropathy measure in 20 individuals receiving ruboxistaurin and a 2% improvement in 20 receiving placebo, with no significant differences in electrophysiology; skin nerve fiber density; quantitative sensory testing of vibration, cold, or warm sensation thresholds; cardiac autonomic reflex testing; skin microvascular blood flow; or neuropathy measure. Endothelium-dependent skin blood flow doubled after local warming in individuals receiving ruboxistaurin but not those receiving placebo. Brooks et al. (abstract 790), however, failed to find effects of ruboxistaurin treatment on the neuropathy measure or in skin blood flow in nine treated individuals compared with nine receiving placebo. Tesfaye et al. (abstract 813) reported no overall effects of ruboxistaurin on neuropathy in data from 519 individuals with symptomatic neuropathy pooled from two 1-year randomized controlled trials, with improvement of at least 50% from baseline in 43%, suggesting that a marked placebo effect exists in diabetic neuropathy. Interestingly, those individuals using insulin at baseline and those with non-Caucasian ethnicity had greater likelihood of clinically significant symptom reduction, while there was a trend to decreased symptom reduction among those receiving statins. King et al. (abstract 506) compared overall clinical safety among 1,396 diabetic individuals treated with ruboxistaurin and 1,408 receiving placebo in 11 clinical trials, finding no evidence of adverse events and excellent tolerability, without change in

blood pressure or glycemic control. Thus, there is a suggestion of clinical benefit for diabetic retinopathy with ruboxistaurin; although the U.S. Food and Drug Administration has not felt these trials offered sufficient evidence to allow its approval (29).

**Diabetic neuropathy**

Solomon Tesfaye (Sheffield, U.K.) discussed pharmacologic approaches to the treatment of individuals with painful diabetic neuropathy (30). Diabetic periperal neuropathy starts in the toes and gradually affects more proximal areas, causing pain in ~30% of patients. Neuropathy is associated with cardiovascular risk factors and, independently, with the presence of CVD; therefore, the presence of neuropathy is a marker of individuals at increased risk for mortality. In his study of 1,172 individuals with type 1 diabetes followed for 7 years, baseline A1C, the change in A1C, and duration of diabetes were risk factors. After adjustment for these factors, higher LDL cholesterol and triglycerides, higher BMI, hypertension, and smoking predicted development of neuropathy, with baseline CVD associated with doubled risk of neuropathy (31).

The clinical syndrome is characterized by burning discomfort with nocturnal exacerbation, as well as by autonomic manifestations and insensitivity leading to foot ulceration and amputation. Intervention can either be symptomatic or pathogenic to alter the course of neuropathy, the latter exemplified by efforts to achieve euglycemia. A number of agents have been used for analgesia. The tricyclic antidepressants are effective, although Tesfaye remarked that he finds these agents to be associated with high levels of side effects, with other relatively established approaches including anticonvulsants, particularly carbemazepine and gabapentin, topical lidocaine, oral mexiletine, and topical isosorbide and capsaicin. Tesfaye referred to Vinik's review, summarizing a variety of agents used in treatment of painful diabetic neuropathy, reviewing anticonvulsants for which benefit has been reported, including carbemazepine, felbamate, gabapentin, lamotrigine, phenytoin, topiramate, and valproate (32). Newer approaches include the serotonin and norepinephrine reuptake inhibitors duloxetine and venlafaxine. Pain is transmitted by A and C fibers. Serotonin and norepinephrine reuptake inhibitors increase synaptic availability of serotonin and norepinephine, with two large studies having been carried out with duloxetine. The first compared placebo with 20, 60, and 120 mg daily doses in 457 individuals with painful diabetic neuropathy, showing significant pain relief with the higher doses and evidence of benefit at the lowest dose as well beginning at 1 week and maintained over the 12 weeks of study (33). The second study compared 120 mg once daily with 60 mg twice daily for 6 months in 449 patients, showing maintenance of pain relief through 28 weeks (34). A number of side effects were reported, including nausea, somnolence, dizziness, constipation, dry mouth, and reduced appetite, with 36 and 37% of the respective groups not completing the second study and 20 and 27% discontinuing because of side effects. Venlafaxine was studied in 75, 150, and 225 mg extended release daily doses, the latter two leading to significant improvement in pain score, although side effects included somnolence, nausea, and myalgia, and 7 of the 244 treated patients developed significant electrocardiographic abnormality (35). A study comparing venlafaxine with the tricyclic imipramine showed similar improvement in neuropathic pain (36).

Several other agents are being studied. Pregabalin reduces neural calcium influx, decreasing neurotransmitter release, and has been studied in four randomized controlled trials including 146–724 individuals with painful diabetic neuropathy, showing pain relief within 1 week and persisting through the 6- to 12-week studies (37–40). A number of prominent side effects were observed, with dose-related somnolence, ataxia, and confusion, as well as peripheral edema and constipation reported. Topiramate leads to significant benefits at 8 and 12 weeks at 400-mg daily dosages but, again, with high frequency of side effects, including diarrhea, loss of appetite (which may be beneficial, as the agent is associated with weight loss), and somnolence, leading to high discontinuation rates (41). An important approach is the use of combination treatments; a recent trial showed that use of morphine and gabapentin together is superior to either alone in individuals with neuropathic pain, with gabapentin similar to placebo, although combination treatment was associated with an increased frequency of side effects, including constipation, dry mouth, and sedation (42). For many patients, Tesfaye suggested, "the remedy is worse than the disease," so that we need to better understand the pathogenesis of pain in neuropathy and distinguish peripheral from central pain, with a potentially important contributory factor being spinal cord abnormality (43), which his group has found to occur early in the development of diabetic neuropathy (44). Magnetic resonance imagining sprectroscopy shows abnormality of the thalamus, which acts as a gateway for pain, to occur in individuals with painful neuropathy. There is also evidence of greater degrees of neuronal function impairment in painless than in painful neuropathy, with nerve blood flow impaired to a greater extent and oxygen saturation lower in individuals with painless than in those with painful neuropathy (45). Acute painful neuropathy occurring in the setting of normalization of glycemia may be associated with proliferative retinopathy and with new vessel formation on the surface of the nerve, further suggesting important functional differences between painful and painless neuropathy. Tesfaye retuned to the theme of pathogenic treatment for neuropathy, suggesting that studies with the PKC-β inhibitor ruboxistaurin and with aldose reductase inhibitors suggest that it may become possible to develop treatment approaches that successfully address the metabolic dysfunction of diabetes.

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