Ophthalmology® ROUNDS

JULY/AUGUST 2009
Volume 7, Issue 4

AS PRESENTED IN THE ROUNDS OF THE DEPARTMENT OF OPHTHALMOLOGY AND VISION SCIENCES, FACULTY OF MEDICINE, UNIVERSITY OF TORONTO

A Review of Diabetic Retinopathy

By Daniel Weisbrod, MD, FRCSC, and Carol Schwartz, MD, FRCSC

Diabetes mellitus is the leading cause of blindness in adults <75 years old,[1] and without proper screening, patients can have significant retinopathy before visual loss even occurs. Primary interventions such as control of glycemia, blood pressure, and lipids can have a major impact on the development and progression of diabetic retinopathy. Nevertheless, a significant number of patients continue to develop vision-threatening complications that require intervention. This issue of *Ophthalmology Rounds* reviews diabetic retinopathy with an emphasis on current management strategies.

The number of people afflicted with diabetes worldwide is expected to rise to an estimated 300 million by the year 2025.[1] Diabetic patients have a 29-fold increased risk of blindness compared with nondiabetics.[2] Since diabetic retinopathy typically affects individuals during their most productive years, it can have tremendous costs in terms of decreased productivity and quality of life; furthermore, vision loss from diabetes is identified as a risk factor for early mortality.[3]

Epidemiology

The prevalence rates for diabetic retinopathy are widely varied in the literature. According to the Eye Disease Prevalence Research Group, 40.3% of the adult diabetic population of the United States (US) – representing 4.1 million adults, or 3.4% of the general population >40 years old – have diabetic retinopathy, and 8.2% have vision-threatening retinopathy.[4] At diagnosis, the prevalence of any retinopathy in type 1 diabetes (T1DM) is low, ranging from 0%-3%, while in type 2 diabetes (T2DM) the range is between 6.7%-30.2%; this suggests that many people with T2DM go undiagnosed for years.[5]

The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) was the largest and most comprehensive epidemiological study of diabetic retinopathy.[6,7] It demonstrated that the most significant risk factor for diabetic retinopathy was disease duration, with 97.5% of T1DM and 77.8% of T2DM exhibiting evidence of diabetic retinopathy after 15 years. Furthermore, the prevalence of proliferative diabetic retinopathy (PDR) was 25% in T1DM and 15.5% in T2DM by 15 years. Other well-established risk factors for diabetic retinopathy include hyperglycemia, hypertension, hyperlipidemia, renal disease, and pregnancy.

Diabetic macular edema (DME) is the most frequent cause of vision loss in patients with diabetes and, although it can occur at any stage of the disease, it is related to disease duration. In patients enrolled in the WESDR, the prevalence rates of DME in T1DM with a disease duration <5 years and >20 years were 0% and 29%, respectively. For T2DM, macular edema developed in 3% and 28% at 5 and 20 years, respectively.[8]

Classification and definitions

Diabetes is a progressive disease resulting from prolonged hyperglycemia that leads to biochemical and physiological changes, which ultimately cause vascular endothelial damage. Histopathologically, the earliest signs include capillary basement membrane thickening and dropout of intramural pericytes, the supportive cells of the vascular endothelial wall. The consequence of this is a breakdown in the blood-retinal barrier and retinal capillary nonperfusion, leading to microaneurysm formation, increased vascular permeability, and finally, the clinical changes associated with diabetic retinopathy.

Diabetic retinopathy can be classified into 2 stages depending on the presence or absence of retinal neovascularization: nonproliferative diabetic retinopathy (NPDR) and the

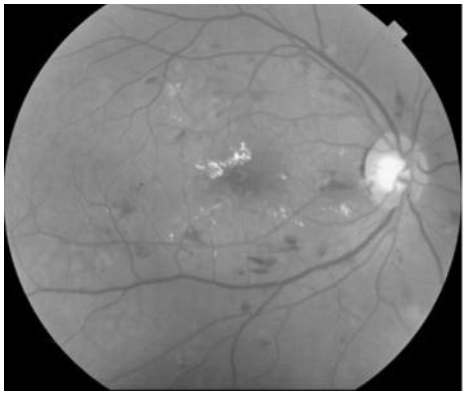
FACULTY OF MEDICINE
University of Toronto

Department of Ophthalmology and Vision Sciences

Department of Ophthalmology and Vision Sciences, Faculty of Medicine, University of Toronto,
60 Murray St.
Suite 1-003
Toronto, ON M5G 1X5

The editorial content of *Ophthalmology Rounds* is determined solely by the Department of Ophthalmology and Vision Sciences, Faculty of Medicine, University of Toronto

Figure 1: Fundus photograph of the right eye showing moderate nonproliferative diabetic retinopathy (NPDR) with intraretinal hemorrhage and exudate



more advanced, proliferative diabetic retinopathy. The causes of vision loss from diabetic retinopathy include macular edema, progressive retinal ischemia, and complications of PDR, such as retinal fibrosis, vitreous hemorrhage, and retinal detachment.

Nonproliferative diabetic retinopathy

Clinical features of NPDR include observed changes resulting from altered vascular permeability, microaneurysm formation, and retinal capillary nonperfusion. Microaneurysms give rise to retinal edema and hard exudates, whereas, features of retinal capillary nonperfusion include dot and blot hemorrhages, nerve fibre layer infarcts (NFLIs), venous beading, and intraretinal microvascular anomalies (IRMAs).

The degree of NPDR depends on the severity of retinal microvascular changes and can be graded according to the Early Treatment Diabetic Retinopathy Study (ETDRS).[9] Mild-to-moderate NPDR was formerly referred to as background diabetic retinopathy; currently, mild NPDR is defined as the presence of at least 1 microaneurysm. More extensive hemorrhages and/or microaneurysms and/or the presence of NFLI, venous beading, or IRMA is classified as moderate NPDR (Figure 1).[10] Features of severe NPDR, formerly termed preproliferative diabetic retinopathy, are associated with a high rate of progression to high-risk PDR. Severe NPDR is summarized by the "4-2-1 rule" and consists of any one of the following:

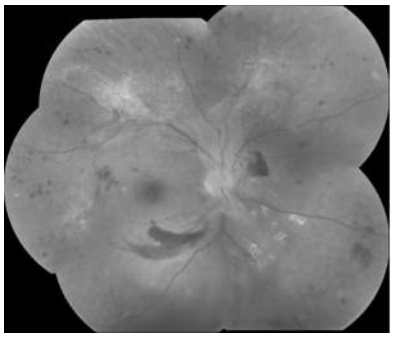
- 4 quadrants of hemorrhages or microaneurysms,
- 2 quadrants of venous beading, or
- 1 quadrant of IRMA.

The presence of any 2 of these features defines very severe NPDR.[10]

Proliferative diabetic retinopathy

With progressive retinal capillary nonperfusion, vascular endothelial growth factor (VEGF) is secreted, stimulating the production of new vessels, identified as retinal neovascularization. Retinal neovascularization is the hallmark of PDR and can occur at the disc or elsewhere in the retina. The Diabetic Retinopathy Study (DRS)[11] defined neovascularization of the disc (NVD) as the presence of new vessels on or within 1 disc diameter of the optic disc, and neovascularization elsewhere (NVE) as the presence of new vessels >1 disc diameter from the disc.[11,12]

Figure 2: Fundus photograph of the right eye showing PDR with high-risk characteristics, ie, neovascularization of the disc (NVD) with preretinal hemorrhage



The DRS also identified high-risk characteristics of PDR associated with vision loss:[13]

- NVD ≥25%-33% of the disc area
- Less extensive NVD with preretinal or vitreous hemorrhage
- NVE ≥50% of the disc area with preretinal or vitreous hemorrhage (Figure 2).

PDR with severe fibrovascular proliferation, tractional retinal detachment involving the macula or vitreous hemorrhage that obscures the ability to grade NVD or NVE is classified as advanced PDR.

Diabetic macular edema

The presence of retinal thickening can be detected by stereoscopic examination techniques and the associated clinical features include microaneurysms and hard exudates. DME can be focal or diffuse and is classified by its location relative to the fovea, the presence and location of hard exudates, and the presence or absence of cystoid macular edema (CME). When thickening involves the centre of the fovea, there is a higher risk of vision loss.[14]

Clinically significant macular edema (CSME) is associated with a higher risk of vision loss. The ETDRS defined CSME as:

- retinal thickening at or within 500 μm of the centre of the macula,
- hard exudates at or within 500 μm of the centre of the macula with adjacent retinal thickening, or
- an area of retinal thickening at least 1 disc diameter in size within 1 disc diameter of the centre of the macula (Figure 3).[15]

Treatment

Canadian screening guidelines have been well outlined.[16] Primary prevention of vision loss from diabetic retinopathy involves control of blood glucose, blood pressure, and serum lipid levels. In addition, kidney function should be optimized and macrovascular complications, including cardiac disease, controlled. Secondary intervention involves laser photocoagulation, as well as other more recent medical and surgical treatment strategies.

Figure 3: Fundus photograph of the left eye showing clinically significant macular edema. Circinate exudates surround leaking microaneurysms with an area of retinal thickening temporal to the fovea

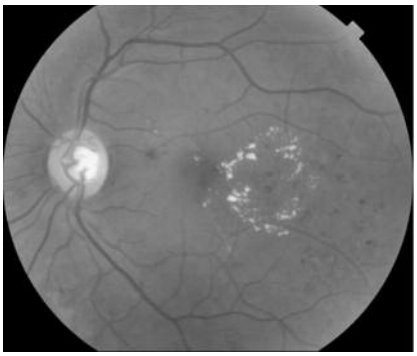
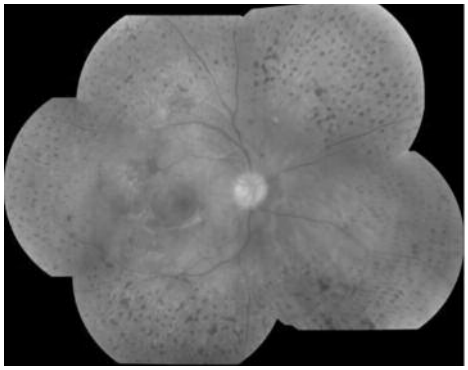


Figure 4: Fundus photograph of the right eye showing panretinal photocoagulation (PRP) scars filling the retinal periphery



Primary prevention

The Diabetes Control and Complications Trial (DCCT),[17] a prospective, multicentre, randomized, controlled clinical trial, was pivotal in illustrating the role of hyperglycemia in the pathogenesis of diabetic retinopathy and of glycemic control in reducing the risk of complications. Published in 1993, the purpose of the DCCT was to determine whether tight control of blood glucose levels would reduce the frequency and severity of microvascular complications, including diabetic retinopathy, in T1DM. It concluded that intensive therapy reduced the risk of developing retinopathy by 76%, slowed the progression of retinopathy in those with existing disease by 54%, and reduced the development of severe NPDR and PDR by 47%.[17] The Epidemiology of Diabetes and Complications (EDIC) study[18] followed patients beyond the end of the DCCT. The study concluded that the benefits of early tight glycemic control extend well beyond the gradual equalization of HbA_{1C} levels;[18] therefore, an HbA_{1C} level $< 7\%$ should be targeted as soon as the diagnosis of diabetes is made.

The United Kingdom Prospective Diabetes Study (UKPDS)[19] was published in 1998 and revealed similar results for T2DM. The study demonstrated a reduction in microvascular complications, including diabetic retinopathy, by 25%, most of which was due to fewer patients requiring photocoagulation.[19] The UKPDS also established that tight control of blood pressure reduced the risk of progression in diabetic retinopathy by 34% and vision loss by 47%, compared with conventional antihypertensive treatment.[20]

Secondary intervention

Laser photocoagulation

Panretinal photocoagulation (PRP) is the gold standard for treatment of PDR with high-risk characteristics (Figure 4). The DRS[21] was designed to determine the effect of photocoagulation in patients with PDR and severe NPDR. Patients with PDR in 1 eye or bilateral severe NPDR were randomized to receive PRP or no treatment. A >50% reduction in severe vision loss (vision <5/200) was observed in all patients; however, this benefit was greatest in those with PDR having high-risk characteristics with severe vision loss developing in 20% of treated eyes versus 44% of control eyes at 4 years. Although there was a treatment benefit in patients with early PDR or severe NPDR, vision loss in these patients was low regardless of whether they were treated; therefore, prompt treatment was not recommended for these patients.[21]

The ETDRS[22] enrolled patients with mild NPDR to early PDR in either eye and was designed to answer 3 questions:

- When in the course of diabetic retinopathy is it most effective to initiate photocoagulation therapy?
- Is photocoagulation therapy effective in the treatment of macular edema?
- Is acetylsalicylic acid (ASA) effective in altering the course of diabetic retinopathy?[15]

One eye of each patient was randomly assigned to early photocoagulation and the fellow eye was assigned to deferral of photocoagulation. This study demonstrated a 50% decrease in progression to high-risk PDR in patients treated with immediate full-scatter PRP, although the risk of severe vision loss at 5 years was low in all patients (3.7% in the group that deferred treatment and 2.6% in the group treated immediately).[22] The benefits of immediate treatment were even lower in patients with less-severe retinopathy. Therefore, immediate full-scatter PRP is not recommended in patients with mild-to-moderate NPDR, since the adverse effects of photocoagulation outweigh the small treatment benefits; however, treatment could be considered in patients with severe NPDR or early PDR, particularly with T2DM or if reliable follow-up cannot be ensured. The main adverse effects of PRP include an immediate loss of vision, visual field constriction, inadvertent laser burns, and exacerbation of macular edema.

A 50% reduction in moderate vision loss at 3 years was demonstrated by the ETDRS in the treatment of CSME with focal macular photocoagulation (12% for treated eyes and 24% for untreated eyes).[14] If most of the leaking microaneurysms are near the centre of the macula, or the centre of the macula is uninvolved or only slightly thickened and the vision is normal or near normal, close observation may be preferable; treatment may be deferred until worsening of DME is evident. Prompt treatment should be initiated if the centre of

the macula is involved, vision is reduced, or treatment is feasible with little risk.[23] If retinal thickening involves the centre of the fovea, the treatment benefits are greatest, but if macular edema does not meet criteria for CSME, treatment should be deferred because the threat to the centre of the macula is small. If high-risk PDR develops, treatment of DME should be performed immediately followed by prompt PRP. Adverse events include scotomas from focal laser scars and choroidal neovascularization.

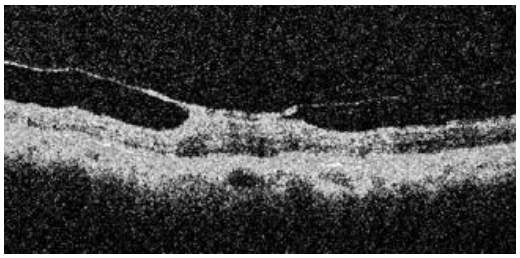
The ETDRS studied 2 types of photocoagulation methods for DME.[24] Focal laser refers to treatment of all leaking microaneurysms between 500–3000 µm from the centre of the fovea. Fluorescein angiography can guide treatment by identifying these leaking microaneurysms; it can also be used to diagnose irreversible macular ischemia. A grid treatment is generally used for areas of diffuse leakage with no identifiable focal sources. A modified grid treatment is often performed, combining focal treatment of identifiable leaking microaneurysms within an area of diffuse retinal thickening that is treated by grid photocoagulation. Despite the well-known benefits of laser photocoagulation, significant vision improvement in the ETDRS is low (<3%); as a result, there has been a growing interest in newer therapies for DME that might improve vision.

Surgery

In the event of vitreous hemorrhage from PDR, the activity of the patient should be restricted and the head of the bed elevated to assist in clearing the blood from the visual axis. If vitreous hemorrhage precludes an adequate view of the fundus, echography should be performed to rule out retinal detachment. When there is an adequate view of the fundus, treatment includes PRP (if no history of laser treatment) or PRP fill-in treatments to stabilize and achieve regression of proliferative disease. A red wavelength or indirect ophthalmoscopy can be used to facilitate treatment through the hemorrhage. Vitreous hemorrhage occurs commonly after PRP as the posterior vitreous detaches; this will often clear spontaneously.

Indications for vitrectomy in diabetes include dense, nonclearing vitreous hemorrhage with no clear view of the fundus, tractional retinal detachment involving the macula, and severe fibrovascular proliferation; a vitrectomy will facilitate a decrease in the risk of vision loss from retinal detachment, vitreous hemorrhage, or macular distortion. The goals of vitrectomy surgery include clearing the media, excising the posterior hyaloid and fibrovascular membranes to relieve vitreoretinal traction, and applying endolaser photocoagulation to attain a regression of proliferative disease.[25] The Diabetic Retinopathy Vitrectomy Study (DRVS)[26] investigated the role of early vitrectomy (<6 months) versus observation in the treatment of severe, nonclearing vitreous hemorrhage. After 2 years, 24.5% of patients who underwent early vitrectomy had a visual acuity ≥20/40 compared with only 15.2% who had surgery deferred. When patients were divided into T1DM and T2DM, only the former showed a benefit and this benefit was maintained to almost 4 years.[26,27]

Figure 5: Optical coherence tomography of the right eye showing diabetic macular edema with vitreomacular traction; the posterior hyaloid is attached to the macula with intraretinal cysts



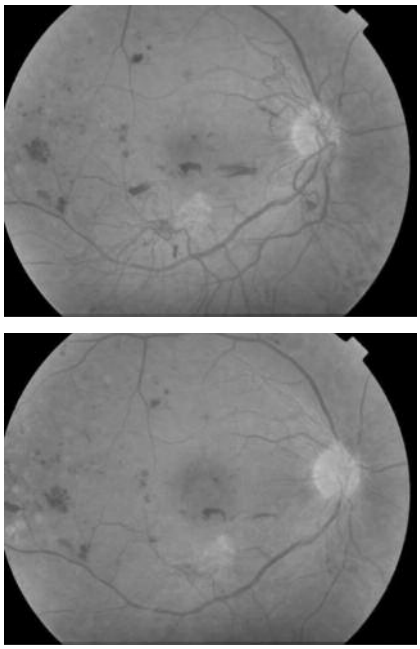
Vitrectomy may be considered when decreased vision occurs secondary to DME, particularly with vitreomacular traction that is readily seen on optical coherence tomography (OCT; Figure 5).[28,29] Although evidence from the literature is inconclusive, patients with diffuse DME unresponsive to laser treatment may benefit from vitrectomy with or without peeling of the internal limiting membrane.[30] However, in one study, vitrectomy did not demonstrate superiority to laser treatment when there was no vitreomacular traction.[31]

Medical treatment

The ETDRS is the largest study evaluating the effects of ASA therapy (650 mg/day) on the progression of diabetic retinopathy. Compared with placebo, no significant difference was found in the progression to high-risk PDR, the development of vitreous hemorrhage, or vision loss.[32,33] Although ASA therapy is not recommended to reduce the complications of diabetic retinopathy, there are no ocular contraindications for its use in these patients. Studies on diabetic retinopathy with other antiplatelet agents, such as dipyridamole and ticlopidine, have been inconclusive.[34,35]

Intraocular steroids decrease the breakdown of the blood-retinal barrier, suppress inflammation, and downregulate the production of VEGF; however, steroids also have significant side effects, including cataracts and glaucoma. Additionally, the evidence from relatively small, randomized clinical trials is inconclusive regarding steroid use in the treatment of DME. The most recent trial by the Diabetic Retinopathy Clinical Research Network (DRCR.net)[36] compared intravitreal triamcinolone acetonide (IVTA) with focal/grid laser macular photocoagulation for DME in 693

Figure 6: Fundus photograph of the right eye with persistent NVD and NVE present after PRP (A); the neovascularization has regressed (B) after an injection of 0.05 mL of intravitreal bevacizumab (1.25 mg)



patients. Although there was an initial benefit with IVTA at 4 months, no benefits were revealed 1 and 2 years after the initiation of treatment.[36] In fact, patients in the laser arm did better than those receiving IVTA for final visual acuity and retinal thickening at 2 years. Furthermore, 83% of phakic eyes receiving 4 mg triamcinolone acetonide required cataract surgery by 3 years.[37] Recently, steroid implants, such as fluocinolone acetonide and dexamethasone, have been developed for delivery into the eye through intravitreous sustained release devices. Although these medications require surgical implantation they can last for a prolonged period of time. Initial studies indicate promising results in improvements of visual acuity and reductions of DME; however, cataracts and glaucoma remain significant concerns.[38, 39]

Three anti-VEGF agents – pegaptanib, ranibizumab, and bevacizumab – are currently under investigation in the treatment of DME. Intravenous bevacizumab is approved for use in the treatment of metastatic colorectal and lung cancer; however, it is used off-label in the treatment of diabetic retinopathy as an intravitreal injection.[40,41] Bevacizumab has been associated with regression of iris and retinal neovascularization (Figure 6), and is often injected prior to vitrectomy surgery in PDR for vitreous hemorrhage or retinal detachment to decrease the risk of intraoperative bleeding and other complications.[41] A few small studies have shown promising results with ranibizumab in the treatment of DME. The Efficacy and Safety of Ranibizumab (Intravitreal Injections) in Patients With Visual Impairment Due to Diabetic Macular Edema (RESTORE) study is a phase III trial designed to assess the efficacy and safety of intravitreal ranibizumab in DME. Patient recruitment has ended but the study is still ongoing. Anti-VEGF agents do not carry the same risks as steroids, but their half-life is much shorter and patients may require multiple injections. Although anti-VEGF agents are currently being used extensively in clinical practice for numerous vascular diseases including diabetes, their role in the management of diabetic retinopathy and DME is still being elucidated.

Conclusions

Diabetes remains the leading cause of vision loss in working-age individuals. Since diabetic retinopathy can irreversibly progress and become severe, with few visual symptoms, adequate screening and prompt treatment remain of utmost importance. Improved screening protocols and primary-prevention strategies, including optimizing glycemic, blood pressure, and serum lipid control have decreased the prevalence of complications from this chronic disease. Laser photocoagulation is a well-established treatment for decreasing the risk of vision loss in patients with DME and PDR. In addition, improvements in vitrectomy surgical techniques have provided superior outcomes for patients requiring surgery. The use of intravitreal medications (eg, corticosteroids and anti-VEGF agents) may eventually play a more significant role with the increase in studies on their use. Finally, in the future it is hoped that potential treatments involving combinations of the above modalities will lessen the risk of blindness from diabetic retinopathy.

Drs. Weisbrod and Schwartz are physicians in the Department of Ophthalmology, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario.

References

1. King H, Aubert RE, Herman WH. Global burden of diabetes, 1995–2025: prevalence, numerical estimates, and projections. *Diabetes Care.* 1998;21(9):1414-1431.
2. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. *Diabetes in America.* 2nd ed. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases: 1995.
3. Cusick M, Meleth AD, Agron E, et al. Associations of mortality and diabetes complications in patients with type 1 and type 2 diabetes: Early Treatment Diabetic Retinopathy Study Report no. 27. *Diabetes Care.* 2005;28(3):617-625.
4. The Eye Disease Prevalence Research Group. The prevalence of diabetic retinopathy among adults in the United States. *Arch Ophthalmol.* 2004;122(5):552-563.
5. Williams R, Airey M, Baxter H, Forrester J, Kennedy-Martin T, Girach A. Epidemiology of diabetic retinopathy and macular oedema: a systemic review. *Eye.* 2004;18(10):963-983.
6. Klein R, Klein BEK, Moss SE, et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy II: prevalence and risk of diabetic retinopathy when age at diagnosis is less than 30 years. *Arch Ophthalmol.* 1984; 102(4):520-526.
7. Klein R, Klein BEK, Moss SE et al. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. III. Prevalence and risk of diabetic retinopathy when age at diagnosis is 30 or more years. *Arch Ophthalmol.* 1984;102(4):527-532.
8. Klein R, Klein BE, Moss SE, Davis MD, DeMets DL. The Wisconsin Epidemiologic Study of Diabetic Retinopathy IV. Diabetic macular edema. *Ophthalmology.* 1984;91(12):1464-1474.

9. Early Treatment Diabetic Retinopathy Study Research Group. Grading diabetic retinopathy from stereoscopic color fundus photographs—an extension of the modified Airlie House classification: ETDRS report number 10. *Ophthalmology.* 1991;98(5 suppl):786-806.
10. Diabetes Control and Complications Trial Research Group. The effect of intensive diabetes treatment on the progression of diabetic retinopathy in insulin-dependent diabetes mellitus. *Arch Ophthalmol.* 1995;113(1):36-51.
11. Diabetic Retinopathy Study Research Group. Design, methods, and baseline results. DRS Report No. 6. *Invest Ophthalmol Vis Sci.* 1981; 21(1):149-209.
12. Diabetic Retinopathy Study Research Group. A modification of the Airlie house classification of diabetic retinopathy. DRS Report No. 7. *Invest Ophthalmol Vis Sci.* 1981;21(1):210-226.
13. Diabetic Retinopathy Study Research Group. Four risk factors for severe visual loss in diabetic retinopathy. The third report from the diabetic retinopathy study. *Arch Ophthalmol.* 1979;97(4):654-655.
14. Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema. ETDRS report no. 4. *Int Ophthalmol Clin.* 1987; 27(4):265-272.
15. Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study Report #1. *Arch Ophthalmol.* 1985;103(12):1796-1806.
16. Boyd SR, Altomare F. Canadian diabetes association 2008 clinical practice guidelines for the prevention and management of diabetes: retinopathy. *Can J Diabetes.* 2008;32(Suppl 1):34-39.
17. Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med.* 1993;329(14):977-986.
18. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Intervention and Complications Research Group. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. *N Engl J Med.* 2000;342(6):381-389.
19. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet.* 1998;352(9131):837-853.
20. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes (UKPDS 38). *BMJ.* 1998;317(7160):703-713.
21. Diabetic Retinopathy Study Research Group. Clinical application of Diabetic Retinopathy Study (DRS) findings, DRS report number 8. *Ophthalmology.* 1981;88(7);583-600.
22. Early Treatment Diabetic Retinopathy Study Research Group. Early photocoagulation for diabetic retinopathy. ETDRS report number 9. *Ophthalmology.* 1991;98(5 Suppl):766-785.
23. Early Treatment Diabetic Retinopathy Study Research Group. Techniques for scatter and focal photocoagulation treatment of diabetic retinopathy. ETDRS Report no. 3. *Int Ophthalmol Clin.* 1987;27(4):254-264.
24. Early Treatment Diabetic Retinopathy Study Research Group. Treatment techniques and clinical guidelines for photocoagulation of diabetic macular edema. ETDRS Report no. 2. *Ophthalmology.* 1987;94(7):761-774.
25. Eliott D, Lee MS, Abrams GW. Proliferative diabetic retinopathy: Principles and techniques of surgical treatment. In: Ryan SJ (ed.) *Retina,* 3rd ed. St Louis, MO: Mosby; 2000:2436-2476.
26. Diabetic Retinopathy Vitrectomy Study Research Group. Early vitrectomy for severe vitreous hemorrhage in diabetic retinopathy. Two-year results of a randomized trial. Diabetic Retinopathy Vitrectomy Study Report 2. *Arch Ophthalmol.* 1985;103(11):1644-1652.
27. Diabetic Retinopathy Vitrectomy Study Research Group. Early vitrectomy for severe vitreous hemorrhage in diabetic retinopathy. Four-year results of a randomized trial. Diabetic Retinopathy Vitrectomy Study Report 5. *Arch Ophthalmol.* 1990;108(7):958-964.
28. Gandorfer A, Messmer EM, Ulbig MW, Kampik A. Resolution of diabetic macular edema after surgical removal of the posterior hyaloid and the inner limiting membrane. *Retina.* 2000;20(2):126-133.
29. Mochizuki Y, Hata Y, Enaida H, et al. Evaluating adjunctive surgical procedures during vitrectomy for diabetic macular edema. *Retina.* 2006;26(2):143-148.
30. Mohamed Q, Gillies MC, Wong TY. Management of diabetic retinopathy: a systematic review. *JAMA.* 2007;298(8):902-916.
31. Kumar A, Sinha S, Azad R, Sharma YR, Vohra R. Comparative evaluation of vitrectomy and dye-enhanced ILM peel with grid laser in diffuse diabetic macular edema. *Graefes Arch Clin Exp Ophthalmol.* 2007;245(3):360-368.
32. Early Treatment Diabetic Retinopathy Study Research Group. Effects of aspirin treatment on diabetic retinopathy. ETDRS Report no. 8. *Ophthalmology.* 1991;98(5 suppl):757-765.
33. Chew EY, Klein ML, Murphy RP, Remaley NA, Ferris FL. Effects of aspirin on vitreous/preretinal hemorrhage in patients with diabetes mellitus. Early Treatment Diabetic Retinopathy Study Report no 20. *Arch Ophthalmol.* 1995;113(1):52-55.
34. DAMAD Study Group. Effect of aspirin alone and aspirin plus dipyridamole in early diabetic retinopathy: a multicenter randomized controlled clinical trial. *Diabetes.* 1989;38(4):491-498.
35. TIMAD Study Group. Ticlopidine treatment reduces the progression of nonproliferative diabetic retinopathy. *Arch Ophthalmol.* 1990;108(11):1577-1583.
36. Diabetic Retinopathy Clinical Research Network. A randomized trial comparing intravitreal triamcinolone acetonide and focal/grid photocoagulation for diabetic macular edema. *Ophthalmology.* 2008;115(9):1447-1459.
37. Diabetic Retinopathy Clinical Research Network (NRCR.net). Three-year follow-up of a randomized trial coparing focal/grid photocoagulation and intravitreal triamcinolone for diabetic macular edema. *Arch Ophthalmol.* 2009;127(3):245-251.
38. Fraser-Bell S, Kaines A, Hykin PG. Update on treatments for diabetic macular edema. *Curr Opin Ophthalmol.* 2008;19(3):185-189.
39. Eliott D. Diabetic macular edema: clinical trials. In: Kertes PJ, Johnson TM (eds.) *Evidence-Based Eye Care.* Philadelphia, PA: Lippincott Williams & Wilkins; 2007:123-142.
40. Spaide RF, Fisher YL. Intravitreal bevacizumab (Avastin) treatment of proliferative diabetic retinopathy complicated by vitreous hemorrhage. *Retina.* 2006;26(3):275-278.
41. Tonello M, Costa RA, Almeida FP, Barbosa JC, Scott IU, Jorge R. Panretinal photocoagulation versus PRP plus intravitreal bevacizumab for high-risk proliferative diabetic retinopathy (IBeHi study). *Acta Ophthalmol.* 2008: 86(4):385-389.
42. Yeoh J, Williams C, Allen P, et al. Avastin as an adjunct to vitrectomy in the management of severe proliferative diabetic retinopathy: a prospective case series. *Clin Experiment Ophthalmol.* 2008;36(5):449-454.

University of Toronto
Department of Ophthalmology and Vision Sciences

Upcoming events

17 October 2009
International Next Generation Eye Surgery, Device and Drug Delivery Symposium
The Sutton Place Hotel, Toronto, Ontario
Website: http://events.cmetoronto.ca/website/index/OPT0906
E-mail: info-opt0906@utoronto.ca

21–22 November 2009
2020: A Vision for Ophthalmology in the Future Walter Wright 2009
CNIB Centre, 1929 Bayview Ave., Toronto, Ontario
Website: http://events.cmetoronto.ca/website/index/OPT0902
E-mail: info-opt0902@utoronto.ca

For Further Information:
Office of Continuing Education & Professional Development
Faculty of Medicine, University of Toronto
TEL: 416.978.2719/1.888.512.8173 FAX: 416.946.7028

Disclosure Statement: Dr. Schwartz has received research and educational grants from Novartis Pharmaceuticals, research grants from Eli Lilly and Alimera, and has acted as an Advisory Board member for Novartis Pharmaceuticals. Dr. Weisbrod has no disclosures.

Change of address notices and requests for subscriptions for *Ophthalmology Rounds* are to be sent by mail to P.O. Box 310, Station H, Montreal, Quebec H3G 2K8 or by fax to (514) 932-5114 or by e-mail to info@snellmedical.com. Please reference *Ophthalmology Rounds* in your correspondence. Undeliverable copies are to be sent to the address above. Publications Post #40032303

This publication is made possible by an unrestricted educational grant from

Novartis Pharmaceuticals Canada Inc.