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Canadian Ophthalmological Society (COS) Diabetic Retinopathy Guidelines: Implications for Daily Clinical Practice

An Overview of Presentations and Panel Discussions at the 75th COS Annual Meeting

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Due to demographic trends of an aging population, more prevalent obesity, and increasing immigration from high-risk populations, the incidence of diabetes mellitus (DM), diabetic retinopathy (DR), and diabetic macular edema (DME) is projected to steadily increase during the upcoming decade,[1] with resultant implications for the Canadian healthcare system and policy makers. To provide guidance to Canadian ophthalmologists caring for patients with diabetes, the Canadian Ophthalmological Society (COS) has developed evidence-based clinical practice guidelines for the management of DR and DME.[2] The guidelines, which are summarized in the Appendix, address screening and diagnosis of DR, management of DM (specifically its impact on vision), and surgical and nonsurgical approaches to the treatment of DR and DME. This issue of *Ophthalmology Scientific Update* provides an overview of the COS guidelines and discussions around their recommendations.

Diabetic retinopathy (DR) remains the leading cause of avoidable blindness in people of working age worldwide.[3-5] In 2008, an estimated 2.4 million Canadians had diabetes mellitus (DM).[1] Of those, 17.5% and 15% had DR and diabetic macular edema (DME), respectively.[6,7] DME, the most common complication of DR, can develop at all stages of retinopathy. It involves a variety of morphological changes leading to retinal thickening and damage of the blood-retinal barrier. Although visual loss due to DME usually develops slowly, it represents the most common cause of visual impairment and blindness among people with diabetes.[8] Reductions in vision-related functions, such as reading and driving, also have significant consequences on quality of life.

Screening for DR

Screening is important for early detection and intervention to prevent the progression of DR.[9] However, studies have revealed that there is low compliance with recommended DR screening in Canada.[10,11] According to a 5-province study by Boucher et al,[10] almost 40% of DM patients have not been examined for DR. Another study demonstrated that only 32% of patients with Type 2 DM (T2DM) had met the Canadian Diabetes Association (CDA) recommended schedule for DR examination.[11] Barriers to regular screening include limited access to eye care professionals, fear of treatment, limited mobility due to poor health, and a lack of awareness of the risk of blindness from DR.[12-15]

The COS guidelines suggest that improvements in healthcare system infrastructure and better coordination among professions and organizations are needed to ensure better access to services.[2] New technologies that use retinal photography, such as digital cameras and teleophthalmology, can decrease barriers to screening, reduce travel time, and cost.[10] The sensitivity and specificity of these methods is equal to or exceeds slit lamp biomicroscopy,[16,17] and several models have demonstrated their effectiveness in Canada.[10,18-20]

As one of the first healthcare professionals whom patients consult for information about vision care, optometrists also play a role in detecting early signs of retinopathy and referring patients for further management.[8] Thus, there is an ongoing need for additional educational initiatives to train this group of eye care professionals to act as gatekeepers to streamline care for

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Table 1: Levels of nonproliferative diabetic retinopathy (NPRD)[2]	
Levels	**Characteristics**
Mild	Microaneurysms only
Moderate	More than microaneurysms, but less than severe NPDR
Severe	Any of: • >20 intraretinal hemorrhages in each of 4 quadrants • Definite venous beading in >2 quadrants • Prominent intraretinal microvascular abnormalities in >1 quadrant and no signs of proliferative diabetic retinopathy

high-risk individuals so referrals to ophthalmologists are made in a timely fashion.

In patients diagnosed with T1DM, vision-threatening DR is rare before puberty.[21,22] Therefore, the COS guidelines recommend initiating screening of children with T1DM at puberty unless other considerations indicate the need for earlier examination.[2] For teens diagnosed with T1DM after puberty, screening should start 5 years post-diagnosis. Subsequent screening should occur annually if no retinopathy is present, and at 3- to 6-month intervals in the presence of any nonproliferative DR (NPDR; Table 1).[8]

T2DM patients should be screened every 1–2 years if no retinopathy is present, depending on their anticipated compliance. Once NPDR is detected, screening should be conducted at least annually for mild NPDR and more frequently (every 3–6 months) for moderate or severe NPDR.[2] Optical coherence tomography (OCT) testing, however, is not recommended for routine screening in patients without retinopathy, or in the absence of macular edema on clinical examination in those with mild to moderate NPDR and vision better than 20/30. A screening schedule is presented in Table 2.[2]

The Increasing Role of Teleophthalmology in Detecting and Diagnosing DR in Canada

The electronic transmission of ocular images and clinical data from a remote site represents the potential for all patients, despite geography or socioeconomic status, to receive a retinal evaluation to determine DR presence and severity. Both DR and DME can be detected with a high level of sensitivity and specificity using properly designed teleophthalmology systems.[23-25] The geography and demographics of Canada are well-suited to this technology, and there already exists a wealth of teleophthalmology experience using both screening and distance evaluation programs.[10,18-20] The COS recommends the use of teleophthalmology to improve access to culturally, economically, or geographically isolated populations, and calls on the federal and provincial governments to recognize teleophthalmology as a legitimate form of assessment and to encourage the development of these programs.

Risk Factors Associated with DR Development and Progression

The COS guidelines emphasize that management of patients with DM requires a multidisciplinary team led by the family physician and/or endocrinologist.[2] Ophthalmologists should discuss the importance of glycemic control with diabetic patients at regular intervals. Regular communication between the ophthalmologist and family physician or endocrinologist is also essential.

Optimal glycemic control and other potential risk factors

The relationship between tight glycemic control and reduction in DR incidence and progression has been demonstrated in

Table 2: Screening schedule for DR[2]		
	Type 1 DM	**Type 2 DM**
Initiation	• 5 years after diagnosis • In children and adolescents, initiate screening at puberty unless there are factors necessitating earlier investigation	• At diagnosis
Frequency	• No DR: annually • Signs of DR: every 3–6 months, depending on severity • After DR treatment: tailor according to residual severity	• No DR: Every 1–2 years* • Signs of DR: at least annually for mild, 3–6 months for moderate, depending on severity • After DR treatment: tailor according to residual severity

* The COS recommends that screening every 2 years is adequate for T2DM patients as long as tight adherence can be maintained; otherwise, screen annually.

large randomized and epidemiological studies.[26,27] Optimal glycemic control was established as a hemoglobin A1C ≤7.0% by the Diabetes Control and Complications Trial Research Group and the United Kingdom Prospective Diabetes Study Group.[28,29] Glycemic levels should always be weighed against the risk of hypoglycemia. This is of particular importance for T2DM patients, where the benefit of achieving an HbA1c ≤ 6.5% must be weighed against the risk of increased cardiovascular mortality in those at increased risk of cardiovascular disease (CVD).[30,31]

Blood pressure (BP) and lipid control

It is important for DM patients to maintain optimal BP control (ie, <130/80 mm Hg) to reduce the risk of onset or delay the progression of DR. Patients should be advised of the need to obtain good BP control throughout their treatment. Although observational studies suggest that dyslipidemia increases the risk of DR and DME,[32,33] there is limited evidence to suggest that treatment of diabetes-associated dyslipidemia affects DR progression. However, the CDA recommends control of blood lipids to reduce the incidence and progression of the nonocular complications of diabetes.[7]

Lifestyle changes

While moderate consumption of alcohol (1-3 drinks/day) is associated with a 33%-56% lower incidence of DM and a 34%-55% lower incidence of DM-related coronary artery disease, heavy consumption (>3 drinks/day) may be associated with up to a 43% increased incidence of DM.[34] Although some studies suggest that smoking increases the risk for DR, nephropathy, and neuropathy in patients with T1DM,[35,36] and increases the risk of coronary artery disease, stroke, and macrovascular complications in T2DM, its role in affecting DR progression is controversial. However, as smoking cessation is important to reduce the risk of CVD and other serious conditions, all smokers with DM should be advised to quit and provided with support. The COS also urges physicians to avoid recommending antioxidant vitamin supplementation in excess of the recommended daily allowance because of the lack of evidence of additional benefits in diabetic retinopathy.[37]

Treatment Modalities

Treatment regimens for patients with DR and DME include laser (focal, grid, and panretinal), intraocular steroids, and vascular endothelial growth factor (VEGF) inhibitors. Although vitrectomy may be beneficial in the treatment of nonclearing vitreous hemorrhage and tractional detachment,[38] its use in the treatment of DME remains controversial.

Treatment of DME

Focal and grid laser

Evidence from the National Eye Institute-sponsored Early Treatment Diabetic Retinopathy Study (ETDRS)[39] demonstrated that focal photocoagulation of clinically significant macular edema (CSME) reduces the chance of moderate vision loss (3 ETDRS lines) by 50% at 3 years. However, visual improvement by ≥3 lines was achieved in only 3% of the treated group. CSME is defined 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
- a zone of retinal thickening of ≥1 disc area within 1 disc diameter of the center of the macula

The COS guidelines recommend focal laser treatment in eyes that demonstrate CSME by ETDRS criteria without central macular thickening.[2]

Intraocular steroids

Although multiple reports have described the benefits of intraocular injection of steroids in patients with DME, including temporary improvement in visual acuity (VA) and rapid reduction in macular thickness,[40-42] their use is associated with a significant increase in cataract formation and rise in IOP.

In 2008, the Diabetic Retinopathy Clinical Research Network (DRCRnet)[43] compared focal/grid laser treatment with intraocular injection of 1 mg or 4 mg of triamcinolone in 693 subjects with DME involving the centre of the fovea. At the 2-year follow-up, VA was significantly better in the laser group as compared to the steroid groups. The study also confirmed higher rates of cataract surgery and IOP in both triamcinolone groups compared to the laser-treated group.

Several intraocular steroid implants are currently being investigated, but the only implant available in Canada is a dexamethasone (0.7 mg) intravitreal implant (Ozurdex®).[44] This agent is approved for ME after central retinal vein occlusion and noninfectious posterior uveitis, but not for DME.

It is important to note that pseudophakic patients may have greater benefit from intraocular steroids, with visual acuity improvements similar to those achieved with anti-VEGF therapies.[45]

VEGF inhibitors

Efficacy of intraocular anti-VEGF therapy in patients with DME has been shown in a number of trials (Table 3)[45-50] in terms of both VA and central macular thickness.

In 2010, the DRCRnet study[45] reported the effectiveness of ranibizumab with immediate or delayed focal/grid laser compared to intraocular triamcinolone with immediate laser or to focal/grid laser alone. Patients in this study had fovea-involving DME on OCT and examination, and VA of 20/32 to 20/320. Both 1- and 2-year analyses revealed that patients receiving ranibizumab have gained, on average, 6 more letters than the groups treated with laser alone and the triamcinolone/laser.[45,46] In the ranibizumab groups, patients received an average of 8.5 treatments in the first year and 2.5 treatments in year 2. At the 1-year endpoint, in the RESOLVE trial,[47] patients receiving

Table 3: Randomized, controlled studies evaluating the use of vascular endothelial growth factor inhibitors in diabetic macular edema

Study	N	Study groups	Visual outcome, mean change (letters)	Endpoint
DRCRnet[45,46]	854 eyes	Focal laser	+3	1 year
		Ranibizumab + laser	+9*	
		Ranibizumab + delayed laser	+9*	
		Triamcinolone + laser	+4	
	628 eyes	Focal laser	+3	2 years
		Ranibizumab + laser	+7*	
		Ranibizumab + delayed laser	+9*	
		Triamcinolone + laser	+2	
RESOLVE[47]	151	Focal laser	-1.4	1 year
		Ranibizumab 0.3 mg	+10.3* (pooled data)	
		Ranibizumab 0.5 mg		
RESTORE[48]	354	Focal laser	+0.9	1 year
		Ranibizumab	+6.8*	
		Ranibizumab + laser	+6.4*	
READ-2[49]	126	Focal laser	+0.5	6 months
		Ranibizumab	+7.4*	
		Ranibizumab + laser	+3.8*	
		Focal laser	+5.1	2 years
		Ranibizumab	+7.7	
		Ranibizumab + laser	+6.8	
BOLT[50]	80	Focal laser	-4.6	1 year
		Bevacizumab	+5.6*	

* Statistically significant difference
Adapted from Hooper P et al. *Can J Ophthalmol.* 2012;47(2 Suppl):S1-S30.

ranibizumab (0.3 or 0.5 mg) gained an average of 10.3 letters compared with the laser arm, which lost an average of 1.4 letters. The RESTORE study[48] compared focal laser to ranibizumab alone or in combination with laser. At 1 year, the ranibizumab groups (with and without laser) improved by approximately 6 letters, and the laser-alone group improved by 0.8 letters. Similarly, in the READ-2 study,[49] patients with DME involving the centre of the macula were randomized to ranibizumab, focal or grid laser, or both. Although the ranibizumab-only group had significantly greater improvement in VA at 6 months, the mean visual outcome at 2 years was not significantly different between the 3 groups, and anatomic outcomes were better in the laser arms of the study. In the prospective, randomized BOLT study (N=80 eyes),[50] patients receiving intravitreal bevacizumab gained 8 letters, whereas those receiving laser lost 0.5 letters.

Based on these results, the COS guidelines recommend that eyes with CSME by ETDRS criteria without central macular thickening receive focal laser.[2] Eyes with central macular thickening should be treated with a VEGF inhibitor alone or in conjunction with focal laser, with Level 1 evidence for ranibizumab and Level 2 evidence for bevacizumab. Although bevacizumab is used extensively in clinical practice and is recommended by COS guidelines for treatment of DME, it is not approved by Health Canada for intraocular use or treatment of ocular complications, and its use is considered "off- label".

Vitrectomy

Evidence suggests that vitrectomy for DME may only benefit eyes with signs of vitreomacular traction on OCT. In the 1990s, Lewis et al[51] noted improvements in vision in 9 of 10 eyes with evidence of DME and vitreomacular traction

that underwent vitrectomy and separation of the posterior hyaloid. In 2010, the DRCRnet conducted a study involving 87 eyes with DME and vitreomacular traction undergoing vitrectomy.[52] At 6 months, retinal thickening was reduced by >50 m in 68% of eyes and 38% showed VA improvement (≥10 letters). Complications of vitrectomy included a small number of vitreous hemorrhages (5 eyes), elevated IOP requiring treatment (7 eyes), retinal detachment (3 eyes), and endophthalmitis (1 eye). Based on these findings, the COS guidelines suggest considering vitrectomy in patients with OCT findings that are suggestive of macular traction and macular edema.[2]

Proliferative Diabetic Retinopathy (PDR)

PDR is characterized by neovascularization of the retina, iris, or angle secondary to retinal ischemia.

Panretinal photocoagulation

The Diabetic Retinopathy Study (DRS) identified high-risk characteristics for DR progression (Table 4) and demonstrated that, in high-risk patients, panretinal photocoagulation (PRP) reduces the risk of severe vision loss (<5/200) by 50%.[53] While visual-field loss may occur after PRP, most patients are able to maintain peripheral vision sufficient for driving.[2] As per COS guidelines, it is recommended that eyes with high-risk DRS characteristics be treated with PRP to reduce the risk of severe vision loss.[2]

VEGF inhibitors

Macular edema may occur or worsen during PRP. In many cases, the edema resolves by 6 months.[39] In order to improve the short-term visual result in eyes with PDR and centre-involving ME, an intravitreal anti-VEGF injection should be considered at the time of PRP. Injection of an anti-VEGF agent with PRP also increases short-term neovascular regression rates.[54,55] Anti-VEGF agents may be used in patients with PDR and vitreous hemorrhage, to allow for sufficient clearing of vitreous hemorrhage so that PRP can be administered.[56] However, caution is warranted as anti-VEGF agents can cause rapid contraction of preretinal neovascular membranes, resulting in tractional detachment or need for vitrectomy.[57]

Vitrectomy

Vitrectomy should be considered in patients with PDR and nonclearing vitreous hemorrhage,[58] macular heteropia,[59] tractional macular detachment[60-63] or tractional rhegmatogenous detachment, or dense premacular hemorrhage.[64,65] Vitrectomy has also been show to improve outcomes in anterior segment neovascularization,[66,67] ghost cell glaucoma,[68] and progressive fibrovascular proliferation despite adequate PRP.[69] To reduce hemorrhage and the complications associated with vitrectomy, an anti-VEGF agent should be considered preoperatively in eyes with active PDR.[70-73]

Table 4: Diabetic Retinopathy Study – Definition of high-risk characteristics[53]

The presence of any 1 of the following constitutes high risk:

- NVD ≥¼ to ⅓ disc area
- Any NVD with vitreous or preretinal hemorrhage
- NVE ≥¼ disc area with vitreous or preretinal hemorrhage

NVD = neovascularization on or within 1 disc diameter of the optic nerve head; NVE = neovascularization elsewhere in the retina

Neovascularization of the iris (NVI)

Severe retinal ischemia can lead to iris neovascularization (NVI). Neovascularization of the angle can disturb the normal egress of aqueous in the eye and may increase IOP, causing neovascular glaucoma (NVG). In patients with DR and NVI or NVG, intravitreal anti-VEGF injection in conjunction with PRP is recommended, to aid in regression of neovascularization and reduce the risk of long-term glaucoma.

DR in Pregnancy

Although pregnancy in women with T1DM carries a transient increased risk of retinopathy, it does not appear to affect its long-term progression.[74] Fewer data are available on women with T2DM in pregnancy. In gestational diabetes, it is uncommon to develop retinopathy unless the diabetes persists beyond pregnancy.

The COS guidelines recommend that women with diabetes who are considering pregnancy undergo an ophthalmic evaluation. Repeat assessments should be conducted during the first trimester. For the remainder of pregnancy and the first year postpartum, assessments should be based on the stage of retinopathy and the rate of progression.

Although there is no clear evidence that fluorescein angiography causes harm in pregnancy, it can usually be deferred until after delivery and breastfeeding. Laser treatment poses no known risk to the fetus. The risks associated with the use of intravitreal anti-VEGF agents during pregnancy remain unclear, as there is insufficient evidence to determine a safety profile in pregnancy.

Economic Considerations for DR and DME Management

When referring to the COS guidelines, clinicians should remember that guidelines are, in general, only one component of medical decision-making. Although the guidelines reflect best evidence and the consensus of professionals in the therapeutic field, physicians should use their individual judgment, experience, and training in managing their patients. The guidelines

APPENDIX: List of COS recommendations[2]

1. For individuals with T1DM diagnosed after puberty, screening for DR should be initiated 5 years after the diagnosis of diabetes [*Level 1*]. For individuals diagnosed with T1DM before puberty, screening for DR should be initiated at puberty, unless there are other considerations that would suggest the need for an earlier exam [*Consensus*].
2. Screening for DR in individuals with T2DM should be initiated at the time of diagnosis of diabetes [*Level 1*].
3. Subsequent screening for DR in individuals depends on the level of retinopathy. In those who do not show evidence of retinopathy, screening should occur every year in those with T1DM [*Level 2*] and every 1–2 years in those with T2DM [*Level 2*], depending on anticipated compliance.
4. Once NPDR is detected, examination should be conducted at least annually for mild NPDR, or more frequently (at 3- to 6-month intervals), for moderate or severe NPDR based on the DR severity level [*Level 2*].
5. Given high-level evidence of effectiveness, properly designed teleophthalmology programs should be implemented to improve access to, and compliance with, monitoring in culturally, economically or geographically isolated populations of individuals with diabetes [*Level 1*].
6. To prevent the onset and delay the progression of DR, individuals with diabetes should be treated to achieve optimal blood glucose control (ie, HbA1C ≤ 7.0%) [*Level 1*].
7. As there is a continuous relationship between HbA1C and microvascular complications with no apparent threshold of benefit, patients should be advised of the incremental benefits associated with incremental reductions in HbA1C [*Level 1*]. In patients with T2DM, the incremental benefits of achieving an HbA1C ≤ 6.5% must be balanced against the risks of hypoglycemia or increased cardiovascular mortality in patients at elevated risk of cardiovascular disease [*Level 1*].
8. To reduce the risk of onset or to delay the progression of DR, individuals with diabetes should be treated to achieve optimal BP control (ie, <130/80 mm Hg) [*Level 1 for T1DM; Level 2 for T2DM*].
9. Eyes that demonstrate clinically significant macular edema by ETDRS criteria without central macular thickening should receive focal laser [*Level 1*]; however, eyes with central macular thickening should be considered for treatment with a VEGF inhibitor alone or in conjunction with focal laser [*Level 1 for ranibizumab; Level 2 for bevacizumab**].
10. Eyes that demonstrate evidence of vitreomacular traction and macular edema should be considered for vitrectomy [*Level 1*].
11. In eyes with DRS high-risk characteristics, PRP should be carried out to reduce the risk of severe vision loss [*Level 1*].
12. In eyes with proliferative retinopathy and centre-involving macular edema, an intraocular VEGF inhibitor injection should be considered at the time of PRP to improve the near-term vision result [*Level 1 for ranibizumab; Level 2 for bevacizumab**].
13. Consideration should be given to vitrectomy in eyes with nonclearing vitreous hemorrhage [*Level 1*], macular heterotopia [*Level 3*] or tractional macular detachment [*Level 3*], tractional rhegmatogenous detachment [*Level 3*], or dense premacular hemorrhage [*Level 3*].
14. In eyes with active PDR undergoing vitrectomy, VEGF inhibitors should be considered preoperatively to reduce hemorrhage and complications associated with vitrectomy [*Level 2 for bevacizumab**].
15. Patients with T1DM or T2DM who are considering pregnancy should be counselled to undergo an ophthalmic evaluation by an eye care specialist before attempting to conceive. Repeat assessments should be carried out during the first trimester and as indicated by the stage of retinopathy and the rate of progression during the remainder of pregnancy and through the first year postpartum [*Level 1 for T1DM and consensus for T2DM*].

* Bevacizumab is not approved by Health Canada for intravitreal use and treatment of ocular complications

T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; DR = diabetic retinopathy; NPDR = nonproliferative diabetic retinopathy; Hb = hemoglobin; BP = blood pressure; ETDRS = Early Treatment Diabetic Retinopathy Study; VEGF = vascular endothelial growth factor; DRS = Diabetic Retinopathy Study; PRP = panretinal photocoagulation; PDR = proliferative diabetic retinopathy

References used to support recommendations were assigned a level of evidence based on the criteria used by previous COS guidelines and other national organizations.

should also be examined in the context of resources and value to the patient and society. Although cost-effectiveness studies are more difficult to conduct than clinical trials and the number of such studies for DR is limited, the evidence thus far suggests that most DR interventions are cost effective.[2] Compared with diseases such as age-related macular degeneration, DR affects younger patients in whom the benefits of treatment are of greater duration. Furthermore, DR and DME are relatively responsive to treatment. The COS guidelines emphasize that there are considerable economic benefits of screening early and regularly, achieving optimal glycemic control, and using appropriate therapies to treat DR in a timely manner.

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