
Canadian Ophthalmological Society evidence-based clinical practice guidelines for the management of diabetic retinopathy

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INTRODUCTION

The objective of this document is to provide guidance to Canadian ophthalmologists regarding screening and diagnosis of diabetic retinopathy (DR), management of diabetes as it pertains specifically to DR, and surgical and non-surgical approaches to the treatment of DR. These guidelines apply to all Canadians with type 1 or type 2 diabetes of all ethnic origins. Other health professionals involved in the care of people with diabetes may find this document helpful.

These guidelines were systematically developed and based on a thorough consideration of the medical literature and clinical experience. These guidelines are not meant or intended to restrict innovation. Guidelines are not intended to provide a “cookbook” approach to medicine or to be a replacement for clinical judgment;¹ rather, they are intended to inform patterns of practice. Adherence to these guidelines will not necessarily produce successful outcomes in every case. Furthermore, these guidelines should not be used as a legal resource, as their general nature cannot provide individualized guidance for all patients in all circumstances.¹ Guidelines are not intended to define or serve as a legal standard of medical care.² Standards of medical care are specific to all the facts or circumstances involved in an individual case and can be subject to change as scientific knowledge and technology advance, and as practice patterns evolve. There is no expectation that these guidelines be applied in a research setting. No comment is made on the financial impact of procedures recommended in these guidelines.

Ideally, guidelines are flexible tools that are based on the best available scientific evidence and clinical information, reflect the consensus of professionals in the field, and allow physicians to use their individual judgment in managing their patients.³ These guidelines

should be considered in this context. Indeed, ophthalmologists must consider the needs, preferences, values, and financial and personal circumstances of individual patients, and work within the realities of their health-care setting. It is understood that there are inequities in human, financial and healthcare resources in different regions of the country and that these factors may affect physician and patient options and decisions.

These guidelines will be periodically reviewed by the Canadian Ophthalmological Society Clinical Practice Guideline Steering Committee, and will be updated as necessary in light of new evidence.

METHODS

An English-language literature search for the years 1997–2010 was conducted using PubMed, EMBASE, the Cochrane Library, the National Guideline Clearing House, and the United States Preventative Services Task Force databases. Furthermore, a hand search of the reference lists, as well as the table of contents of the most recent issues of major ophthalmology and diabetes journals, was carried out to locate seminal papers published before 1997 and to take into account the possible delay in the indexation of the published papers in the databases. Selected references were independently reviewed by at least 2 reviewers to ensure they were relevant and of acceptable methodological quality.

Recommendations were formulated using the best available evidence with consideration of the health benefits, risks, and side effects of interventions. References used to support recommendations were assigned a level of evidence based on the criteria used by previous COS guidelines (periodic eye examination in adults,⁴ cataract surgery,⁵ and glaucoma⁶) and other national organizations^{7–9} and are outlined in Table 1. In the absence of direct evidence, recommendations were written to

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Table 1—Criteria for assigning levels of evidence to the published studies	
Level	Criteria
Studies of diagnosis	
Level 1	i. Independent interpretation of test results (without knowledge of the result of the diagnostic or gold standard) ii. Independent interpretation of the diagnostic standard (without knowledge of the test result) iii. Selection of people suspected (but not known) to have the disorder iv. Reproducible description of both the test and diagnostic standard v. At least 50 patients with and 50 patients without the disorder
Level 2	Meets 4 of the Level 1 criteria
Level 3	Meets 3 of the Level 1 criteria
Level 4	Meets 1 or 2 of the Level 1 criteria
Studies of treatment and prevention	
Level 1A	Systematic overview or meta-analysis of high-quality randomized controlled trials a) Comprehensive search for evidence b) Authors avoided bias in selecting articles for inclusion c) Authors assessed each article for validity d) Reports clear conclusions that are supported by the data and appropriate analysis OR Appropriately designed randomized, controlled trial with adequate power to answer the question posed by the investigators a) Patients were randomly allocated to treatment groups b) Follow-up at least 80% complete c) Patients and investigators were blinded to the treatment* d) Patients were analyzed in the treatment groups to which they were assigned e) The sample size was large enough to detect the outcome of interest
Level 2	Randomized, controlled trial or systematic overview that does not meet Level 1 criteria
Level 3	Nonrandomized clinical trial or cohort study
Level 4	Other
Studies of prognosis	
Level 1	a) Inception cohort of patients with the condition of interest, but free of the outcome of interest b) Reproducible inclusion/exclusion criteria c) Follow-up of at least 80% of subjects d) Statistical adjustment for extraneous prognostic factors (confounders) e) Reproducible description of outcome measures
Level 2	Meets criterion a) above, plus 3 of the other 4 criteria
Level 3	Meets criterion a) above, plus 2 of the other criteria
Level 4	Meets criterion a) above, plus 1 of the other criteria
*In cases where such blinding was not possible or was impractical (e.g., intensive vs conventional insulin therapy), the blinding of individuals who assessed and adjudicated study outcomes was felt to be sufficient.	

reflect unanimous consensus of the expert committee. In the event of disagreement, wording changes to recommendations were proposed until all committee members were in agreement. The citations used by the committee to arrive at consensus are indicated in the relevant preamble accompanying each recommendation.

The guidelines highlight key points from the data in 2 ways. “Key Messages” are key inferences from the dataset and, in some cases, extrapolations from it. Although considered important, they are not assigned an evidence-based weighting.

“Recommendations” are evidence-based statements regarding patient management and are supported by the cited literature.

In some instances, treatment recommendations were based on evidence from studies of 1 medication from a given class (e.g., vascular endothelial growth factors [VEGF] inhibitors). When evidence relates to 1 or more

medications from a recognized class of agents, the recommendation was written to pertain to the class, with the specifically studied agents identified within the recommendation and/or the cited references. It is important to note that the relative effectiveness and side effect profile of class members may vary.

Where possible, the content of this document was developed in accordance with the Canadian Medical Association *Handbook on Clinical Practice Guidelines*¹ and the criteria specified in the 6 domains of the *Appraisal of Guidelines Research and Evaluation II (AGREE II) Instrument*.¹⁰ These domains cover the following dimensions of guidelines: scope and purpose, stakeholder involvement, rigor of development, clarity and presentation, applicability, and editorial independence. A draft version of the document was reviewed by numerous individuals (including comprehensive

Levels	Characteristics
Mild	Microaneurysms only
Moderate	More than microaneurysms, but less than severe NPDR
Severe	Any of: <ul style="list-style-type: none"> ● >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 DR

Note: DR, diabetic retinopathy; NPDR, nonproliferative diabetic retinopathy.

ophthalmologists, retina subspecialists, optometrists, and family physicians) from a variety of practice and regional settings. Revisions were incorporated where relevant.

DEFINITIONS

Diabetic retinopathy

Diabetic retinopathy is a term that refers to the retinal changes induced by diabetes. It is subdivided into nonproliferative and proliferative stages, either of which may be associated with macular edema.

Nonproliferative diabetic retinopathy

For current clinical practice purposes, the International Classification of Diabetic Retinopathy¹¹ describes 3 levels of nonproliferative diabetic retinopathy (NPDR) (Table 2) based on risk of progression.

More detailed grading of DR, such as the Airlie House classification (Wisconsin system), based on grading 7 30° stereoscopic fields has been used in major studies of risk factors and treatment.¹² It has become the basis for detailed grading in DR studies. As well, a clinical grading scale of the Early Treatment Diabetic Retinopathy Study (ETDRS) quantified the risk of DR progression associated with the severity of specific lesions.^{13,14}

Proliferative diabetic retinopathy

Proliferative diabetic retinopathy (PDR) is the presence of neovascularization of the retina or iris in DR secondary to retinal ischemia. The Diabetic Retinopathy Study (DRS)^{15,16} definition of high-risk characteristics is outlined in Table 3.

The presence of any 3 of the following constitutes high risk: <ul style="list-style-type: none"> ● Neovascularization ● NVD ● Severity of neovascularization <ul style="list-style-type: none"> – NVD > ¼ disc area in size – NVE > ½ disc area in size ● Preretinal or vitreous hemorrhage
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Note: DRS, Diabetic Retinopathy Study; NVD, neovascularization of the disc; NVE, neovascularization elsewhere.

<ol style="list-style-type: none"> 1. Retinal thickening at or within 500 µm of the centre of the fovea 2. Hard exudates at or within 500 µm of the centre of the fovea associated with retinal thickening 3. Retinal thickening 1 disc area in size 1 disc diameter from the centre of the fovea
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Note: ETDRS, Early Treatment Diabetic Retinopathy Study.

Diabetic macular edema

The ETDRS^{17,18} defined diabetic macular edema (DME) as retinal thickening at or within 1 disc diameter of the centre of the fovea. It further defined clinically significant macular edema (CSME) by the 3 criteria outlined in Table 4. Introduction of optical coherence tomography (OCT) into clinical practice has significantly enhanced our ability to detect small amounts of retinal edema,¹⁹ and more recent studies have used the presence of central macular thickening on OCT to define “clinical significance” for treatment purposes.

EPIDEMIOLOGY OF DIABETES

KEY MESSAGES

- The incidence and prevalence of diabetes in Canada are projected to increase steadily due to demographic trends, including an aging population and high rates of obesity.
- The prevalence of DR is projected to increase as the prevalence of diabetes increases. This has important implications for healthcare human resources and costs, and hence policy implications.
- Aboriginal populations in Canada are disproportionately affected by diabetes and DR. Strategies are needed to provide culturally appropriate programs to prevent, screen, and treat diabetes and DR in these populations, who often reside in remote and under-served areas.

Prevalence of diabetes

In 2008, there were an estimated 2.4 million Canadians with diabetes. This represented a 70% increase from 1998. It is estimated that the prevalence could increase to 3.7 million by 2018/19.²⁰ It is conservatively estimated that 20% of all diabetes cases are undiagnosed, so the actual prevalence is likely significantly higher.²⁰

Incidence of diabetes

Canada’s National Surveillance System notes a significant increase in the incidence of diabetes.²⁰ In Ontario, the overall age and sex-adjusted incidence rose from 5.2% in 1995 to 8.8% in 2005.²¹

Factor	Trends and impact
Aging population	Because the prevalence of diabetes increases around middle age, and the number of senior citizens is predicted to increase from 13.7% of the total population in 2006 to ~24% in 2031, the projected increase in diabetes prevalence will be dramatic. ³²
Increasing prevalence of obesity	Obesity rates increased from 11% in 1972 to 24% in 2005. A total of 59% of adult Canadians are overweight and 23% are obese. Obesity and the incidence of diabetes are directly related. ³³
Increasing immigration from high-risk populations	Between 2001 and 2006, 80% of Canadian immigrants came from high-risk populations including 58.3% from Asia and the Middle East, 10.8% from Central and South America, and 10.6% from Africa. By 2031, between 25% and 28% of the population could be foreign-born, and between 29% and 32% of the population could belong to a visible minority group, as defined in the Employment Equity Act. This would be nearly double the proportion reported by the 2006 Census. This would surpass the proportion of 22% observed between 1911 and 1931, the highest during the twentieth century. About 55% of this population would be born in Asia and South-East Asian countries—nations with a very high incidence of type 2 diabetes. ³⁴
Aboriginal population growth	The prevalence varies also by economic development, and as a result, the prediction of marked economic development in populous nations of the world such as India leads to a marked increase in the predicted diabetes prevalence in people from these countries. ²⁰ Aboriginals in Canada have 2.5–5 times higher rates of diabetes than the general population. ^{35,36} Between 1996 and 2003, the Aboriginal population grew by 45%, almost 6 times the growth rate of non-Aboriginals. ³⁷

Type 1 diabetes versus type 2 diabetes

Estimates of the proportion of diabetes that is type 2 range from 70% to 90%²² (see Appendix A for definitions). Although type 2 diabetes is more prevalent in the general population, type 1 diabetes is among the most common chronic diseases in children. The documented increasing prevalence of type 2 diabetes in children, however, may reverse this order within 2 decades.^{23,24} An increase in the frequency of type 2 diabetes in the pediatric age group has been noted in several countries^{24–28} and has been associated with the increased frequency of childhood obesity.²⁹ Recent studies suggest that up to 45% of children with newly diagnosed diabetes have diabetes with a type 2 pattern.³⁰ This decrease in the age at onset of type 2 diabetes will be an important factor influencing the future burden of the disease and its complications.³¹

What factors affect prevalence and incidence of diabetes?

Factors impacting the prevalence of diabetes in Canada include increasing prevalence of obesity, an aging population, increasing immigration from high-risk populations, Aboriginal population growth, and socioeconomic factors. These are discussed in greater detail in Table 5. These factors have important implications with respect to health-care planning and resource allocation. The trends predict an increase in the number of individuals with diabetes as well as associated complications. Increased healthcare and societal costs are expected.

Diagnostic thresholds for diabetes

A fasting plasma glucose of 7.0 mmol/L correlates most closely with a 2-hour plasma value of ≥ 11.1 mmol/L in a 75-g oral glucose tolerance test and best predicts the development of retinopathy.⁸ Current criteria for the diagnosis of diabetes are summarized in Appendix B. With any change in the diagnostic criteria for diabetes, the incidence and prevalence of the disease will change.

EPIDEMIOLOGY OF DIABETIC RETINOPATHY

KEY MESSAGES

- DR remains the leading cause of legal and functional blindness for persons in their working years (ages 25–75) worldwide. The overall incidence continues to increase given the epidemic of new-onset diabetes.
- The rates of both NPDR and PDR have been found to be higher in the Canadian Aboriginal population, compared with indigenous populations around the world, and are second only to cataract as a cause of visual loss.

Diabetic retinopathy remains the leading cause of legal and functional blindness for persons in their working years (ages 25–75) worldwide.^{38–40} The most recent U.S. data support the findings that DR is directly correlated with age, duration of diabetes, elevated glycosylated hemoglobin (A1C), hypertension, non-white ethnicity, and insulin use.³⁹ In Canada, it is expected that almost all patients with type 1 diabetes and >60% of patients with type 2 diabetes will develop some form of DR in the first 2 decades after the diagnosis of diabetes.⁴¹ The increased prevalence of diabetes has also increased the incidence of sight-threatening forms of retinopathy (PDR and CSME). Although the rates of progression to DR have decreased due to better glycaemic, blood pressure (BP), and cholesterol control, the overall incidence continues to increase given the epidemic of new-onset diabetes.^{38–40,42,43}

The rates of both NPDR and PDR have been found to be higher in the Canadian Aboriginal population, compared with indigenous populations around the world. In Canada, 28.5%–40% of indigenous peoples with diabetes examined revealed some DR, with PDR found in 2.5%.⁴⁰ In Kahnawake, Quebec, 25% of patients had retinopathy 10 years after diagnosis of the disease.⁴⁴ A major shortcoming remains the accurate

Table 6—Prevalence of reported vision loss in Canada by cause and ethnicity, 2007*

	All ethnicities		Non-Aboriginal/non-visible minority		Aboriginal/visible minorities	
	n	%	n	%	n	%
Macular degeneration	89,241	10.9	84,641	10.8	4380	12.0
Cataract	133,836	16.4	120,685	15.5	13,151	36.1
Diabetic retinopathy	29,920	3.7	20,992	2.7	8928	24.5
Glaucoma	24,937	3.1	22,565	2.9	2373	6.5
Refractive error/other	539,236	66.0	531,650	68.1	7586	20.8
All vision loss	817,170	100.0	780,533	100.0	36,418	100.0

*Adapted with permission from Cruess et al.⁴⁵ ©Elsevier 2011.

collection of vision loss data among Canada’s Aboriginal and visible minority populations.

Canada has no major population eye health studies on which to draw guidance. Data from available Canadian sources was summarized in a recent publication (Table 6).⁴⁵ Based on this publication, in 2007, an estimated 817,170 Canadians had vision loss (defined as <20/40 [$<6/12$] in the better-seeing eye). For the non-Aboriginal/non-visible minorities population, the largest source of vision loss is refractive error (68.1%), with DR in fifth place at 2.7%; for the Aboriginal/visible minorities population, cataract was the most common cause (36.1%), with DR in second place (24.5%).

PATHOPHYSIOLOGY OF DIABETIC RETINOPATHY

The exact mechanism by which chronic hyperglycemia causes the development of DR is not completely understood, and is most likely multifactorial. Pathways that have been implicated in the pathogenesis of DR include effects on cellular metabolism, signaling, and growth factors. Some of the most important features include the accumulation of sorbitol and advanced glycation end products, oxidative stress, protein kinase C (PKC) activation, inflammation, upregulation of the renin-angiotensin-aldosterone system, and increases in VEGF.⁴⁶

Retinal vascular changes were known to occur in DR before the advent of fluorescein angiography. A widening of the retinal arteriolar caliber is an early physiological indicator of microvascular dysfunction.⁴⁷ The retinal arteriolar widening is postulated to lead to increased capillary pressure that results in microaneurysm formation, leakage, and edema as well as intraretinal hemorrhage from capillary rupture.⁴⁸ Widening of the retinal venules is correlated with DR progression and predicts the development of proliferative DR.⁴⁹ The mechanisms of venule dilatation include hypoxia, inflammation and endothelial dysfunction.^{50,51}

Diabetes-related retinal vascular dysfunction commences within weeks of diabetes onset and is characterized by increased blood flow, impaired autoregulation, and abnormal

permeability to plasma proteins.^{52,53} NPDR is manifested by excessive capillary permeability leading to inner blood retinal barrier dysfunction,⁵⁴ capillary basement membrane thickening,⁵⁵ pericyte and smooth muscle depletion,^{56,57} microaneurysm formation,⁵⁸ capillary closure, and nonperfusion.⁵⁹ Levels of vasoactive factors such as VEGF in the vitreous increase as nonperfusion increases and contribute to the development of new vessels on the surface of the retina and optic nerve (i.e., PDR).

It has traditionally been felt that DR was due only to microvascular abnormalities, but neuroretinal compromise may occur even before microvascular changes.⁴⁶ It is felt that diabetes can adversely affect the entire neurosensory retina through accelerated neuronal apoptosis and altered metabolism of neuroretinal supporting cells.⁶⁰

NON-RETINAL DIABETIC OCULAR PATHOLOGIES CONTRIBUTING TO VISION COMPROMISE

In addition to its causative role in the development of DR, diabetes has been implicated in a number of other ocular disorders that may affect vision. People with diabetes are at increased risk of developing keratopathy ranging from punctate epithelial erosions to epithelial loss, and may manifest delayed wound healing after surgical and nonsurgical trauma.⁶¹

The effects of diabetes on the lens are well known and include refractive changes associated with shifts in blood glucose as well as accelerated development of cataract.

The association between diabetes and chronic open-angle glaucoma is less clear, with some studies demonstrating an association and others not.⁶ A recent meta-analysis suggests that the balance of evidence favours an association.⁶²

Similarly, although diabetes has generally been considered to have a strong association with the development of both central and branch retinal vein occlusion, a recent analysis demonstrated the association to be less pronounced (odds ratio [OR], 1.5; 95% confidence interval [CI], 1.1–2.0) and significantly less than for hypertension (OR, 3.5; 95% CI, 2.5–5.1).⁶³

People with diabetes also seem to be at increased risk for nonarteritic ischemic optic neuropathy, with the best data coming from the Ischemic Optic Neuropathy Decompression Trial, which demonstrated a prevalence of diabetes within the study population of 23.9%.⁶⁴

SCREENING

KEY MESSAGES

- Compliance with recommended screening is low in the Canadian population.
- Improvement of the healthcare system infrastructure and better coordination and cooperation across a wide range of professions and organizations will help to ensure better availability of quality services to people with diabetes.
- Provided adequate sensitivity and specificity are maintained, clinical examination to detect the presence and severity of DR may be achieved by dilated retinal examination by slit lamp ophthalmoscopy, or by retinal photography.
- The use of new technologies such as digital cameras and teleophthalmology can improve access to screening.
- There is little reason to routinely obtain OCT in eyes of people with diabetes and no retinopathy, or in eyes with mild to moderate DR (with vision better than 20/30) when clinical examination fails to show evidence of macular edema.
- Timely and appropriate follow-up care with quality assurance needs to be ensured after screening.

RECOMMENDATIONS

1. For individuals with type 1 diabetes diagnosed after puberty, screening for DR should be initiated 5 years after the diagnosis of diabetes [Level 1⁶⁵⁻⁶⁷]. For individuals diagnosed with type 1 diabetes 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 type 2 diabetes should be initiated at the time of diagnosis of diabetes [Level 1^{68,69}].
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 type 1 diabetes [Level 2⁷⁰] and every 1–2 years in those with type 2 diabetes [Level 2^{71,72}] 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^{73,74}].

Effectiveness of current screening methods

Screening plays an important role in early detection and intervention to prevent the progression of DR, as low vision/blindness is substantially reduced among people with diabetes

who receive recommended levels of care.⁷⁵ Despite the high level of clinical efficacy and cost effectiveness of DR screening and treatment, problems remain with screening and treatment compliance. Many people with diabetes do not access regular eye examinations and the barriers that prevent them from attending for screening are numerous.

Successful distribution of comprehensive guidelines to ophthalmologists and optometrists in many locations has not resulted in any significant impact on management practices for DR, and recommendations for screening and examination have been poorly followed.⁷⁶⁻⁷⁹ A 52% rate of compliance with screening guidelines has been measured in the U.S. population⁸⁰ and an Australian study found that 50% of individuals with diabetes had not seen an eye care professional in the previous 2 years.⁸¹

In Canada, only 32% of people with type 2 diabetes met the Canadian Diabetes Association⁷ guideline-recommended schedule of evaluation for DR.⁸² Another study that examined diabetes screening patterns in 5 Canadian provinces showed that 38% of this diabetic cohort had never had an eye examination for DR and an additional 30% had not had an eye examination in the last 2 years.⁸³ In Alberta, most of those who obtained eye examinations had them within the first year after the diagnosis of diabetes. In the second and third year post-diagnosis of diabetes, the proportion of patients who met the CDA recommendation did not increase, remaining under two-thirds of the eligible population.⁸⁴

Factors affecting nonadherence to recommended guidelines are numerous. They include lack of awareness that DR can lead to blindness or that severe retinopathy can be asymptomatic.⁸⁵ Limited access to eye care professionals, particularly in remote areas⁸⁶⁻⁸⁸ can play a significant role. Fear of laser treatment, guilt about poor diabetes control causing retinopathy, the inconvenience of regular attendance,⁸⁵ limited personal mobility due to poor overall health, and self-reported apathy⁸⁹ may also deter patients from attending screening.

Physician recommendation regarding the necessity of a regular eye examination is the most significant predictor for receiving screening, and once a physician recommends it the screening rate improves.⁹⁰ Thus, all physician encounters with individuals with diabetes should be used as an opportunity for education regarding the need for regular eye screening and as well as risk factors associated with DR.

Evidence⁹¹ indicates that increasing patient awareness of DR, improving provider and practice performance, improving healthcare system infrastructure processes to make attendance more convenient for patients, using patient recall systems, and better outreach to disadvantaged populations can significantly improve screening rates for DR.

The use of new technologies such as mydriatic and non-mydriatic digital cameras⁹² and incorporating teleophthalmology in the healthcare system may lower barriers to screening, reduce travel time and cost, and create new

screening opportunities⁸³ and valuable educational opportunities for patients.⁸⁵

Any chosen screening strategy or program requires sufficient resource allocation and access to information technology to ensure comprehensive coverage and compliance with quality-assurance standards.⁹³

Initiation of screening in people with type 1 diabetes

In type 1 diabetes, sight-threatening retinopathy is very rare in the first 5 years of diabetes or before puberty.^{66,67} However, almost all patients with type 1 diabetes develop retinopathy over the subsequent 2 decades⁹⁴ and duration of diabetes is strongly associated with the development and severity of DR.^{73,74,95,96}

Data on temporal development of DR in relation to prepubertal or pubertal onset of diabetes appear conflicting, as prepubertal or postpubertal duration of diabetes may contribute differently to the development and progression of retinopathy. Postpubertal duration may be a more accurate determinant of development and progression of microvascular complications.^{67,97}

Based on the available evidence, for individuals with type 1 diabetes diagnosed after puberty, screening for DR should be initiated 5 years after the diagnosis of diabetes.^{65–67} For individuals diagnosed with type 1 diabetes before puberty, screening for DR should be initiated at puberty, unless there are other considerations that would suggest the need for an earlier exam.

Initiation of screening in people with type 2 diabetes

Duration of diabetes is the strongest risk factor linked to the development of retinopathy.^{96,98–102} The risk is continuous with no evident glycemic threshold. In addition, retinopathy is often found in individuals with other microvascular complications such as neuropathy and nephropathy.

At the time diabetes is diagnosed, up to 3% of persons who develop diabetes over age 30 have CSME or high-risk DR findings.¹⁰³ After a 10-year duration of diabetes, 7% of persons with diabetes were shown to have retinopathy, rising to 90% after 25 years.⁷⁴ Proliferative disease was found in 20% of people with diabetes who had the disease for more than 20 years.¹⁰⁴ DR prevalence was shown to be lower in patients diagnosed with diabetes after age 70, and patients with DR had a significantly higher median duration of diabetes (5.0 years) than those without DR (3.5 years).¹⁰⁵

Reports have suggested that the interval between the onset of type 2 diabetes and its diagnosis is 4–7 years.¹⁰⁶ Given this and the foregoing information, screening for DR in people with type 2 diabetes should be initiated at the time of diagnosis.

Screening intervals for people with diabetes

Since 1985, lower rates of progression to PDR and of severe visual loss from DR have been reported. This may reflect an increased awareness of retinopathy risk factors, earlier

identification and care for patients with retinopathy, as well as improved glucose, BP, and serum lipids management.¹⁰⁷

Type 1 diabetes

The EURODIAB Prospective Complications Study found that diabetes duration, onset before 12 years of age, and metabolic control were significant predictors of progression, even when adjusted for presence of baseline retinopathy.¹⁰⁸

No retinopathy Available evidence indicates that annual screening needs be carried out.⁷⁰

With retinopathy In the presence of any NPDR, patients should be examined at 3- to 6-month intervals according to the DR severity.⁷⁴

After treatment After laser or surgical treatment for DR, examination intervals for follow-up should be tailored to the residual DR severity level.

Type 2 diabetes

No retinopathy In the absence of any DR, screening intervals of 19–24 months, compared with screening intervals of 12–18 months, are not associated with an increased risk of referable retinopathy.⁷¹ Screening every 2 years has been shown to be safe and effective with no person progressing from having no retinopathy to sight-threatening retinopathy in <2 years.⁷² This approach reduces the number of screening visits by >25%, considerably reducing health-care costs, strain on resources and relieving patients with diabetes from unnecessary examinations.¹⁰⁹ However, screening intervals of >24 months are associated with an increased risk of sight-threatening DR.⁷¹

Based on the foregoing, in individuals with type 2 diabetes without retinopathy it would appear feasible to reduce screening intervals to every 2 years if tight adherence can be maintained. In most Canadian populations, however, such adherence to screening cannot be maintained. In this circumstance, annual screening may be safer.

With retinopathy 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 NPDR according to DR severity level.⁷³

After treatment After laser or surgical treatment for DR, screening intervals should be tailored to the residual DR severity level.

Evaluation tools

A screening evaluation for DR should include measurement of visual acuity, intraocular pressure and an evaluation to look for the presence of neovascularization of the iris and angle. Pupils should be dilated for the fundus examination,

except where non-mydriatic photography is used. Adequate sensitivity and specificity are required for the technique chosen. A comprehensive examination by a trained examiner should yield a sensitivity of 87% and a specificity of 94% in detecting DR.¹¹⁰ Using a photographic approach, the minimum sensitivity (compared with 7-field stereoscopic photographs read by trained graders) required for screening for DR has been suggested to be 80%^{111,112} or, in the case of repeated examinations that would detect DR missed at earlier examinations, 60%.¹¹³ Specificity levels of 90%–95% and technical failure rates of 5%–10% are considered appropriate.¹¹¹ It must be kept in mind that the lower the sensitivity and specificity of any given screening technique the higher the potential cost to the system and the patient, through missed treatment opportunities and the potential need for additional visits.

Biomicroscopy Slit lamp biomicroscopy with a 90D or 78D lens after pupil dilation is the current accepted routine practice for DR detection (sensitivity of 87.4% and specificity of 94.4%), and is preferred to direct ophthalmoscopy, which has lower and more variable sensitivity even when done by an experienced examiner (sensitivity 56%–98%, specificity 62%–100%).¹¹⁰ Use of contact lens biomicroscopy or OCT should be considered if the findings are equivocal, particularly if there is unexplained vision reduction.¹⁹ Training should ensure examiners have sufficient diagnostic accuracy, and adequate sensitivity and specificity.^{114,115}

Retinal photography Stereoscopic 7-field fundus 35-mm photography evaluated by a trained grader is the gold standard method of detecting DR and has been used in most of the large clinical trials in this area. However, it is costly and time consuming, and is rarely used in routine practice. Digital retinal photography is increasingly used in DR screening. On its own, it is not a substitute for a comprehensive eye examination, as other pathology may be missed, but there is high-level evidence that it can serve as a screening tool to identify patients with DR who require further evaluation and management.^{116–124} Fundus imaging has the additional advantage of being perceived by patients as a valuable educational resource.⁸⁵ It can be carried out with dilated pupils or with undilated pupils using non-mydriatic cameras.¹²⁵ The chosen technology, along with the number of fields examined will influence the sensitivity of screening.¹²⁶ In 1 representative study, the sensitivity for detecting sight-threatening retinopathy using a single camera field with mydriasis was measured at 82%, compared with 67% without mydriasis. By using 2 45° camera fields, an increase in sensitivity was measured to 95% with mydriasis and 54%–80% without mydriasis. Specificity was high (99%) and similar in all groups.¹²⁶

The detection of retinopathy by photographs and digital images read by various healthcare professionals generally reaches sensitivities of at least 80%, comparable to levels

reached by experienced clinicians using ophthalmoscopy.^{114,124,127}

Fluorescein angiography Fluorescein angiography has no role in screening for DR. It is an invasive examination with an inherent small risk of significant side effects, from mild and transient to severe such as anaphylaxis or cardiac arrest.

Optical coherence tomography OCT is a noncontact, non-invasive technique that produces cross-sectional images of the retina and optic disc similar to histological sections. It has an axial resolution of 10 μm (or better with newer instruments) and provides qualitative and quantitative data that correlate well with fundus stereophotography or biomicroscopy to diagnose DME. OCT may, in fact, be superior to biomicroscopy in detecting small amounts of retinal thickening.^{19,128} It has good reproducibility and provides accurate measurements of retinal thickness.^{129,130} OCT seems useful to detect macular thickening in the early stages of DR in patients with retinopathy with vision less than 20/25 and no clinical evidence of macular edema, enabling closer follow-up for eyes with early centre-involving DME.^{19,128,131,132} However, OCT does not help in predicting which eyes with subclinical DME (macular edema less than the ETDRS definition or centre-involving macular edema detected by OCT, yet clinically undetectable) will progress to clinically significant DME as defined by the ETDRS.¹³³ OCT has been incorporated as a routine measure in numerous ongoing studies of new treatments for DR.

Current data suggest that there is little reason to obtain OCT routinely in eyes with diabetes and no retinopathy, or mild to moderate DR with vision better than 20/30 when clinical examination fails to show evidence of macular edema.¹³⁴

Personnel

People with diabetes present to a variety of examiners, including family physicians, endocrinologists, optometrists, and ophthalmologists. DR screening should be a part of comprehensive care for people with diabetes and embedded in the health service system.

Adequate training and experience are essential for those involved in DR screening.¹¹⁴ Significant variability can exist in the ability of individual examiners to detect and stage DR; however, training improves accuracy and appropriateness of referrals.¹³⁵ Integrating remote health care workers into DR screening programs using retinal cameras has been shown to be useful with high photograph quality, and with quality not related to operator qualifications, certification or experience.¹³⁶

Combined approaches using different examiners may be an effective strategy to increase access to screening and respond to its increasing demand.^{137,138} A combined-examiner screening approach, such as that used in the United Kingdom, has been shown to increase routine, regular examinations.¹¹⁰

Category 1	System allows identification of those who have no or mild NPDR (ETDRS level 20 or below) from those that have more than mild NPDR (ETDRS level worse than 20).
Category 2	System can accurately determine if sight-threatening DR is present or not, as evidenced by any level of DME, severe NPDR (ETDRS level 53 or worse), or PDR (ETDRS level 61 or worse).
Category 3	System that can identify ETDRS-defined levels of NPDR (mild, moderate, severe), PDR (early, high risk), and DME with accuracy sufficient to determine appropriate follow-up and treatment strategies. This system allows patient management to match clinical recommendations based on clinical retinal examination through dilated pupil.
Category 4	This system matches or exceeds the ability of ETDRS photos to identify lesions of DR to determine levels of DR and DME. Indicates a program can replace ETDRS photos in any clinical or research program.

Note: DME, diabetic macular edema; DR, diabetic retinopathy; ETDRS, Early Treatment Diabetic Retinopathy Study; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

Effective diabetes eye screening and eye care for DR requires the coordination and cooperation of many people working across a wide range of professions and organizations. Collaborative efforts amongst professional organizations involved in diabetes care are needed to ensure the availability of high-quality services to every person with diabetes. Further and continuing education and training, implementation of quality-assurance standards and sustained efforts over many years will be required.

TELEHEALTH AND TELEOPHTHALMOLOGY

KEY MESSAGES

- Both DR and DME can be detected with a high level of sensitivity and specificity using properly developed teleophthalmology platforms.
- Teleophthalmology programs need to be constructed to match the needs of the particular jurisdiction and target population.
- Appropriate standards need to be upheld for all aspects of a teleophthalmology program including image acquisition, image reading, evaluation, quality assurance, scheduling and management of patients and their information, and image data and storage.
- The geography and demographics of Canada are particularly suited to the attributes of teleophthalmology.

RECOMMENDATION

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 I^{118,124,139}].

Teleophthalmology refers to the acquisition of ocular images and clinical data from a patient at a site distant from, and transmitted electronically to, the site of the reader and interpreter of these images. With its large land mass and relatively low density of population outside of urban centres, the geography and demographics of Canada

are particularly suited to the attributes of teleophthalmology.

The goals of teleophthalmology in diabetes are to improve access to allow all people with diabetes, despite being disadvantaged due to geography or socioeconomic status, the ability to receive retinal evaluation to determine the presence and severity of DR.

The American Telemedicine Association has established 4 categories of validation for telehealth for DR (Table 7).¹⁴⁰ Choice of a system for given application should be based on the needs of a particular population.

It is well accepted from major diabetes clinical trials that stereoscopic, 7-standard 30° field, colour 35-mm slides can be successfully used to evaluate DR.^{13,65,68,141} This then becomes the gold standard by which to evaluate and validate teleophthalmology digital imaging systems.^{121,123,142,143}

Can screening be accomplished by teleophthalmology?

There is evidence that certain teleophthalmology systems are acceptable for the evaluation of, or screening for, DR. There is considerable strong evidence that sensitivity and specificity >95% in detection of NPDR can be obtained by various teleophthalmology algorithms. More detailed discussion of these studies is found in Appendix C.

Can teleophthalmology detect macular edema?

Macular edema is traditionally detected by slit lamp biomicroscopy or stereoscopic fundus photography. Teleophthalmology systems must then compare themselves to these standards. Although not entrenched in teleophthalmology programs, newer objective and quantitative measures of macular edema like OCT may play a larger role in the near future.¹⁴⁴

There is considerable high-level evidence that teleophthalmology systems are capable of detecting DME, compared with the gold standards.¹²³ This is particularly true for stereoscopic systems.¹⁴⁵ Teleophthalmology platforms that do not incorporate stereoscopic use the presence of surrogate markers such as hard exudates, intraretinal hemorrhages, and microaneurysms located near to the fovea to suggest that there is macular edema present. It has been estimated that 95% of eyes with CSME and 97% of eyes

with any macular edema would be identified by the presence of hard exudates within 1 disc diameter of the fovea.¹⁴⁶ This approach would tend to over-refer patients who do not actually have CSME, but would have the advantage of identifying patients in need of closer follow-up.

If one is operating a Category 1 screening teleophthalmology program where any patient with more than mild NPDR is referred, stereopsis and detection of CSME may be less of an issue.¹⁴⁷ Furthermore, the difference in detection between monoscopic and stereoscopic photography in practice may be less than expected.^{148,149} For further information, see Appendix D.

Requirements of a teleophthalmology system

The equipment used for teleophthalmology should meet federal standards, including image acquisition hardware, systems for retinal image transmission, storage and retrieval, software for image analysis, and clinical workflow management. Equipment should provide image quality appropriate to meet clinical needs and current clinical guidelines. The diagnostic accuracy of any imaging system should be validated before its incorporation into a telehealth system.¹⁴⁰

Teleophthalmology programs

A teleophthalmology platform needs to be tailored to the type of teleophthalmology program that is being developed. Considerations include whether it is urban or rural, non-mydratic or mydratic, stereoscopic or not, compression, the goal of screening or distance evaluation, and the number and percentage of referral patients that will be generated. All programs need to include inter-reader quality control and reviews of telehealth program outcomes.

Teleophthalmology programs need to dovetail into existing traditional methods of managing DR. To be successful, it is essential to have a teleophthalmology coordinator linking patients and their information into this setting, organizing referrals and coordinating their return to the teleophthalmology program.

There is a wide spectrum of possible teleophthalmology programs available, which may provide different screening levels that can be tailored to different population needs, from basic screening (Category 1) to evaluative screening (Category 4). Programs need to be structured keeping in mind the limitations of teleophthalmology in evaluation of the peripheral retina.

A telescreening program can be used to differentiate eyes that are normal or have mild levels of retinopathy from those with more significant disease, thereby lessening the burden of screening by a traditional dilated fundus exam. One such system incorporated history and visual acuity, and evaluated a nonsystematic mydratic approach.⁸³ Pupil dilation with tropicamide 1% was deemed useful or necessary in 33.7% of the cohort to obtain sufficient image quality for grading.

Distance evaluation uses a teleophthalmology platform that tries to simulate, as closely as possible, clinical evaluation. It includes taking a history, obtaining visual acuity and intraocular pressure (IOP) measurement, stereoscopic photographs of the anterior segment, stereoscopic photographs of the disc and macula, and peripheral fundus photos.¹³⁹ These teleophthalmology platforms generally utilize American Telemedicine Association Category 3 or 4 teleophthalmology systems.^{123,140} Because these systems can accurately detect treatable DR and can be designed to grade cataracts and screen for glaucoma, this approach is ideally suited, but not limited, to a more rural or geographically isolated situation where transportation can be difficult and costly.¹⁵⁰

Teleophthalmology future directions

There is much ongoing research in teleophthalmology, particularly in the area of automated and computer-assisted grading.^{151,152} Automated detection of DR using published algorithms cannot yet be recommended for clinical practice,¹⁵³ as it is currently limited by technical failures due to vessel identification and artifacts, but algorithms are quickly maturing.¹⁵⁴ However, automated assessment does pose concern, as it may not detect findings other than DR such as emboli, hematologic concerns, findings suggestive of glaucoma, or other potentially abnormal findings during manual screening.^{83,150} Additional validation studies on larger and more diverse populations of patients with diabetes are needed, as automated grading may represent a cost-effective alternative to manual grading^{155,156} for early detection of DR. Although still very expensive and not very portable, OCT may play an important role in teleophthalmology in the future.¹⁴⁴

Canadian teleophthalmology programs

Canada has a wealth of teleophthalmology experience using both screening and distance evaluation programs. A telescreening program using mobile cameras in pharmacies has been operating in Quebec, and in some areas of other provinces.⁸³ As well, a DR teleophthalmology screening program working in collaboration with optometrists and aimed at urban or semi-urban DR populations have been successful in both Quebec¹⁵⁷ and Alberta.¹⁵⁸ In Alberta, starting in 2001, a prototype distance evaluation program was implemented for all First Nations people living on reserve.¹⁵⁹ This program continues to provide care by teleophthalmology to all First Nations reserves in Alberta.¹⁶⁰ Another teleophthalmology program was set up in 3 rural Alberta cities that do not have ophthalmologists.¹⁵⁰ In Quebec, a Health Canada/First Nations DR screening program for screening and follow-up for DR, as well as detection of macular degeneration and glaucoma, was initiated in 2008 with the aim of reaching all First Nation communities by 2012. Other smaller-scale and pilot programs have been initiated across the country.

RISK FACTORS FOR AND PREVENTION OF PROGRESSION OF DIABETIC RETINOPATHY

KEY MESSAGES

- Patients with diabetes benefit from care provided by a multidisciplinary team. Although diabetes management is primarily the responsibility of the patient's family doctor and/or endocrinologist, the ophthalmologist should discuss the importance of achieving target values with the patient and enquire about control at regular intervals.
- Patients with diabetes who are taking antiplatelet agents do not need to alter their medication regimen following the development of diabetic retinopathy.
- Given the lack of evidence to substantiate the benefit of antioxidant vitamin supplementation in excess of the recommended daily allowance in patients with diabetes, physicians should avoid recommending this to their patients.

RECOMMENDATIONS

6. To prevent the onset and delay the progression of DR, individuals with diabetes should be treated to achieve optimal blood glucose control (i.e., A1C \leq 7.0%) [Level 1^{161,162}].
7. As there is a continuous relationship between A1C and microvascular complications with no apparent threshold of benefit, patients should be advised of the incremental benefits associated with incremental reductions in A1C [Level 1^{161,162}]. In patients with type 2 diabetes, the incremental benefits of achieving an A1C \leq 6.5% must be balanced against the risks of hypoglycemia or increased cardiovascular mortality in patients at elevated risk of cardiovascular disease [Level 1¹⁶³⁻¹⁶⁵].
8. To reduce the risk of onset or to delay the progression of DR, individuals with diabetes should be treated to achieve optimal control of BP (e.g., $<$ 130/80 mm Hg) [Level 1^{74,166} for type 1 diabetes; Level 2¹⁶²⁻¹⁶⁴ for type 2 diabetes].

Glycemic control

Epidemiologic studies have shown a consistent relationship between A1C levels and the incidence of DR. Large RCTs and cohort studies have demonstrated that tight glycemic control reduces both the incidence and progression of DR.^{167,168} Some relevant studies are summarized in Appendix E. The benefits of tight control must always be weighed against the risk of hypoglycemia.^{161-163,165}

Long-term observational data from the Diabetes Control and Complications Trial (DCCT) showed that despite gradual equalization of A1C values after study termination, the rate of DR progression in the former

intensively treated group remained significantly lower than in the former conventionally treated group,^{169,170} emphasizing the importance of instituting tight glycemic control early in the course of diabetes. This concept is supported by the results of another RCT,¹⁷¹ in which participants initially assigned to intensive glucose control versus conventional treatment had lower 10-year incidence of severe retinopathy.¹⁷²

Patients should be questioned about their glycemic control at the first visit and at regular intervals subsequently, and the importance of good control should be stressed. Regular communication with the individuals who are primarily responsible for the management of the patient's blood glucose and overall diabetes care is essential.

Blood pressure control

Evidence from RCTs seems to indicate that tight control of BP is a modifiable factor for the incidence and progression of retinopathy among patients with diabetes. Results from several key studies are summarized in Appendix F. The best approach to achieve tight control of BP and the optimal target in each individual is beyond the scope of these guidelines. It is important for patients to be advised of the need to obtain good BP control and they should be questioned about the status of their BP throughout the course of their treatment. Again, regular communication with the individuals who are primarily responsible for the management of the patient's BP and overall diabetes management is essential.

Lipid control

Observational studies suggest that dyslipidemia increases the risk of DR, particularly DME.^{173,174} A small RCT conducted among 50 patients with DR found a nonsignificant trend in visual acuity improvement in patients receiving simvastatin treatment,¹⁷⁵ whereas another study reported a reduction in hard exudates, but no improvement in visual acuity in those with clinically significant DME treated with clofibrate.¹⁷⁶

In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study,¹⁷⁷ among 9795 participants with type 2 diabetes, those treated with fenofibrate were less likely than controls to need laser treatment (5.2% vs 3.6%, $p < 0.001$). However, the severity of DR, indications for laser treatment and type of laser treatment (focal or pan-retinal) were not reported.

Overall, the available evidence that treatment of diabetes-associated dyslipidemia results in a significant change in the progression of diabetic retinopathy is limited. Control of blood lipids is recommended by the Canadian Diabetes Association to reduce the incidence and progression of nonocular complications of diabetes.⁸

Antiplatelet therapy

The ETDRS showed that acetylsalicylic acid (ASA) (650 mg/day) had no beneficial effect on DR progression or loss of visual acuity in patients with DME or severe NPDR during 9 years of follow-up.^{178,179} ASA treatment was not associated with an increased rate of vitrectomy, nor was there an increase in the rate of severe vitreous hemorrhage or visual loss.^{178,179} A smaller RCT evaluating ASA alone and in combination with dipyridamole reported a reduction in microaneurysms on fluorescein angiograms in both groups, compared with placebo.¹⁸⁰ A similar trend was observed in a small RCT¹⁸¹ evaluating ticlopidine, although results were not statistically significant.

At this time, antiplatelet therapy, including ASA therapy, has not shown any demonstrable effect on the progression of DR. However, as the Canadian Diabetes Association recommends that antiplatelet therapy may be considered in people with stable CVD,⁸ many patients with DR may require antiplatelet therapy for concomitant CVD. There is no evidence to suggest that antiplatelet therapy should be modified in the presence of DR.¹⁷⁸

Protein kinase C inhibitor use

The PKC-DMES Study reported no significant reduction in progression of DR or incidence of DME after treatment with a PKC inhibitor in 686 patients with mild to moderate NPDR and no prior laser therapy.^{182,183}

Aldose reductase inhibitor use

Aldose reductase is the rate-controlling enzyme in the polyol pathway of glucose metabolism and is involved in pathogenesis of DR. Two aldose reductase inhibitors, sorbinil and tolrestat, did not reduce DR incidence or progression in individuals with type 1 diabetes in RCTs of 3–5 years' duration.¹⁸⁴

Growth hormone/insulin-like growth factor inhibitor use

Observations of improvements in DR after surgical hypophysectomy^{185,186} and of increased serum and ocular levels of insulin-like growth factor in patients with severe DR led to studies investigating the use of agents inhibiting the growth hormone/insulin-like growth factor pathway for prevention of DR.¹⁸⁷ A small RCT conducted over 15 months among 23 patients reported reduction in retinopathy severity with octreotide, a synthetic analogue of somatostatin that blocks growth hormone;¹⁸⁸ however, another RCT conducted over 1 year among 20 patients evaluating continuous subcutaneous infusion of octreotide found no significant benefits.¹⁸⁹ Two larger RCTs evaluating long-acting-release octreotide injection^{190,191} reported inconclusive results,¹⁹² with significant adverse effects.

Antioxidant use

Diabetes is associated with increased tissue content of lipid peroxidation byproducts and a reduced antioxidant defense system. Information showing increased oxidative

stress in diabetes comes mostly from experimental models of diabetes. Studies in human subjects with diabetes are controversial and have shown conflicting results. Epidemiologic studies have shown a correlation between dietary or supplemental intake of antioxidant and the incidence of CVD.¹⁹³ However, interventional studies using select antioxidant supplements failed to show significant benefits of supplementation;^{194–196} indeed, in some instances there was evidence of potential harm.

The Beta-Carotene and Retinol Efficacy Trial (CARET) revealed an increased incidence of lung cancer in patients who were smokers or who had a history of asbestos exposure and were on vitamin A supplementation.¹⁹⁷ Similarly, in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC), a greater incidence of lung cancer was observed in a subset of males who were smokers and were on vitamin A supplementation.¹⁹⁸

The San Luis Valley Diabetic Study found no protective effect of antioxidant intake on DR. Depending on insulin use, there appeared to be potential deleterious effects of nutrient antioxidants. Increased intake of vitamin E was associated with increased severity of DR among those not taking insulin. However, increased intake of β -carotene was associated with increased severity of DR among those taking insulin.¹⁹⁹

Given the lack of evidence to substantiate the benefit of antioxidant vitamin supplementation in excess of the recommended daily allowance in patients with diabetes, this practice should not be recommended.

Alcohol consumption

Reports of an association between alcohol consumption and DR have been limited mainly to cross-sectional data.^{200–202} A systematic review of 32 studies conducted between 1966 and 2003 assessed the effects of alcohol use on the incidence, management, and complications of diabetes in adults. Compared with no alcohol use, moderate consumption (1–3 drinks per day) was associated with a 33%–56% lower incidence of diabetes and a 34%–55% lower incidence of diabetes-related coronary artery disease. Compared with moderate consumption, heavy consumption (>3 drinks/day) may be associated with up to 43% increased incidence of diabetes.²⁰³

Cigarette smoking

Cigarette smoking has not generally been considered a strong risk factor for retinopathy. Studies in patients with type 1 diabetes suggest smoking increases the risk for DR, nephropathy, and neuropathy.^{204,205} It also increases the risk for macrovascular complications, coronary artery disease, stroke, and peripheral arterial disease among patients with type 2 diabetes. Besides increased risk for CVD, cigarette smoking is an independent and modifiable risk factor for the development of type 2 diabetes.²⁰⁶ Although smoking cessation is important to reduce the risk for CVD, its role in affecting progression in DR remains controversial.

TREATMENT MODALITIES

Treatment regimens for patients presenting with DR traditionally include laser (focal, grid, and panretinal), which has been demonstrated to be effective for selected patients in the DRS and ETDRS. More recently, intravitreal steroid and intravitreal VEGF inhibitors have been used alone or as a supplement to laser with good effect. Vitrectomy has been shown to be superior to observation in certain forms of nonclearing vitreous hemorrhage²⁰⁷ and remains the only way to remove fibrous proliferation and relieve tractional detachment (although the visual results of this surgery are mixed). The use of vitrectomy to treat DME remains controversial.

Treatment of macular edema

KEY MESSAGES

- There is increasing evidence that intravitreal injections of VEGF inhibitors are an effective treatment for DME and produce a larger gain in vision than focal or grid laser alone.
- Intravitreal injection of steroid results in rapid resolution of DME; however, the improvement is not sustained and is associated with a significant increase in the incidence of raised IOP and cataract. For pseudophakic patients, visual acuity improvements may approach those of anti-VEGF therapies.

RECOMMENDATIONS

9. Eyes that demonstrate clinically significant macular edema by ETDRS criteria without central macular thickening should receive focal laser [Level 1¹⁷]; however, eyes with central macular thickening should be considered for treatment with a VEGF inhibitor alone or in conjunction with focal laser [Level 1^{208,209} for ranibizumab; Level 2²¹⁰ for bevacizumab].
10. Eyes that demonstrate evidence of vitreomacular traction and macular edema should be considered for vitrectomy [Level 1^{211,212}].

Focal and grid laser The ETDRS^{17,18,213} found that focal and grid laser photocoagulation for CSME reduced the chance of moderate vision loss (3 ETDRS lines) by 50%, from 24% for the control group to 12% for the treatment group at 3 years. However, only 3% of the treated group achieved a 3 or more line gain in vision over the same period. Analysis of the subgroup with vision worse than 20/40 at baseline demonstrated 40% improved 6 or more letters after 3 years.²¹⁴ A recent study comparing focal laser to intravitreal triamcinolone also showed that 51% of laser-treated patients in the focal laser arm improved 5 letters or more at 2 years.²¹⁵

Intravitreal steroid Multiple case reports and case series have described the benefits of intravitreal injection of steroid in patients with macular edema, including temporary improvement in visual acuity and reduction of macular thickness.^{145,216–218} The use of intravitreal steroid is associated with significant increases in the rate of cataract formation and IOP rise. In 2008, the Diabetic Retinopathy Clinical Research Network (DRCRnet) reported on the results of an RCT of 693 subjects with DME involving the centre of the fovea, comparing focal/grid laser treatment with intravitreal injection of 1 or 4 mg of triamcinolone. Retreatment was carried out every 4 months if the edema persisted. At the 2-year follow-up, the visual acuity was significantly better in the laser group than in the 2 intravitreal injection groups. The rate of cataract surgery and of an IOP increase of 10 mm Hg or more was 51% and 33%, respectively, in the 4 mg of triamcinolone group and 13% and 4%, respectively, in the laser-treated group.²¹⁵ Later, the DRCRnet reported a comparison study between ranibizumab (RBZ) or triamcinolone combined with focal/grid laser compared with focal/grid laser alone. The study included patients with DME involving the centre of the macula both on clinical examination and as measured by OCT, and a visual acuity of 20/32 to 20/320. At 1 year there was no significant difference seen between the groups, although there was earlier improvement in vision with the use of steroid. IOP rise and cataract development were seen in a significant proportion of the steroid-treated patients.²¹⁹ Another study examined the effectiveness of a dexamethasone intravitreal delivery system in the treatment of macular edema. The proportion of eyes achieving 10 or more ETDRS letter gain in vision was significantly greater in the implant groups at 60 days, but was not statistically different from control at 180 days. The incidence of raised IOP was higher in the treated groups, but none required surgery for this rise, and in most cases the rise was observed on 1 visit only.²²⁰ An open-label study that examined the effectiveness of the 700- μ g dexamethasone implant in improving vision and reducing macular thickness in previously vitrectomized eyes showed that improvements in both parameters over baseline may be demonstrated for up to 180 days, despite the more rapid drug clearance seen after vitrectomy.²²¹ These trials are summarized in Table 8.

VEGF inhibitors Intravitreal injection of anti-VEGFs, including pegaptanib, RBZ and bevacizumab (BVZ), for the treatment of DME has been investigated in a number of trials, which have demonstrated a beneficial effect of these agents on visual acuity and central macular thickness. As with intravitreal steroid injections, the effect is time limited; however, in contrast to the intravitreal steroid injections, complications are rare.²²² The READ-2 study randomized patients with centre-involving DME to RBZ, focal or grid laser, or both. The mean visual outcome at month 24 was not significantly different in the 3 groups, however, the RBZ-only group showed a significantly greater improvement in vision at 6 months. Twenty-four-

Table 8—Randomized controlled studies evaluating the use of intraocular steroid in DME

Study	n	Study groups	Visual outcome/significance	Endpoint
DRCRnet 2008 ²¹⁵	693	Focal laser Triamcinolone 1 mg Triamcinolone 4 mg	+1 letter −2 letters/ns −3 letters/ns	2 years
DRCRnet 2010 ²¹⁹	854	Focal laser Triamcinolone 4 mg Ranibizumab 0.5 mg	+3 letters +4 letters/ns +9 letters/s	1 year
Haller 2010 ²²⁰	171	Dexamethasone 700 µg Dexamethasone 350 µg Observation	>10 letters 33%/s (30%/ns) >10 letters 21%/s (19%/ns) >10 letters 12%/23%	90 days (180 days)

Note: DME, diabetic macular edema; ns, not significant; s, significant.

month anatomic outcomes were better in the 2 groups exposed to laser, with significantly fewer injections required and no impact on the final visual outcome.²⁰⁸ The RESOLVE study also examined the effectiveness of RBZ versus laser. Subjects were randomized to receive either 0.5 mg or 0.3 mg RBZ in conjunction with laser or a sham injection and laser alone. At the 1-year endpoint, the RBZ arms had improved significantly, gaining an average of 10.3 letters compared with laser alone arm, which lost an average of 1.4 letters.²²³ The RESTORE study compared focal laser to RBZ alone or in combination with laser. At 1 year, the RBZ-alone group improved 6.1 letters, the RBZ plus laser group improved 5.9 letters; and the laser-alone group improved 0.8 letters. There was no statistically significant difference between the outcomes of the RBZ-alone and the RBZ plus laser groups.²⁰⁹ Another DRCRnet study compared RBZ with immediate or delayed focal/grid laser or intraocular triamcinolone with immediate laser to focal/grid laser alone. This study included patients with DME involving the centre of the macula both on clinical examination and as measured by OCT, and a visual acuity of 20/32 to 20/320. At 1 year, the RBZ-treated groups gained on average 6 more letters than the group treated with laser alone and the triamcinolone/laser

group was equivalent to laser alone.²¹⁹ At the 2-year follow-up, the significant differences between the RBZ and laser groups remained similar. An average of 8.5 treatments were needed in the RBZ-treated groups in year 1 and 2.5 treatments in year 2.²²⁴ The BOLT study prospectively compared intraocular bevacizumab (BCZ) to focal laser in patients with centre-involving macular edema who had had at least 1 prior macular laser treatment. At the primary endpoint of 1 year, patients in the BCZ arm gained 8 letters, whereas those in the laser arm lost 0.5 letters.²¹⁰

Taken together, these results suggest that eyes with centre-involving macular edema should be considered for treatment with a VEGF inhibitor alone or in conjunction with focal laser. These studies are summarized in Table 9.

Vitreectomy In 1992, Lewis et al.²²⁵ reported improved vision in 9 of 10 eyes that underwent vitrectomy and separation of the posterior hyaloid for eyes with DME and associated vitreomacular traction. Several case series reporting success have followed.^{226–230} Many prospective nonrandomized case series have reported visual benefit after vitrectomy with removal of the internal limiting membrane (ILM) in the

Table 9—Randomized controlled studies evaluating the use of VEGF inhibitors in DME

Study	n	Study groups	Visual outcome/significance	Endpoint
READ-2 (Nguyen et al. ²⁰⁸)	126	Focal laser RBZ Focal laser/RBZ	+0.5 letter (5.1) 7.4 letters/s (7.7/ns) 3.8 letters/s (6.8/ns)	6 months (24 months)
RESOLVE (Massin ²²³)	151	Focal laser RBZ 0.3 mg RBZ 0.5 mg	−1.4 letters +10.3 letters/s (pooled data)	1 year
DRCRnet (Elman et al. ²²⁴)	854	Focal laser RBZ/laser RBZ/delayed laser Triamcinolone/laser	+3 letters +9 letters/s +9 letters/s +4 letters/ns	1 year
RESTORE (Mitchell et al. ²⁰⁹)	345	Focal laser RBZ Focal laser/RBZ	+0.8 letter +6.1 letters/s +5.9 letters/s	1 year
BOLT (Michaelidis et al. ²¹⁰)	80	Focal laser BVZ	−0.5 letters +8.0 letters	1 year

Note: BVZ, bevacizumab; DME, diabetic macular edema; ns, not significant; RBZ, ranibizumab; s, significant; VEGF, vascular endothelial growth factors.

Table 10—Randomized controlled trials of vitrectomy versus laser for DME

Study	n	Evidence level	Study design	VA results	OCT thickness	Beneficial effects of PPV
Thomas et al. ²³⁹	40	2	Laser versus PPV + ILM	No difference	No difference	No
Yanyali et al. ²⁴⁰	24	2	Laser versus PPV + ILM	PPV logMAR 0.75 to 0.53 ($p = 0.006$)	PPV decrease 219 μm	Yes
			Paired eye trial	Laser 0.59 to 0.49 ($p = 0.058$)	Laser decrease 28 μm ($p = 0.001$)	
Stolba et al. ²⁴¹	56	2	Observation versus PPV + ILM	PPV better than observation ($p = 0.035$ to 0.005)	PPV significantly better than observation ($p < 0.0001$)	Yes
Yanyali et al. ²⁴²	2	2	Observation versus PPV + ILM	PPV logMAR 0.71 to 0.54 ($p = 0.125$) Observation 0.43 to 0.59 ($p = 0.235$)	PPV decrease 166 μm Observation decrease 38 μm ($p = 0.016$)	Yes
Patel et al. ²⁴³	20	2	Laser versus PPV + PVD	No difference	No difference	No
Kumar et al. ²⁴⁴	24	2	Laser versus PPV + ILM	ns ($p = 0.52$)	PPV group significantly less ($p = 0.001$)	No

Note: ILM, internal limiting membrane; OCT, optical coherence tomography; PPV, pars plana vitrectomy; PVD, posterior vitreous detachment; VA, visual acuity.

absence of vitreomacular traction.^{231–238} However, there are few RCTs. Of 6 small RCTs in the literature, 3 reported no benefit of vitrectomy with ILM peeling when compared with laser, and only 1 reported a benefit. The other 2 studies reported benefit of vitrectomy and ILM peeling compared with observation alone. These studies are summarized in Table 10.

With improvements in resolution and widespread availability of OCT, imaging of the diabetic macular vitreoretinal interface is identifying many cases of macular traction that are not clinically apparent. Some authors have suggested that the benefit of vitrectomy may be confined to patients with OCT signs suggestive of macular traction.^{245,246} The DRCRnet reported a study of 87 eyes with DME and vitreomacular traction that underwent vitrectomy. Retinal thickening was reduced by $>50 \mu\text{m}$ in 68% of eyes at 6 months; between 28% and 49% of eyes showed improvement of VA, whereas between 13% and 31% worsened. Complications included a worsening of lens opacities in 78% of phakic patients and a small number of vitreous hemorrhages and retinal detachments.²¹¹

Treatment of proliferative retinopathy

KEY MESSAGES

- Patients should be advised that field loss may occur after panretinal photocoagulation (PRP), but most patients are able to maintain fields sufficient for driving after routine PRP.
- Macular edema may develop after PRP, but resolves by 6 months in the majority of eyes.
- The addition of an injection of VEGF inhibitor to PRP increases short-term neovascular regression rates.

RECOMMENDATIONS

11. In eyes with DRS high-risk characteristics, PRP should be carried out to reduce the risk of severe vision loss [Level 1¹⁶].
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 1²⁴⁷ for ranibizumab; Level 2²⁴⁸ for bevacizumab].
13. Consideration should be given to vitrectomy in eyes with nonclearing vitreous hemorrhage [Level 1²⁴⁹], macular heterotopia [Level 3²⁵⁰] or tractional macular detachment [Level 3^{251,252}], tractional rhegmatogenous detachment [Level 3^{253,254}], or dense premacular hemorrhage [Level 3^{255,256}].
14. In eyes with active PDR undergoing vitrectomy, VEGF inhibitors should be considered preoperatively to reduce hemorrhage and complications associated with vitrectomy [Level 2^{257–260} for bevacizumab].

Panretinal photocoagulation The DRS¹⁶ found that the risk of severe vision loss (5/200) was reduced by 50% in the “high-risk” (see Table 3 for definition) group treated with PRP. The beneficial effect of laser persisted to at least 6 years, with 37% of control eyes and only 17% of treated eyes developing severe visual loss. Patients with less advanced proliferative pathology (early PDR) were evaluated in the ETDRS. In this group, PRP decreased the risk of patients developing high-risk characteristics by 50%; however, the incidence of severe visual loss was very low in both the early treatment and deferred treatment groups. Although effective in controlling the proliferation of retinal neovascularization, PRP can be associated with the development or progression of DME, vitreous hemorrhage, tractional retinal detachment, loss of

night vision, and constricted peripheral visual fields. Vision loss within 6 weeks of treatment has also been reported in 10%–23% of patients compared with 6% of controls.²⁶¹

Macular edema can appear, and existing macular edema can worsen, after laser for PDR.²⁶² The ETDRS demonstrated that DME develops in ~16% of subjects with no pre-existing macular edema 4 months after PRP. This compares with 12% in those who did not receive PRP. In most instances, the macular edema was short lived and had resolved after 6 months.¹⁷ The reduction of intraocular VEGF levels after PRP would be expected to reduce the hyperpermeability of macular vessels over time.²⁶³ In a large RCT, patients with PDR and centre-involving macular edema who were about to be treated with PRP were randomized to receive either focal laser combined with RBZ injections at the time of initiation of PRP and at 4 weeks or focal laser alone. The group that received RBZ had significantly better vision at 14 weeks (study endpoint).²⁴⁷ Another smaller RCT with similar methodology showed similar results.²⁴⁸

PRP does not seem to significantly affect the ability of patients to maintain peripheral vision adequate to pass standard driving field testing. Although the data are not extensive, a small retrospective cohort study and case series from the United Kingdom both suggest that field constriction severe enough to fail to meet government driving standards is rare after routine PRP laser treatment.^{264,265} Approximately 90% of patients undergoing PRP continue to meet U.K. driving standards after treatment.^{266,267}

Intraocular steroid Triamcinolone acetonide inhibits cellular proliferation at high doses; as such, it may have a direct stabilizing effect on intraocular neovascularization.²⁶⁸ Via its suppressive effect on plasmin, steroid inhibits the collagenase activation that is responsible for breaking down basement membranes as part of the early neovascular cascade.²⁶⁹ The effect of steroid in suppressing neovascularization is well documented for other organ systems as well as the eye.²⁷⁰ However, only case studies have evaluated the use of steroid as a treatment for PDR, with conflicting results.

VEGF inhibitors VEGF has been implicated in the development of retinal neovascularization.²⁷¹ In light of this, anti-VEGF treatments have been postulated to be of benefit in the management of PDR. The Macugen Diabetic Retinopathy Study Group carried out a post-hoc evaluation of subjects with baseline retinal neovascularization who received 6 weekly intravitreal injections of pegaptanib sodium in a phase II RCT of DME.²⁷² Of 13 subjects who received pegaptanib, 8 had regression of retinal neovascularization at week 36. None of 3 sham treatment eyes and none of 4 contralateral eyes had regression of pre-existing neovascularization. Although these results are suggestive of a possi-

ble therapeutic effect, 9 of 13 pegaptanib patients had prior PRP, whereas none of the control patients had received this treatment. Recurrence of neovascularization occurred in 3 of 8 subjects after discontinuation of pegaptanib. A small clinical trial directly compared pegaptanib with PRP for the management of PDR. At the 36 weeks, no subjects receiving pegaptanib had active neovascularization.²⁷³ Retinal neovascularization has been noted to resolve for up to 6 months after even a single dose of intravitreal BCZ.^{274,275} Case series and small prospective studies data also suggest a possible benefit to BCZ in producing a reduction in neovascular fluorescein leakage in patients with refractory PDR that had previously been treated with PRP.²⁷⁶ Two small RCTs demonstrated that a single injection of BCZ at the initiation of PRP resulted in a more rapid regression of neovascularization. This effect was not sustained to 16 weeks.^{277,278} It has also been suggested that anti-VEGF agents can be used in the setting of PDR and vitreous hemorrhage to facilitate sufficient clearing of the hemorrhage to allow administration of PRP.²⁷⁹ However, rapid contracture of preretinal neovascular membranes can occur with intravitreal anti-VEGF therapy²⁸⁰ and vitrectomy surgery may thus be required.

Vitrectomy Vitrectomy surgery was initially used to clear vitreous hemorrhage. The Diabetic Retinopathy Vitrectomy Study (DRVS) 2-year results demonstrated that in eyes with central vitreous hemorrhage that reduced acuity to 5/200 or less for at least a month, vitrectomy carried out before 6 months resulted in an increase in the number of eyes achieving 20/40 or better acuity compared with eyes in which vitrectomy was deferred to a year.²⁰⁷ In the subgroup of people with type 1 diabetes, the difference was even greater. In the subgroup of patients with type 2 diabetes, there was no advantage between early vitrectomy and deferred vitrectomy. Endolaser was not used in the DRVS. As vitrectomy techniques and instrumentation have improved, the indications for vitrectomy surgery in DR have expanded and the timing of vitrectomy intervention is earlier.²⁴⁹ Vitrectomy for vitreous hemorrhage has been shown in case series to improve outcomes when there is anterior segment neovascularization by removing the vitreous hemorrhage and allowing immediate endophotocoagulation.^{281,282} Vitrectomy has also been shown in case series to be of benefit when there is ghost cell glaucoma²⁸³ or dense subhyaloid hemorrhage covering the macula.^{255,256} Tractional retinal detachment recently involving or imminently threatening the fovea is another common indication for surgery.²⁸⁴ Fibrovascular tissue proliferation and contraction attached to multiple retinal foci results in macular distortion (heterotopia) or tractional detachment. Extramacular tractional retinal detachments usually are not operated on, as only 15% extend into the macula within 1 year.²⁸⁵ Sato et al.²⁵⁰ compared the results of vitrectomy for 15 macular heterotopia patients versus 88 tractional macular detachment patients. They found vision better

Table 11—Results of vitrectomy for tractional retinal detachment involving the macula

Study	n	Evidence level	Comments	Eyes improved (%)	Eyes VA ≥ 20/100 (%)	Eyes VA ≥ 5/100 (%)	Eyes worse (%)	Eyes NLP (%)
Thompson et al. ²⁵²	360	3	— —	59 —	21* 36†	57* 72†	36* 31†	19* 19†
Williams et al. ²⁸⁶	69	3	88% macular reattachment	—	—	71	—	—
Flynn et al. ²⁵¹	243	3	46% had TRD	—	—	48	—	—
Han et al. ²⁸⁷	30	3	97% macular reattachment	—	—	77	—	—
Meier and Wiedemann ²⁸⁸	27	3	89% macular reattachment	—	50	—	—	—

Note: NLP, no light perception; TRD, traction retina detachment; VA, visual acuity.
 *1974–1980.
 †1981–1983.

than 20/200 in 93% of the macular heterotopia group and 48% in the tractional macular detachment group. Forty-seven percent of the macular heterotopia group had better than 20/40 vision, compared with 10% in the tractional macular detachment group. The authors concluded that macular heterotopia is a good indication for early vitrectomy.²⁵⁰ Results of key studies evaluating vitrectomy for tractional macular detachment are summarized in Table 11. Combined tractional/rhegmatogenous retinal detachment is another indication for vitrectomy in DR. Progressive traction produces a retinal break usually posterior to the equator and near an area of fibrous proliferation. These detachments progress quickly and usually result in a worse prognosis. Table 12 summarizes results of studies for combined tractional and rhegmatogenous retinal detachments.

Progressive fibrovascular proliferation is a manifestation of severe neovascularization that can occur despite adequate PRP. Visual acuity can range from normal to very poor, and there is often a lack of posterior vitreous separation. In 1 study, de Bustros et al.²⁸⁹ operated on 105 eyes with progressive fibrovascular proliferation and found an improvement in final vision in 70% of eyes.

Combination therapy Anti-VEGF agents are currently used as a preoperative injection before vitrectomy surgery in eyes with PDR.²⁵⁹ The purpose of this approach is to reduce the vascularity of retinal neovascularization at the time of surgery, facilitating a more complete removal of preretinal membranes. Work in this area suggests good results with anti-VEGF injections delivered ~1 week preoperatively.^{258,260,290} This approach car-

ries risk if surgery is delayed, as the rapid contraction of fibrovascular tissue can promote tractional detachment. A pre- or intraoperative injection may also decrease the risk of postoperative vitreous hemorrhage that can delay the recovery of vision in patients undergoing surgery.^{257,291,292}

Treatment of macular ischemia

There is currently no known treatment for established macular ischemia secondary to DR. Macular ischemia can occur as a result of excessive laser, although it is more commonly seen as a result of disease progression. Conflicting data exist regarding the development of macular ischemia following intravitreal injection of anti-VEGF agent. Some small case series suggest this is a possibility,²⁹³ whereas others fail to demonstrate a link.²⁹⁴

PREGNANCY

KEY MESSAGE

- There is insufficient evidence available to determine the safety of intraocular VEGF inhibitors during pregnancy. Thus, caution should be exercised if using them in women who are pregnant or could become pregnant. Women of child-bearing age should be questioned specifically about possible pregnancy during pretreatment evaluation.

Table 12—Results of vitrectomy for combined tractional and rhegmatogenous retinal detachment

Study	n	Evidence level	Comments	Eyes improved (%)	Eyes VA ≥ 20/100 (%)	Eyes VA ≥ 5/100 (%)	Eyes worse (%)	Eyes NLP (%)
Thompson et al. ²⁵³	172	3	—	48	24	56	45	—
Yang et al. ²⁵⁴	40	3	93% macular reattachment	70	—	48 (>20/400)	—	15

Note: NLP, no light perception; VA, visual acuity.

RECOMMENDATION

15. Patients with type 1 or type 2 diabetes 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*^{295,296} for type 1 diabetes and *Consensus* for type 2 diabetes].

Effect of pregnancy on diabetic retinopathy

The DCCT reviewed 270 pregnancies in 180 women with type 1 diabetes randomized to either conventional or intensive therapy for a mean of 6.5 years. Although pregnancy in women with type 1 diabetes induced a transient increased risk of retinopathy, it did not seem to affect the long-term progression of retinopathy. In the intensive treatment group, pregnant women had a 1.63-fold greater risk of progression of retinopathy during pregnancy compared, with a similar period before pregnancy ($p < 0.05$). In the conventional treatment group, the risk of retinopathy progression was 2.5-fold greater ($p < 0.001$).²⁹⁵

Less information has been published on women with type 2 diabetes during pregnancy. A single-centre study followed 80 women with diabetes through pregnancy and compared retinal photographs obtained early in pregnancy with those obtained late in pregnancy. Progression was seen in 11 patients, but this was greater than 1 grade in only 1 patient.²⁹⁷

Patients who develop gestational diabetes do not develop retinopathy unless the diabetes persists beyond pregnancy.

Diagnosis and treatment of retinopathy during pregnancy

The use of cyclopentolate or tropicamide for pupillary dilation or the use of topical anesthetic drops and fluorescein have not been associated with fetal risk. No clear evidence of harm exists for fluorescein angiography; however, it can usually be deferred until completion of the pregnancy and breastfeeding. Laser treatment poses no known risk to the fetus. Although there are case reports of safe use of intraocular VEGF inhibitors during pregnancy,^{298,299} the risks associated with the use of anti-VEGF agents during human pregnancy are unclear. Maternal hypertension and fetal malformations have been reported as possible issues in animal studies.^{298–302}

NEOVASCULARIZATION OF THE IRIS

KEY MESSAGE

- In patients with DR and iris neovascularization or neovascular glaucoma, consideration should be given to VEGF inhibitor injection in conjunction with PRP to produce regression of the neovascularization and reduce the risk of long-term glaucoma.

Severe retinal ischemia can result in new blood vessel growth on the surface of the iris, which is known as neovascularization of the iris (NVI). When fibrovascular tissue grows into the angle producing neovascularization of the angle, it can disrupt the normal egress of aqueous from the eye and result in increased IOP. If severe, this will produce neovascular glaucoma. The clinical manifestations of this are raised IOP, neovascularization of the iris and angle and, if severe, microcystic edema of the cornea, and damage to the optic nerve.

The goals of management of neovascular glaucoma (in order) are: 1) acute reduction in IOP; 2) regression of iris neovascularization; 3) reduction of retinal ischemia; and 4) long-term management of IOP, if it remains high after initial management.

Acute reduction of intraocular pressure

As long as there is no contraindication to their use, topical pressure-lowering medications, as well as systemic carbonic anhydrase inhibitors or osmotic agents, should be used immediately in an attempt to lower IOP.

Regression of iris neovascularization

An intravitreal injection of a VEGF inhibitor should be given to acutely reduce iris neovascularization.^{303–306} This procedure is generally followed with an anterior chamber paracentesis to prevent further IOP elevation.

Reduction of retinal ischemia

PRP should be done to reduce posterior segment ischemia and provide a long-term means to reduce repopulation of NVI. Hyperosmotic agents such as glycerol can be applied to the cornea to reduce microcystic edema and facilitate immediate PRP. Additional laser may be required as visibility improves and hemorrhage lessens.

Long-term management of intraocular pressure

If the IOP does not remain controlled after this treatment approach, a glaucoma specialist should be consulted to provide a definitive treatment to control IOP.³⁰⁷ This may include trabeculectomy with or without mitomycin C,^{308,309} a tube shunt procedure, or cyclophotocoagulation.

ECONOMIC CONSIDERATIONS

KEY MESSAGE

- Available evidence suggests that there are considerable economic benefits to screening and early treatment of DR.

A full discussion of the cost of DR and the cost-effectiveness of screening and management is beyond the scope of this clinical practice guideline. However, the following provides some information regarding the economic burden of DR on the Canadian healthcare system.

Diabetes has reached epidemic proportions in some Canadian populations and can be expected to have a consistent impact on costs associated with DR in the future. Because of the age at which DR occurs and the expected lifelong duration of disease, there is a significant economic impact with respect to the costs of treatment and effect on patient income. The evidence-based management of DR has moved beyond surgical modalities to reliance on medications, yet formulary coverage and reimbursement policies regarding medications vary widely across Canada, creating inequities in patient access and financial burden.

The literature is consistent in demonstrating that screening and treatment of DR are of economic benefit,^{310–315} however, the magnitude of the benefit varies with prevalence and severity of diabetes in the target population, the number of individuals evaluated, the geographic location of those being evaluated, and the technology and methodology chosen for detecting disease.

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APPENDICES

APPENDIX A: CLASSIFICATION OF DIABETES

Table A—Classification of type 1 and type 2 diabetes⁹

Type 1	Encompasses diabetes that is primarily a result of pancreatic β cell destruction and is prone to ketoacidosis. This form includes cases due to an autoimmune process and those for which the etiology of β cell destruction is unknown.
Type 2	May range from predominant insulin resistance with relative insulin deficiency to a predominant secretory defect with insulin resistance.
Other	Gestational diabetes (glucose intolerance with onset or first recognition during pregnancy) and a variety of relatively uncommon conditions, including genetically defined types of diabetes, or diabetes associated with other diseases or drug use.

APPENDIX B: CRITERIA FOR DIAGNOSIS OF DIABETES

Table B—Current Canadian criteria for diagnosis of diabetes^{8,316}

Fasting plasma glucose	≥ 7.0 mmol/L
Casual plasma glucose	≥ 11.1 mmol/L + symptoms of diabetes
2-h plasma glucose in a 75-g oral glucose tolerance test	≥ 11.1 mmol/L
A1C*	$\geq 6.5\%*$

Note: A1C, glycated hemoglobin.
*For diagnosis of type 2 diabetes in adults.³¹⁶

APPENDIX C: EVIDENCE SUPPORTING THE USE OF TELEOPHTHALMOLOGY TO DETECT DR

Bursell et al.¹⁴² used 3 45° field non-mydratric stereoscopic digital-video color images compared to

Table C—Evidence supporting the use of teleophthalmology to detect DR

Study	Digital imaging technique	n	Diagnostic category	Sensitivity (%)	Specificity (%)	Pearson κ correlation
Bursell et al. ¹⁴²	3-field 45° non-mydratric stereoscopic	108	Mild/moderate NPDR	86	76	0.60
			Severe NPDR	57	99	0.64
			PDR	89	97	0.78
Tennant et al. ¹³⁹	7-field 30° mydratric stereoscopic	121	MA	—	—	0.92
			IRH	—	—	0.80
			IRMA	—	—	0.45
			NVE/NVD	—	—	1.00
			CSME	—	—	0.97
Fransen et al. ¹²¹	7-field 30° mydratric stereoscopic	290	Referral threshold (ETDRS level 53)	98	90	—
Lin et al. ³¹⁷	Single 45° non-mydratric monochromatic	197	Referral threshold (ETDRS level ≥ 35)	78	86	0.97
Gómez-Ulla et al. ³¹⁸	4-field 45° non-mydratric stereoscopic	126	Exact level of retinopathy	94*	—	—
Cavallerano et al. ³¹⁹	3-field 45° non-mydratric stereoscopic	268	Exact level of DR	73*	—	—
			Within 1 level of DR	89*	—	—
Boucher et al. ¹¹⁸	2-field 45° non-mydratric stereoscopic	98	Mild NPDR (ETDRS level 35)	97	97	—
			Moderate NPDR (ETDRS level 43)	53	97	—
Rudnisky et al. ¹²⁴	7-field 30° mydratric stereoscopic	204	Moderate NPDR	80	93	0.71
			PDR	94	98	0.84
			CSME	87	93	0.80
			Refer patient	90	88	0.78

Note: CSME, clinically significant macular edema; DME, diabetic macular edema; DR, diabetic retinopathy; ETDRS, Early Treatment Diabetic Retinopathy Study; IRH, intraretinal hemorrhage; IRMA, intraretinal microvascular abnormalities; MA, microaneurysms; NPDR, nonproliferative diabetic retinopathy; NVD, neovascularization of the disc; NVE, neovascularization elsewhere; PDR, proliferative diabetic retinopathy.
*Simple agreement.

ETDRS 7-standard field 35-mm stereoscopic colour 30° fundus photographs. In the detection of mild or moderate NPDR, severe or very severe NPDR, and any PDR, their system had sensitivities of 86%, 57%, and 89% respectively. The specificities were 76%, 99%, and 97% with κ scores of 0.60, 0.64, and 0.78 respectively. There was substantial agreement ($\kappa = 0.65$) between the clinical level of DR assessed from the undilated images and the dilated ETDRS photos. Agreement was excellent ($\kappa = 0.87$) for suggested referral to ophthalmology specialists for eye examinations.

Tennant et al.¹³⁹ compared 7-standard 30° stereoscopic slide film images to 7-standard 30° high-resolution stereoscopic digital images. The images were read by masked independent readers. Pearson’s correlation coefficient was 0.92 for microaneurysms, 0.80 for hemorrhages, 0.45 for intraretinal microvascular abnormalities, 0.32 for venous beading, 1.00 for neovascularization of the disc, 1.00 for neovascularization elsewhere, and 0.97 for clinically significant macular edema ($p < 0.001$).

Fransen et al.¹²¹ compared 7 30° fields to 35-mm film using an ETDRS protocol with the results read by 2 masked graders. The presence of ETDRS level 53, questionable or definite CSME in either eye, or ungradeable images was defined as a threshold event requiring referral. The prevalence of threshold events was 19.3%. The sensitivity of the digital system in detecting threshold

events was 98.2% (95% CI, 90.5%–100.0%) and specificity 89.7% (95% CI, 85.1%–93.3%).

Lin et al.³¹⁷ compared a single 45° non-mydratric monochromatic digital field, dilated ophthalmoscopy by an ophthalmologist, and 7 ETDRS-standardized 35-mm colour stereoscopic mydratric images. There was highly significant agreement ($\kappa = 0.97$, $p = 0.0001$) between the degree of retinopathy detected by a single non-mydratric monochromatic digital photograph and that seen in 7-standard 35-mm colour stereoscopic mydratric fields. The sensitivity of digital photography compared with colour photography was 78%, with a specificity of 86%. Agreement was poor ($\kappa = 0.40$, $p = 0.0001$) between mydratric ophthalmoscopy and the 7-field standard 35-mm colour photographs. Sensitivity of ophthalmoscopy compared with colour photography was 34%, with a specificity of 100%.

Gómez-Ulla et al.³¹⁸ used 4 45° non-mydratric stereoscopic images compared to clinical examination by 2 independent ophthalmologists. All eyes with DR (69 of 69, 100%) were correctly identified ($\kappa = 1$) by inspecting the digital images. In 118 eyes (118 of 126, 94%), 57 with no DR and 61 with DR, there was an agreement between the gradation made after the direct examination and the gradation made after the inspection of the images (intraclass correlation coefficient = 0.92). In 8 eyes with DR (8 of 126, 6%), there was disagreement in the grading made with both techniques.

Cavallerano et al.³¹⁹ compared 3 45° field non-mydratic stereoscopic digital-video colour images with a cohort of patients who were examined clinically by a retinal specialist. Diagnosis of a clinical level of DR agreed exactly with clinical findings in 388 eyes (72.5%) or within 1 level in 478 eyes (89.3%).

Boucher et al.¹¹⁸ compared the use of 2 45° non-mydratic digital fields with 7-standard 30° stereoscopic photographic fields. There were 98 patients with diabetes enrolled. The sensitivities for very mild NPDR (ETDRS level 20), mild NPDR (ETDRS level 35), and moderate NPDR (ETDRS level 43) were 98%, 97%, and 53%, respectively, and the specificities were 81%, 96%, and 97%, respectively. There were 17% ungradable images due to insufficient image quality.

In a study by Rudnisky et al.,¹²⁴ patients with diabetes underwent 2 sets of 7-standard 30° field photos—1 with film, the other digital. The digital photos were compressed 16 times, uploaded to a secure website, and graded by 2 masked graders using a web-based, computer-assisted ETDRS-algorithm. Film and digital gradings were highly correlated, with exact agreements for level of DR, CSME and referral thresholds >87% and κ levels >0.71. McNemar’s testing found no statistically significant difference between compressed digital images and film when comparing referral thresholds (defined as the presence of CSME and/or ETDRS level ≥ 61 ; $p = 0.76$). This evidence presented above is summarized in Table C.

APPENDIX D: EVIDENCE SUPPORTING THE USE OF TELEOPHTHALMOLOGY TO DETECT DME

Bursell et al.¹⁴² compared 3 45° non-mydratic stereoscopic digital images to 7-standard 30° stereoscopic photographs for evaluation of macular edema. The sensitivity for DME was reported as 62% with a specificity of 95%, for CSME the sensitivity was 27% and the specificity was 98%.

Rudnisky et al.¹²³ compared high-resolution stereoscopic digital photography to contact lens biomicroscopy for the diagnosis of CSME. Exact agreement was high for all identified diabetic features: CSME overall 83.6%, CSME1 83.6%, CSME2 96.1%, CSME3 88.5%. Sensitivity was 90.6% and specificity was 92.4% for CSME overall.

Fransen et al.¹²¹ compared 7-standard field dilated stereoscopic digital images to 7-standard field dilated stereoscopic photographs. For CSME the sensitivity was 88% and the specificity was 94%.

Cavallerano et al.³¹⁹ compared non-mydratic stereoscopic digital images to clinical exam. They found the sensitivity of digital imaging for the detection of CSME was 100% and the specificity was 97%. For detecting DME the sensitivity was 76% and the specificity was 99%. The evidence presented above is presented in Table D.

APPENDIX E: KEY STUDIES DEMONSTRATING THE NEED FOR TIGHT CONTROL OF BLOOD GLUCOSE TO REDUCE THE INCIDENCE AND PROGRESSION OF DIABETIC RETINOPATHY

The Diabetes Control and Complications Trial (DCCT),^{161,169,320,321} conducted between 1983 and 1993, randomized 1441 patients with type 1 diabetes to receive intense glycemic therapy or conventional therapy. Over 6.5 years of follow-up, intensive treatment (median A1C of 7.2%) reduced the incidence of DR by 76% and progression of DR by 54%, compared with conventional treatment (median A1C of 9.1%).^{161,169,320,321}

The United Kingdom Prospective Diabetes Study (UKPDS)¹⁶² reported similar findings in people with type 2 diabetes. In this study, 3867 newly diagnosed patients were randomized to receive intensive or conventional therapy. Intensive therapy reduced microvascular endpoints by 25% and the need for laser photocoagulation by 29%.³²² These findings have been replicated in other studies, including a meta-analysis.^{166,323,324}

Table D—Evidence supporting the use of teleophthalmology to detect macular edema

Study	Digital imaging technique	n	Gold standard	Diagnostic category	Sensitivity (%)	Specificity (%)	Pearson κ correlation
Bursell et al. ¹⁴²	3-field 45° non-mydratic stereoscopic	108	7-standard field stereoscopic photos	DME	62	95	—
				CSME	27	98	
Rudnisky et al. ¹²³	7-field 30° mydratic stereoscopic	204	Contact lens biomicroscopy	DME	82	90	0.72
				CSME	91	92	0.81
Fransen et al. ¹²¹	7-field 30° mydratic stereoscopic	290	7-standard field stereoscopic photos	CSME	88	94	—
Cavallerano et al. ³¹⁹	3-field 45° non-mydratic stereoscopic	268	Dilated eye examination by retinopathy specialist	DME	76	99	—
				CSME	100	97	

Note: CSME, clinically significant macular edema; DME, diabetic macular edema.

In the DCCT, a 10% reduction in A1C (e.g., from 8.0% to 7.2%) was associated with a 40%–50% lower risk of retinopathy progression.¹⁶¹ In the UKPDS, each 1.0% (absolute) reduction in mean A1C was associated with a 37% decline in the risk of microvascular complications.¹⁶²

APPENDIX F: KEY STUDIES DEMONSTRATING THE NEED FOR TIGHT CONTROL OF BLOOD PRESSURE TO REDUCE THE INCIDENCE AND PROGRESSION OF DIABETIC RETINOPATHY

The UKPDS¹⁰² randomized 1048 patients with diabetes with hypertension to receive tight BP therapy (target BP < 150/< 85 mm Hg) or conventional therapy (target BP < 180/< 105 mm Hg). After 9 years of follow-up, patients with tight control had a 34% reduction in DR progression, 47% reduction in visual acuity deterioration, and 35% reduction in need for laser photocoagulation compared with those with conventional control.

In the Appropriate Blood Pressure Control in Diabetes (ABCD) trial,^{325,326} 470 people with type 2 diabetes and hypertension were randomized to receive intensive or moderate BP control. Over 5 years, there was no difference in retinopathy progression between the groups. The lack of efficacy in this study may be related to poorer glycemic control, shorter follow-up, and lower BP levels at baseline as compared with the UKPDS. However, the ACCORD study results also failed to show a relationship between BP

control and retinopathy progression in people with type 2 diabetes. In another group of the ABCD trial, among 470 hypertensive patients with type 2 diabetes, intensive BP control significantly reduced DR progression over 5 years compared with moderate control.³²⁵

The EURODIAB controlled trial of lisinopril in insulin-dependent diabetes mellitus (EUCLID)³²⁷ evaluated the effects of the angiotensin-converting enzyme (ACE) inhibitor lisinopril on DR progression in normotensive, normoalbuminuric patients with type 1 diabetes. Over 2 years, lisinopril reduced the progression of DR by 50% and progression to proliferative DR by 80%. This study, along with another smaller RCT,³²⁸ suggested that ACE inhibitors may have an additional benefit on DR progression independent of BP lowering. However, data from the UKPDS³²⁹ and the ABCD^{325,326} study did not find ACE inhibitors to be superior to other BP medications.

Whether newer BP medications have additional beneficial effects is unclear. The Action in Diabetes and Vascular Disease (ADVANCE) study³³⁰ evaluated the effect of a perindopril-indapamide combination on the incidence of DR, could not demonstrate significant reduction in retinopathy either with BP-lowering treatment or intensive glucose control in patients with type 2 diabetes. The Diabetic Retinopathy Candesartan Trial (DIRECT) evaluated the angiotensin receptor blocker (ARB) candesartan on progression of retinopathy³³¹ and reported a nonsignificant 13% reduction in retinopathy with candesartan treatment compared with placebo among patients with type 2 diabetes.

Appendix G—Glossary of acronyms			
Acronym	Definition	Acronym	Definition
ACE	Angiotensin-converting enzyme	NPDR	Nonproliferative diabetic retinopathy
AMD	Age-related macular degeneration	NVD	Neovascularization of the disc
ARB	Angiotensin receptor blocker	NVE	Neovascularization elsewhere
BVZ	Bevacizumab	NVI	Neovascularization of the iris
CSME	Clinically significant macular edema	OCT	Optical coherence tomography
DME	Diabetic macular edema	PDR	Proliferative diabetic retinopathy
DR	Diabetic retinopathy	PKC	Protein kinase C
DRCRnet	Diabetic Retinopathy Clinical Research Network	PPV	Pars plana vitrectomy
DRS	Diabetic Retinopathy Study	PRP	Panretinal photocoagulation
DRVS	Diabetic Retinopathy Vitrectomy Study	RBZ	Ranibizumab
ETDRS	Early Treatment Diabetic Retinopathy Study	READ-2	Ranibizumab for Edema of the Macula in Diabetes
IOP	Intraocular pressure	TRD	Tractional retina detachment
IRH	Intraretinal hemorrhage	VA	Visual acuity
NLP	No light perception	VEGF	Vascular endothelial growth factor

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