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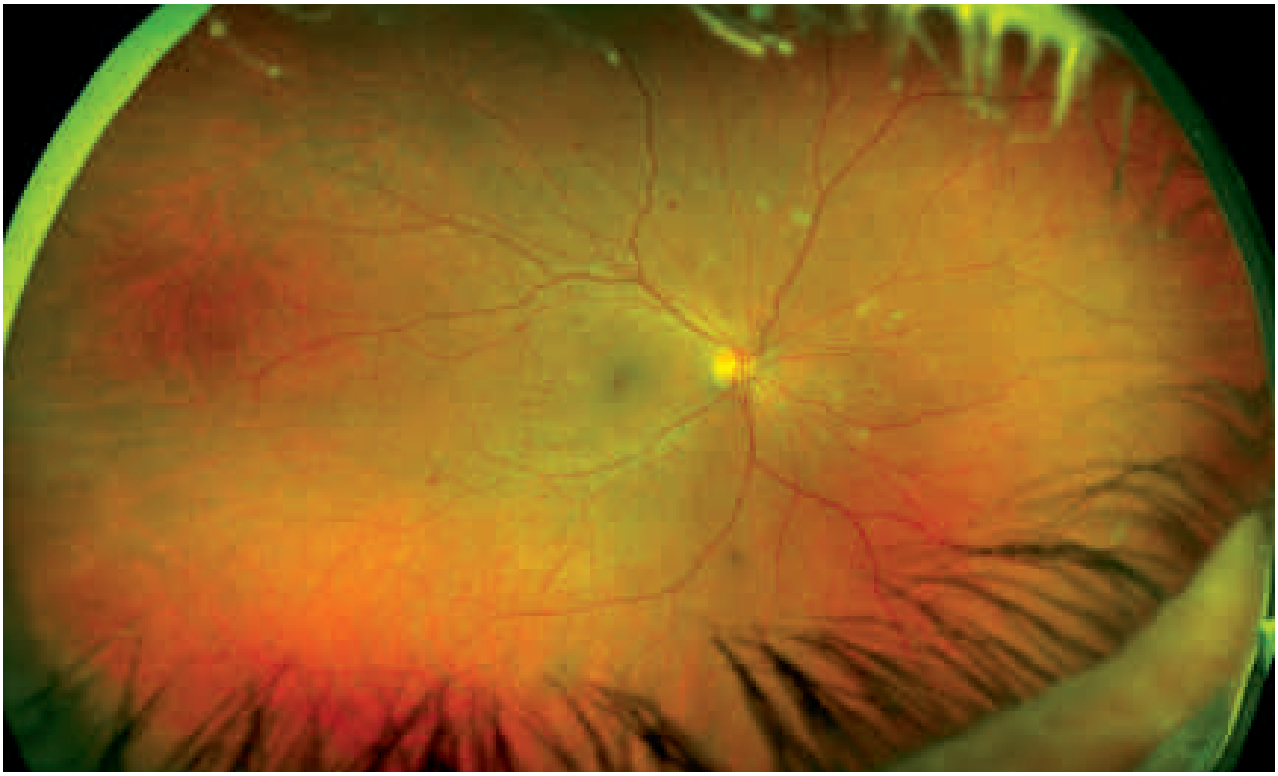

CLINICAL RESEARCH

2017 CAO Clinical Practice Guideline: Optometric Care of the Patient with Diabetes

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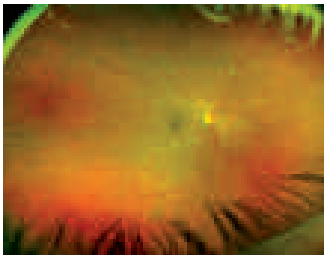

On the Cover

An example of severe non-proliferative diabetic retinopathy. Image courtesy of Prof. Paolo Stanga.

2017 CAO Clinical Practice Guideline: Optometric Care of the Patient with Diabetes

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Introduction

The Canadian Association of Optometrists (CAO) is the national voice of optometry and is dedicated to collaboratively advancing the highest standard of primary eye care through the promotion of optimal vision and eye health, in partnership with all Canadians.

Optometrists are the front line of eye health and vision care. They are experts in primary eye care and are well-positioned to help combat the vision-related complications of diabetes.

CAO assembled the Diabetes Guidelines Working Group to create national guidelines on the clinical management of diabetes mellitus in an effort to further educate Canadian optometrists and assist them in the management of this chronic disease. The Working Group consists of optometrists from private practice, research and academia, chosen on the basis of their expertise, experience and representation from across Canada.

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DISCLOSURE STATEMENT

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DISCLAIMER

These guidelines do not represent a standard of care. Instead, they are intended to assist the clinician in the decision-making process. Patient care and treatment should always be based on a clinician's independent professional judgment, given the patient's circumstances, and in compliance with applicable laws and regulations.

The information in this guideline is current to the extent possible at the time of publication.

Abbreviations

A1c	Glycated hemoglobin
AGE	Advanced glycation end product
AT	Artificial tears
BCVA	Best corrected visual acuity
CDA CPG	Canadian Diabetes Association Clinical Practice Guidelines (CDA is now Diabetes Canada)
CE	Cataract extraction
CSME	Clinically significant macular edema (or CSDME: clinically significant diabetic macular edema)
CWS	Cotton wool spots
DCCT	Diabetes Control and Complications Trial
DED	Dry eye disease
DKA	Diabetic ketoacidosis
DM	Diabetes mellitus
DME	Diabetic macular edema
DR	Diabetic retinopathy
DRS	Diabetic Retinopathy Study
ECFV	Extracellular fluid volume
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	Fluorescein angiography
FAZ	Foveal avascular zone
FPG	Fasting plasma glucose
GFR	Glomerular filtration rate
HE	Hard exudates
HHS	Hyperosmolar hyperglycemic state
IDRCS	International Diabetic Retinopathy Classification System
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
IOP	Intraocular pressure
IRH	Intra-retinal hemorrhages
IRMA	Intra-retinal microvascular abnormalities
MA	Microaneurysms
ME	Macular edema
MRI	Magnetic resonance imaging
NAION	Non-arteritic anterior ischemic optic neuropathy
NEI	National Eye Institute
NPDR	Nonproliferative diabetic retinopathy
NVA	Neovascularization of the angle
NVD	Neovascularization of the disc
NVE	Neovascularization elsewhere
NVG	Neovascular glaucoma
NVI	Neovascularization of the iris
OCT	Optical coherence tomography
OGTT	Oral Glucose Tolerance Test
OIS	Ocular ischemic syndrome
PDR	Proliferative diabetic retinopathy
PG	Plasma glucose
POAG	Primary open angle glaucoma
PRH	Preretinal hemorrhage
PRP	Panretinal photocoagulation
PSC	Posterior subcapsular cataract
RD	Retinal detachment
RNFL	Retinal nerve fibre layer
SLT	Selective laser trabeculoplasty
UKPDS	United Kingdom Prospective Diabetes Study
UWFA	Ultra-widefield fluorescein angiography
VB	Venous beading
VEGF	Vascular endothelial growth factor
VH	Vitreous hemorrhage
VMT	Vitreomacular traction

Classification, Definitions, Risk Factors

DEFINITION OF DIABETES

Diabetes mellitus is a metabolic disorder characterized by the presence of hyperglycemia due to defective insulin secretion, defective insulin action, or both.[1] The chronic hyperglycemia of diabetes is associated with microvascular complications affecting the eyes, kidneys and nerves, and an increased risk for cardiovascular disease. The criteria for diagnosing diabetes are based on thresholds of glycemia that are associated with microvascular disease, particularly retinopathy.

CLASSIFICATION AND DEFINITIONS

Type 1 diabetes is characterized by the destruction of beta cells in the pancreas. Although the etiology of beta cell destruction cannot be established in all cases, it is often the result of an autoimmune process. This usually leads to severe insulin deficiency and the patient is prone to develop diabetic ketoacidosis (DKA). DKA is an accumulation of ketones in the blood and a decrease in serum pH that occurs when there is insufficient insulin to convert glucose to energy and the body breaks down fat cells for energy instead.

Type 2 diabetes is usually characterized by a combination of insulin resistance and relative insulin deficiency. Insulin resistance is often the predominant factor, but deficient insulin secretion can play a more significant role in other cases. Between 90 and 95% of all diabetic patients have type 2 diabetes.[2] Although type 1 diabetes is associated with more frequent and severe ocular complications, because of the much higher incidence of type 2 diabetes, most cases of diabetic retinopathy and visual impairment will be type 2.[3]

Gestational diabetes mellitus refers to glucose intolerance with an onset, or first recognition, during pregnancy.

Prediabetes is a term used to describe impaired fasting glucose (IFG), impaired glucose tolerance (IGT) or a glycated hemoglobin (A1c) level of 6.0 to 6.4%. Any of these findings places an individual at a higher risk of developing diabetes. However, individuals with prediabetes do not always progress to diabetes. In fact, a significant proportion of people with prediabetes who are diagnosed with IFG or IGT will revert to normal glycemic levels. People with prediabetes and concurrent metabolic syndrome (see below) would benefit from cardiovascular risk factor assessment and lifestyle modification.

Metabolic syndrome is diagnosed when a person has at least three of the following risk factors:

- abdominal obesity
- a high triglyceride level
- a low HDL cholesterol level
- high blood pressure
- high fasting blood sugar

The presence of metabolic syndrome increases a person's risk of developing heart disease, stroke and diabetes.

Hypoglycemia is defined as:[4]

1. The development of autonomic or neuroglycopenic symptoms
2. A low plasma glucose level (<4.0 mmol/L for patients treated with insulin or an insulin secretagogue)
3. Symptoms that respond to the administration of a carbohydrate

Symptoms of hypoglycemia include trembling, palpitations, sweating, anxiety, hunger, nausea, tingling, difficulty concentrating, irritability, impatience, confusion, weakness, drowsiness, vision changes, difficulty speaking, headaches, light-headedness and dizziness.

Episodes of hypoglycemia may cause injury if they occur while a patient is driving or engaged in other potentially dangerous activities. Over the long term, some studies have shown that frequent episodes of hypoglycemia (five or more since diagnosis) may be associated with a mild decrease in intellectual performance.[5,6,7] Patients with type 2 diabetes who have experienced severe hypoglycemia requiring a visit to the hospital may also be at a greater risk of developing dementia in later years.[8] After experiencing hypoglycemia, some patients may self-adjust their treatment in an attempt to prevent a future episode, potentially leading to worse overall glycemic control.[9,10,11]

Symptoms of hypoglycemia can usually be relieved by the ingestion of 15 grams of glucose (monosaccharide), which will produce an increase in blood glucose of approximately 2.1 mmol/L within 20 minutes. Although many patients with previous episodes of hypoglycemia carry an 'emergency' supply of carbohydrates with them, it would be prudent for optometry offices to have at least one of the following items on hand at all times to support patients who experience an in-office episode of hypoglycemia:[1]

- 15 g glucose in the form of glucose tablets
- 15 mL (3 teaspoons) or 3 packets of table sugar to dissolve in water
- 175 mL (3/4 cup) of juice or regular soft drink
- 6 LifeSavers (1 = 2.5 g carbohydrate)
- 15 mL (1 tablespoon) of honey

Hyperglycemic crisis is a medical emergency that should be suspected and investigated in unwell patients with diabetes. It is characterized by DKA and hyperosmolar hyperglycemic state (HHS), and requires immediate treatment and monitoring for metabolic abnormalities and systemic complications.

Under insulin deficiency, hyperglycemia causes the urinary loss of water and electrolytes (sodium, potassium, chloride), resulting in depletion of the extracellular fluid volume (ECFV). Whereas DKA occurs as a result of elevated glycation levels and absolute insulin deficiency in the case of type 1 diabetes, high catecholamine levels that suppress insulin release are implicated in the case of type 2 diabetes.

Symptoms of hyperglycemia include Kussmaul (deep laboured) respiration, acetone-odoured breath (beware misinterpretation as alcohol consumption), loss of extracellular fluid volume, nausea, vomiting and abdominal pain. As with hypoglycemia, there may also be a decreased level of consciousness.

Patients with DKA or HHS are best managed in a hospital setting. Treatment is directed toward the restoration of normal ECFV and tissue perfusion, resolution of ketoacidosis, and correction of electrolyte imbalances and hyperglycemia. The existence of concurrent illness should be investigated and treated as required.

CRITERIA FOR DIAGNOSIS

Canadian Diabetes Association (Diabetes Canada) Clinical Practice Guidelines (CPG) list the diagnostic criteria for diabetes as follows:[12]

- Fasting Plasma Glucose (FPG) ≥7.0 mmol/L (where fasting is defined as no caloric intake for at least 8 hours);
- A1c ≥6.5% (in adults, using a standardized, validated assay in the absence of factors that affect the accuracy of A1c (see below));
- 2-hour Plasma Glucose (PG) in a 75 g Oral Glucose Tolerance Test (OGTT) ≥11.1 mmol/L;
- Random PG ≥11.1 mmol/L (where random is defined as any time of the day, without regard to the interval since the last meal).

If the individual does not exhibit any symptoms of hyperglycemia and a single laboratory test result falls in the diabetes range, a repeat confirmatory test (FPG, A1c, 2-hour PG in a 75 g OGTT) must be performed on another day. Ideally, the same test should be repeated for confirmation. A random PG in the diabetes range should be confirmed with an alternate, non-random test. If the results of 2 different tests are available and both exceed the diagnostic standard, the diagnosis of diabetes is confirmed.

If the patient already exhibits symptoms of hyperglycemia, the diagnosis can be made on the basis of a single positive laboratory finding, and treatment can be initiated without delay. When the diagnosis of type 1 diabetes is likely (younger or lean individuals with symptomatic hyperglycemia, especially with ketonuria or ketonemia), treatment should be initiated on an urgent basis even in the absence of confirmatory testing.

A FPG level of 7.0 mmol/L correlates most closely with a 2-hour PG in a 75 g OGTT value of ≥11.1 mmol/L, and each predicts the development of retinopathy. Factors affecting A1c include hemoglobinopathies, iron deficiency, hemolytic anemias, and severe hepatic and renal disease. A1c may be misleading in individuals with these and other conditions.[13] A1c values are also affected by ethnicity and age, and increase by up to 0.1% per decade of life.[14] A1c is not recommended for diagnostic purposes in children, adolescents, pregnant women, or those with suspected type 1 diabetes.

PREVALENCE OF DIABETES MELLITUS

Prevalence is a measurement of all individuals affected by a disease at a particular time, whereas *incidence* is a measurement of the number of new individuals who contract a disease during a particular period of time. Table 1 (from the CANSIM Statistics Canada Socioeconomic Database) shows the prevalence of diabetes in the Canadian population aged 12 and older (individuals who report that they have been diagnosed by a health professional as having type 1 or type 2 diabetes).[15] The data appear to indicate that the prevalence of diabetes is higher among females in the under-35 age group, but significantly higher in males in later years. However, Statistics Canada advises that, due to the relatively low absolute numbers, the data for the under-35 age group should be used with caution.

Table 1: *Number of Canadians with Diabetes (by Age Group and Gender)*

Number of Canadians with Diabetes (by Age Group and Gender)			
	Males	Females	Total
12 to 19 Years	5,966	9,910	15,876
20 to 34 Years	29,576	37,057	66,632
35 to 44 Years	73,340	55,453	128,793
45 to 64 years	509,880	323,117	832,997
65 Years and Over	501,670	465,378	967,048

Source: Statistics Canada. (2015). CANSIM, Table 105-0501 and Catalogue no.82-221-X

In July 2011, the Public Health Agency of Canada[16] compiled the age-standardized prevalence of persons with diabetes by province and territory based on 2008 data from the Canadian Chronic Disease Surveillance System (Table 2). While there are relatively small regional differences, diabetes undoubtedly represents a pan-Canadian health care issue.

Table 2: *Age-Standardized Prevalence of Diabetes by Province (%)*

Age-Standardized Prevalence of Diabetes by Province (%)	
Newfoundland and Labrador	6.5
Prince Edward Island	5.6
Nova Scotia	6.1
New Brunswick	5.9
Quebec	5.1
Ontario	6.0
Manitoba	5.9
Saskatchewan	5.4
Alberta	4.9
British Columbia	5.4
Yukon	5.4
Northwest Territories	5.5
Nunavut	4.4

Source: Public Health Agency of Canada. (2011). http://www.phac-aspc.gc.ca/cd-mc/publications/diabetes-diabete/facts-figures-faits-chiffres-2011/images/fig_1-2_lg-eng.gif

SCREENING FOR DIABETES

Type 1 diabetes is the result of an immune-mediated destruction of pancreatic beta cells in genetically predisposed individuals. Various serological markers may identify at-risk individuals. As there is no intervention at present that can delay or prevent the onset of type 1 diabetes, screening is generally not carried out even in persons who have been identified as being at risk.

There are a significant number of individuals with undiagnosed type 2 diabetes in the general adult population who can be identified by testing for hyperglycemia. Because many of the complications of diabetes are preventable, screening of individuals considered to be at risk of type 2 diabetes is beneficial in that treatment can be initiated in a timely manner. The CDA CPG recommends that persons over 40 years of age and persons identified as being at risk by a valid risk assessment tool be screened for diabetes every three years.[17] When additional risk factors are present, testing should be initiated earlier and carried out more frequently. Risk factors include:

- having a first-degree relative with type 2 diabetes
- being a member of a higher-risk ethnic group (Indigenous, African descent, Hispanic, Asian)
- having a history of prediabetes or gestational diabetes
- having microvascular (retinopathy, nephropathy, neuropathy) complications associated with diabetes
- having macrovascular (coronary, peripheral, cerebrovascular) complications associated with diabetes
- having metabolic syndrome

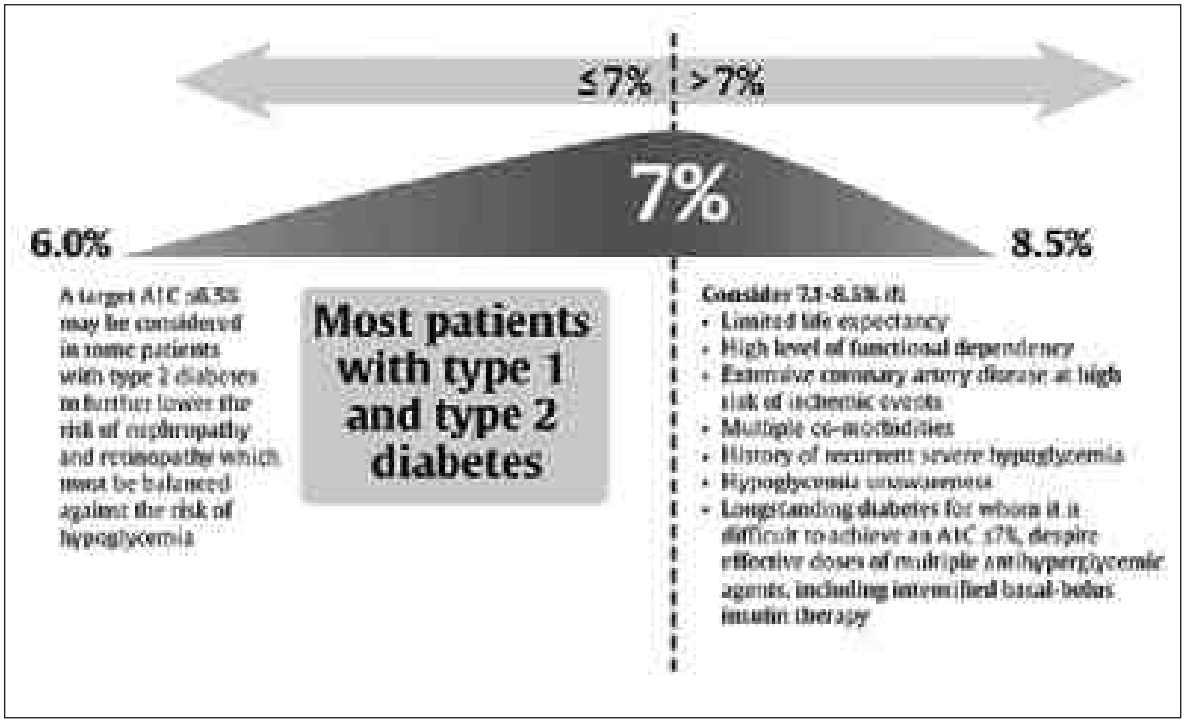
IMPORTANCE OF GLYCEMIC CONTROL

Optimal glycemic control is essential in the management of diabetes and its ocular and systemic complications. A1c levels in excess of 7.0% are associated with increased risk of both microvascular and macrovascular complications, regardless of the underlying treatment.[18] In the Diabetes Control and Complications Trial (DCCT; which studied type 1 diabetes), the risk of diabetic retinopathy progression was reduced by 40 to 50% when there was a 10% reduction in A1c, although the absolute reduction in risk was significantly less at lower A1c levels.[19] In the United Kingdom Prospective Diabetes Study (UKPDS; which studied type 2 diabetes), the relationship between A1c levels

and diabetes complications was found to be linear: each 1.0% (absolute) reduction in mean A1c was associated with a 37% decline in the risk of microvascular complications, a 14% lower rate of myocardial infarction, and a 21% reduction in deaths from diabetes.[20]

While relatively stringent glycemic control has been demonstrated to be beneficial, the potential benefits of intensive therapy need to be weighed against the risks of inducing episodes of hypoglycemia. Personalized and higher A1c targets may be indicated in older patients with type 2 diabetes who have had diabetes for a long time, have experienced previous episodes of severe hypoglycemia, and who have coexistent cardiovascular risk factors. The CDA CPG provides the following recommended targets for glycemic control (Figure 1):[21]

Figure 1: *CDA CPG-recommended targets for glycemic control*



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MONITORING GLYCEMIC CONTROL

For most individuals, A1c provides a dependable estimate of the mean plasma glucose over the previous three to four months: 50% of the result is determined by the mean blood glucose level over the 30 days immediately preceding the testing; 40% by levels from 30 to 90 days prior to the test; and the remaining 10% by blood glucose levels from the previous 90 to 120 days. A1c testing is often carried out quarterly if glycemic targets are not being met and therapy is being adjusted. When glycemic targets are consistently being met, A1c testing can be carried out less frequently.

While A1c testing provides very useful average information, it is not an accurate indicator of fluctuating blood glucose levels. Self-monitoring of blood glucose can provide additional information about episodes of hypoglycemia and hyperglycemia, and more timely feedback on the short-term effects of diet, lifestyle and pharmacological agents. With this additional information, patients can become empowered to make diet and lifestyle choices that can reduce the likelihood of large fluctuations in blood sugar levels and subsequent disease complications.

For persons with type 1 diabetes, daily self-monitoring is essential. Testing three or more times daily has been associated with a significant reduction in A1c.[22] The evidence supporting self-monitoring is less compelling for persons

with type 2 diabetes being treated with insulin. However, for persons with type 2 diabetes who are treated with lifestyle management and oral antihyperglycemic medications, self-monitoring coupled with education on how to adjust their lifestyle according to the readings can result in a significant reduction of both A1c levels and body mass index.[23] For people with type 2 diabetes, the benefits of self-monitoring are more significant in the first six months after diagnosis.[24] In the long term, however, frequent self-checking may not be necessary for patients with type 2 diabetes who manage their condition with lifestyle changes, with or without oral antihyperglycemic agents.[1]

EXERCISE AND DIABETES

Physical activity can help individuals with type 2 diabetes achieve better glycemic control, reduce insulin resistance, improve lipid profiles, reduce blood pressure, and assist with achieving and maintaining weight loss.[25] Aerobic exercise (activity that involves continuous engagement of large muscle groups for at least 10 minutes) and resistance exercise (brief repetitive exercise with weights, weight machines or resistance bands) provide greater benefits for diabetes management than exercise directed solely toward improving flexibility. Individuals with diabetes who wish to embark on a new regimen of increased physical activity should do so under medical supervision, especially when comorbidities are present.

NUTRITION AND DIABETES

Nutrition counselling and appropriate food choices are integral components of an individual's self-management of diabetes, and can improve glycemic control and prevent or reduce some of the long-term complications of diabetes. Nutrition counselling provided by registered dieticians with expertise in diabetes management or trained diabetes educators should be individualized, reinforced as needed, and provide the necessary skills for self-management. There is no universal prescription for a 'diabetes diet,' and effective meal planning should consider factors including the patient's age, length of time with the disease, cultural influences and food preferences, financial circumstances and physical activity level. Components of a healthy diet include carbohydrates (preferably from sources with a low glycemic index), dietary fibre, fats (monounsaturated fats are preferred over saturated and hydrogenated fats) and protein from a variety of plant or animal sources. CDA's CPG on Nutrition Therapy[1] provides information on dietary considerations.

It is estimated that 80 to 90% of individuals with type 2 diabetes are either overweight or obese. Reducing total caloric intake to achieve weight loss of 5 to 10% of initial body weight has demonstrable benefits that include better glycemic control, improved insulin sensitivity, reduced blood pressure and improved lipid profiles.[26,27,28]

Diabetic Retinal Disease

Diabetes mellitus (DM) is a systemic disease with both macro- and micro-vascular complications. The latter often involve the retina, and diabetic retinopathy (DR) is the leading cause of preventable vision loss in the working population.[29,30] The global prevalence of DR in patients with diabetes exceeds 35%, with nearly one in 13 having proliferative disease.[31] In light of the fact that one-third to one-half of all people with DM are unaware that they have the disease and that early DR is often asymptomatic, regular eye examinations (including dilated retinal assessment, particularly for at-risk populations) are of paramount importance for patients diagnosed with or at risk for DM.[32]

Diabetic retinal disease is multifactorial, and is influenced by both modifiable and non-modifiable risk factors.[33,34] Poor glycemic control is strongly associated with the development of DR, while early and intensive management of blood sugar, blood pressure and serum cholesterol has been proven to delay, and in some cases prevent, the onset and progression of DR.[19,35,36] However, given enough time, most patients with DM will develop some degree of retinopathy.[37] Some ethnicities (Indigenous, African descent, Hispanic and Asian) are more likely to develop diabetes and DR.[38] Physical activity is beneficial, while smoking and obesity are significant risk factors.[39,40,41,42,43] All these processes can be exacerbated by the onset of puberty or pregnancy.[44,45] Also, the initiation of intensive insulin treatment may result in an initial worsening of DR six to 12 months later, which then improves over time. The risk of early worsening is acceptable in light of the long-term benefits of intensive treatment.[46]

Through several pathways, chronic hyperglycemia leads to leukostasis, basement membrane thickening, loss of retinal capillary pericytes and endothelial cells, and a loss of smooth muscle in retinal arterioles, resulting in capillary bed instability, decompensation, and eventual collapse.[47,48,49,50] Ischemia and advanced glycation end products (AGEs) up-regulate vascular endothelial growth factor (VEGF), which is thought to be the primary cytokine that mediates increased vascular permeability and new blood vessel growth.[51,52] While VEGF is essential for cell survival, the over-expression of VEGF can

be catastrophic: increased vascular permeability resulting in diabetic macular edema and new blood vessel growth in both posterior and anterior segments of the eye are major causes of vision loss in patients with DM.

While microvascular complications have received the most attention, a growing body of evidence suggests that primary neuronal (glial cell) impairment, chronic vascular and neuronal inflammation, and insulin resistance within the retina itself play important roles, particularly in early (preclinical) DR.[53] Ideally, further investigation will enable the earlier diagnosis of DR through both functional (electrophysiological and psychophysical) and structural assessments, and identify alternate and perhaps more effective treatment strategies.

These and other events have been proposed to drive the progression of diabetic retinal disease through a series of well-defined stages of increasing severity defined by the landmark Early Treatment Diabetic Retinopathy Study (ETDRS), each of which carries an elevated risk of loss of vision.[54] Diabetic macular edema (DME), the most common cause of vision loss in persons with diabetes, may present at any point in the DR continuum.[55]

THE DIABETIC RETINOPATHY CONTINUUM

The International Diabetic Retinopathy Classification System (IDRCS), which is based on the ETDRS, defines the progression of DR.[54] The ETDRS followed the Diabetic Retinopathy Study (DRS), commissioned by the National Eye Institute (NEI) to evaluate the efficacy of laser photocoagulation, which had become widely used in the management of advanced nonproliferative and proliferative DR despite a lack of good-quality supporting evidence.[56] The DRS treated one eye in each of nearly 1,800 patients, with the fellow eye as an untreated control, and concluded that argon laser photocoagulation reduced the risk of severe vision loss by at least 50%, particularly in the presence of high-risk neovascularization involving the optic nerve head and/or accompanied by vitreous hemorrhage.[57] Questions about the timing of laser treatment and its effect on macular edema (ME) prompted the follow-up ETDRS, a multicentre study involving nearly 4,000 patients with bilateral retinopathy in which one eye was randomized to early photocoagulation and the other to deferred photocoagulation.[58] The results indicated that early and relatively aggressive photocoagulation reduced the risk of severe vision loss by nearly 25% and the development of high-risk proliferative DR by approximately 50%.[59]

Based on these landmark trials, the natural history of untreated but carefully monitored DR was studied, and the following continuum of DR development was articulated.

a) No apparent retinopathy

Diabetes-related microvascular dysfunction can begin very shortly after the onset of DM.[60] Early and clinically undetectable changes (preclinical DR, often beginning with subtle venous dilation) initiate the progression through the DR continuum.[61]

b) Nonproliferative diabetic retinopathy (NPDR)

i. Mild NPDR
Mild NPDR encompasses the earliest clinically detectable diabetes-related retinal abnormalities.

a. Microaneurysms (MA)
Mild NPDR is characterized by increased vascular permeability due to the development of retinal MA, which reflect the focal weakening of capillary walls possibly resulting from a loss of pericyte support.[62] During retinal examination, MA appear as sharp isolated red dots of varying size. Only MA at least 30 microns in diameter are visible on ophthalmoscopy.[63] Leakage of MA may lead to local retinal edema, hard exudates and/or intra-retinal hemorrhages (IRH). IRH are distinguished from MA primarily on the basis of diameter; they are larger than 125 microns.[64] If MA leakage involves the fovea, mild NPDR can still result in significant vision loss.

ii. Moderate NPDR
Moderate NPDR includes the characteristics of mild NPDR and one or more of the following:

a. Intra-retinal hemorrhages (IRH)
As noted above, leakage of MA, or retinal capillaries or venules, may lead to IRH. Their appearance

depends upon their location in the retina. IRH within the outer plexiform or inner nuclear layers have a dot (smaller and relatively well-defined) or blot (larger and ill-defined) appearance, respectively, whereas hemorrhages within the retinal nerve fibre layer (RNFL) appear flame- or splinter-shaped as a result of the anatomic contours of the nerve fibre layer.[65] Spontaneous occlusion of MA or accumulation of platelet/fibrin material may result in a white-centred retinal hemorrhage, or Roth spot. Although they are not specific to DR, when found in a patient known to have diabetes, Roth spots are not likely to be the sequelae of other serious systemic conditions (leukemia, bacterial endocarditis, or anemia, among others).[66] IRH secondary to DM are usually restricted to the posterior pole, resolve within several months, and have no impact upon vision unless they are physically at the fovea. Isolated atypical hemorrhaging (for example, extensive RNFL hemorrhaging or mid-to-far peripheral IRH) should raise suspicion of alternate etiologies (retinal vein occlusion or ocular ischemic syndrome, respectively).[67,68] However, mid-peripheral retinal ischemia is strongly associated with DME and proliferative retinopathy. Mid-to-far peripheral IRH in a patient with longstanding diabetes warrants further investigation, likely including wide-field fluorescein angiography.[69,70]

b. Hard exudates
Hard exudates (HE) represent the intra-retinal accumulation of serum lipoproteins that have leaked from excessively permeable capillaries, and herald the presence of past or current retinal edema.[71] Appearing as well-defined glistening yellow/white crystals, HE can be isolated or assume a circinate or star-shaped pattern around a leaking capillary or MA. HE may be resorbed spontaneously or following laser surgery that reduces retinal edema. Like IRH, they typically remain asymptomatic unless there is foveal photoreceptor involvement or, in the case of longstanding HE, disciform scar formation.[72]

c. Cotton wool spots (CWS)
Cotton wool spots, also referred to as soft exudates, are focal fluffy gray/white lesions that result from axoplasmic stasis and expulsion of axoplasmic material into the surrounding retinal tissue within the RNFL.[73] These lesions arise following pronounced retinal ischemia from several etiologies. In patients with DM, they are often accompanied by extensive dark-blot IRH secondary to partial arteriolar occlusion or complete occlusion followed by reperfusion, and usually signify more advanced NPDR.[74,75] CWS are typically asymptomatic and resolve within several months, but if persistent may cause permanent localized RNFL atrophy.[76,77] Clinicians should note that a transient increase in CWS is possible in early DR following the initiation or augmentation of systemic treatment that achieves better glycemic control.[78] For this reason, CWS alone are not reliable indicators of ischemic-driven progression of DR. However, if accompanied by other ischemic indicators, the presence of CWS corroborates concern regarding a substantial loss of retinal perfusion.

iii. Severe NPDR
As the course of DR progresses, arteriolar rather than capillary closure is thought to cause more severe ischemia, resulting in CWS, an increase in IRH (particularly dark-blot hemorrhages), and venous beading (VB).[79] The diagnosis of severe NPDR is based upon the extent and severity of the following abnormalities:

a. Intra-retinal hemorrhages
As described previously, but particularly including dark-blot hemorrhages.

b. Venous beading (VB)
Venous beading represents a focal irregularity in the venous calibre secondary to degeneration of the vessel wall within or adjacent to areas of extensive capillary closure.[80] These and other less common retinal vascular changes, including venous loops and reduplications, are strong predictors of progression to proliferative diabetic retinopathy (PDR).[81]

c. Intra-retinal microvascular abnormalities
Intra-retinal microvascular abnormalities (IRMA) are dilated telangiectatic capillaries connecting diseased arterioles and venules within or adjacent to areas of extensive capillary non-perfusion.[82] Like VB, IRMA are considered to be precursors of PDR and can be difficult to differentiate from neovascularization. PDR results in the growth of new vessels forward to incarcerate the vitreous while IRMA are limited to within the same retinal tissue. IRMA tend to leak less than new vessels during fluorescein angiography.[83]

Severe NPDR is diagnosed by satisfying any single criterion of the "4:2:1 Rule" with no evidence of proliferative (neovascular) disease:[84]

- IRH in all 4 of the retinal quadrants
- definite VB in 2 or more retinal quadrants
- prominent IRMA in 1 or more retinal quadrant(s)

iv. Very severe NPDR
Very severe NPDR is diagnosed by satisfying any two or more criteria of the "4:2:1 Rule" with no evidence of proliferative (neovascular) disease.

In the ETDRS,[84] one eye of each patient was assigned to early photocoagulation and the other to deferral of treatment so that the natural history of DR could be observed (treatment was initiated in the deferred eyes once patients became at high risk for the development of neovascularization). Data analysis showed that dark-blot hemorrhages, VB and IRMA were indicators of retinal ischemia, and all were significantly associated with the progression of DR to proliferative disease. For this reason, the advent of dark-blot hemorrhages, VB and IRMA should be interpreted with caution due to the much higher propensity for sight loss. From an optometric perspective, dark-blot hemorrhages, VB and IRMA usually justify referral to a retinal specialist for evaluation, including fundus fluorescein angiography to determine the presence and severity of capillary non-perfusion. CWS are also thought to reflect ischemic changes, but do not predict progression partly because they can transiently increase following intensive PG control. Unless associated with the other retinal lesions indicative of increased ischemia, careful monitoring of patients with CWS is appropriate.

c) Proliferative diabetic retinopathy (PDR)

Proliferative diabetic retinopathy is characterized by the growth of new and structurally fragile blood vessels (neovascularization) into the subhyaloid space, and eventually into the vitreous itself. These vessels are often accompanied by a developing framework of fibrous/glial tissue and arise most often at the boundary of perfused and non-perfused retinal tissue:[85] New vessels on or within one disc diameter of the optic nerve head (disc) are referred to as neovascularization of the disc (NVD), while new vessels beyond this boundary are called neovascularization elsewhere (NVE). While both NVD and NVE are ominous signs, the former carries a more guarded prognosis for future vision loss.

The sight-threatening sequelae of PDR are subhyaloid/vitreous hemorrhage and tractional retinal detachment.[86] These new vessels incarcerate the vitreous and are prone to hemorrhage with any amount of vitreous traction.[87] This hemorrhage can empty into the subhyaloid or preretinal space as a preretinal hemorrhage (PRH) or into the vitreous cavity as a vitreous hemorrhage (VH). Vitreous contraction can result in tractional retinal detachment (RD), especially in the presence of accompanying fibrous/glial tissue proliferation.[88,89]

Although the ETDRS differentiated between early and high-risk PDR (the latter shows more extensive NVD or any NVD/NVE accompanied by PRH/VH), progression to severe vision loss is unfortunately common with any degree of proliferative disease, and necessitates the consideration of panretinal photocoagulation and/or anti-VEGF injection should it be detected.[90,91]

The identification of retinopathy as early as possible affords the best opportunity for timely and effective intervention, and the maintenance or restoration of optimal vision and vision-related quality of life.

d) Diabetic macular edema (DME)

Diabetic macular edema is defined as retinal thickening within one disc diameter (~1500 microns) of the centre of the macula.[92] DME is the most common cause of vision loss in patients with diabetes and may present at any point in the DR continuum from no apparent DR to NPDR to PDR.[93] DME arises from a loss of integrity of the blood-retina barrier, and may be focal or diffuse. The former is due to localized leakage of individual MA within the retinal circulation and is often accompanied by HE, while the latter involves widespread leakage of the damaged capillary bed and/or choroidal plexus.[94]

The International Clinical Diabetic Macular Edema Disease Severity Scale classifies DME as absent or present based on the results of a stereoscopic retinal exam. If present, the examiner must determine whether it meets the criteria for clinical significance, implying that it represents an imminent threat to vision by encroaching upon the fovea.[58,95]

i. DME absent
DME is classified as *absent* if there is no apparent retinal thickening or HE detected through stereoscopic examination of the posterior pole.

ii. DME present
DME is classified as *present* if there is retinal thickening or HE detected through stereoscopic examination of the posterior pole.[96]

- minimal DME: edema or HE distant from the fovea
- moderate DME: edema or HE encroaching upon but not involving the fovea
- severe DME: edema or HE involving the fovea

For clinicians who are primarily concerned about the risk of vision loss secondary to DME, the ETDRS defined clinically significant (diabetic) macular edema based upon the proximity of the edema with respect to the centre of the macula.

iii. Clinically significant (diabetic) macular edema (CSME or CSDME)[95,97]
Clinically significant (diabetic) macular edema represents an imminent threat to vision because it encroaches upon or involves the fovea, and was specifically defined by the ETDRS as:

- retinal thickening at or within 500 microns (approximately one-third of a vertical disc diameter) of the centre of the macula; and/or
- HE at or within 500 microns (approximately one-third of a vertical disc-diameter) of the centre of the macula with adjacent retinal thickening; and/or
- retinal thickening of one disc-diameter in size, at least part of which is within one disc-diameter of the centre of the macula.

Subsequent to the ETDRS, objective imaging technologies such as optical coherence tomography (OCT) have reinforced the notion that the risk of vision loss from DME, as well as the need for treatment, is greatest when the fovea is involved.

iv. Central-involved (diabetic) macular edema
The advent of OCT has allowed the detection of subtle amounts of retinal edema and the recognition of central-involved diabetic macular edema, defined as ME affecting the central 1mm retinal subfield.[98]

e) Ischemic maculopathy

Ischemic maculopathy is characterized by the presence of foveal avascular zone (FAZ) abnormalities. Ischemic maculopathy is the consequence of extensive capillary closure and non-perfusion in the posterior pole and may result in significant and irreversible loss of central vision as a result of capillary 'drop-out.'[99] Fundus fluorescein angiography (FA) is required to definitively diagnose ischemic maculopathy.[100] "Optical coherence tomography angiography (OCTA) may become an alternative to FA for this purpose."[101] On clinical examination, CWS associated with dark-blot hemorrhages within the macula are also indicative of ischemic maculopathy. From an optometric perspective, ischemic maculopathy may present as an otherwise unexplained loss of vision in a patient with diabetes.

Given the devastating impact of diabetes, early detection (through annual comprehensive eye examinations) and timely treatment of DR is critical to avoiding permanent impairment.[102,103]

The presence of DR is also predictive of other micro- and macrovascular complications (including mortality, cardiovascular disease, cerebrovascular disease, peripheral neuropathy and nephropathy), further emphasizing the important role and responsibility of the primary care optometrist in the care of the patient.[104,105,106,107,108,109]

SUMMARY OF STAGING OF DIABETIC RETINOPATHY

See the table in Appendix 1, which incorporates the diagnostic characteristics, recommended follow-up, and referral criteria for different stages of DR.

Non-Retinal Ocular Complications of Diabetes Mellitus

Family physicians and endocrinologists often look to optometrists for information about the status of their patient's diabetes. While they are most often concerned about DR, diabetes mellitus can have many other effects on the eye and visual system.

REFRACTIVE CHANGES

It is not uncommon for a patient with diabetes to present with complaints that their vision has changed dramatically in a short period of time. Sometimes these changes can be found in established diabetic patients, but this may be the first symptom of diabetes that a patient experiences. The timeframe for return of refraction to the pre-hyperglycemic state depends on how quickly the patient's blood sugar returns to a more appropriate level; the patient must be counselled that stabilization may take weeks or months.

OCULAR-SURFACE DISEASE

Patients with diabetes have a higher prevalence of ocular-surface disease including Meibomian gland dysfunction, elevated tear-film osmolarity and tear-film instability, and corneal anesthesia.[110,111,112,113,114] Diabetes-related neuropathy and proliferative disease can also be risk factors for tear-film and ocular-surface disorders in DM.[115] The most common symptom that patients present is dry eye, both aqueous-deficient and evaporative. These patients have an up to a 33% higher prevalence of dry eye, and women are approximately 50% more susceptible than men.[116] Reduced corneal sensitivity associated with diabetes leaves the cornea vulnerable to asymptomatic trauma and may cause a delay in wound healing, resulting in persistent epithelial defects and corneal ulcers.[117] Impaired re-epithelialization of corneal defects has been well-documented, primarily due to weak and abnormal adhesions between the epithelium and the basement membrane directly beneath it.[118] The accumulation of AGEs on the basement membrane is a contributing factor. As a result, the cornea in the diabetic patient is not always an effective barrier to infection: as the patient's A1c increases, the ability of the cornea to act as a barrier decreases.[119] An abrasion that typically heals in a day in most patients may take 2 to 3 days to heal in a patient with diabetes, and treatment must therefore be tailored with this in mind.

CATARACT

While everyone can expect to develop a cataract if they live long enough, cataracts are more common and seen much earlier in patients with diabetes. One theory regarding the mechanism behind this greater frequency is that higher glucose levels in the blood lead to the oxidation of crystalline lens proteins.[120] Specifically, aldose reductase catalyzes the reduction of glucose to sorbitol and initiates the oxidative pathway. As the levels of sorbitol accumulate in the crystalline lens, osmotic stress leads to apoptosis (programmed cell death), which in turn leads to cataract formation.[121] Cataracts are classified by the layer or location of the opacity: in order of decreasing frequency, diabetes tends to cause posterior subcapsular (PSC) cataracts, followed by cortical cataracts, then nuclear sclerotic cataracts. Snowflake cataracts, while rare, are essentially pathognomonic of diabetes.

PRIMARY OPEN ANGLE GLAUCOMA

Glaucoma is a group of diseases that damage the retinal ganglion cells that form the optic nerve and can result in permanent vision loss, including blindness, if left untreated. Glaucoma is usually asymptomatic until a considerable amount of permanent damage has occurred. There are many types of glaucoma, and primary open angle glaucoma (POAG) is the most common in the North American population. The role of diabetes in the development of glaucoma has been controversial, and several studies have reached contradictory conclusions.[122,123] Recently however, several systematic reviews and meta-analyses have demonstrated that individuals with diabetes have on average a two- to three-fold increased risk of developing POAG, likely a result of the chronic micro-vascular compromise that characterizes diabetes and contributes to glaucomatous optic neuropathy.[124,125] Certain populations of patients

with diabetes have a higher risk of developing glaucoma, including those with poor glycemic control and those of Hispanic ethnicity.[126,127]

RUBEOSIS IRIDIS (NEOVASCULARIZATION OF THE IRIS; NVI)

Neovascularization of the iris is the result of ischemia secondary to chronic retinal vessel disease, and may be found in most patients with proliferative retinopathy. Profound hypoxia results in the formation of new blood vessels on the surface of the iris and in the anterior chamber angle of the eye. These weak and leaky vessels can hemorrhage, become fibrotic and shut down the angle, leading to increased intraocular pressure (IOP) and often painful neovascular glaucoma.

NEOVASCULAR GLAUCOMA (NVG)

As noted above, neovascular glaucoma is a devastating complication of the release of VEGF that accompanies the chronic retinal ischemia characterizing PDR. Physical obstruction of the trabecular meshwork often leads to significant elevations in IOP that require incisional surgery (trabeculectomy or a glaucoma drainage device), cyclodestructive procedures, or goniotomy.[128] Regardless of the intervention, unfortunately, the prognosis is guarded.

DIABETIC PAPILLOPATHY AND ANTERIOR ISCHEMIC OPTIC NEUROPATHY

Diabetic papillopathy is edema of the optic nerve in a diabetic patient caused by leakage of the vascular bundles and swelling of the retinal ganglion cell axons in and around the optic nerve.[129] It is rare, often self-limiting, presents with little impact on visual acuity, and can be unilateral or bilateral. Individuals with either type 1 or 2 diabetes are at an increased risk for developing this condition, which can occur even in the metabolically controlled population, often when they are quite young. While vision is initially unaffected, diabetic papillopathy may be associated with rapid progression of retinopathy, including NVD.

Although this position is controversial, some investigators have argued that diabetic papillopathy and non-arteritic anterior ischemic optic neuropathy (NAION) exist on a continuum, with the former representing a relatively minor manifestation of the latter, which may result in optic atrophy and permanent impairment of vision. The incidence of NAION is significantly higher in the presence of diabetes,[130,131] and as many as one in four patients with NAION have concurrent diabetes mellitus.[132]

OCULAR ISCHEMIC SYNDROME

Ocular ischemic syndrome (OIS) is a relatively rare condition that arises due to the ocular hypo-perfusion that accompanies carotid artery occlusive disease.[133] Symptoms include, but are not limited to, ocular pain and transient or permanent visual loss. Approximately half of patients initially present with visual acuities ranging between 20/20 and 20/50 in the affected eye, but nearly 1/3 have count fingers or worse vision.[134] Pain that results from ischemia can develop over the course of a few days, is typically dull, and can be alleviated by lying down. In contrast, pain from IOP can come on quickly. The pain accompanying OIS can radiate to the periorbital and temple regions, and care must be taken to differentiate it from giant cell arteritis. Retinal signs of the chronic hypoperfusion that accompanies OIS can include dilated vessels, mid-peripheral dot and blot hemorrhages and proliferation of neovascular membranes.[135] Anterior segment findings may include uveitis and neovascularization of the iris.[135]

The ocular manifestations of OIS can be difficult to differentiate from DR, especially when the two conditions are concurrent, and over 50% of patients with OIS have diabetes.[136] Unilateral or marked asymmetry of DR or NVI warrants further evaluation for carotid occlusive disease.[136]

CRANIAL NERVE PALSIES RESULTING IN OCULAR MOVEMENT DISORDERS

The three cranial nerves (oculomotor [CN3], trochlear [CN4] and abducens [CN6]) that control the six extraocular muscles can be affected by diabetic microvascular compromise. The oculomotor and abducens nerves are involved most frequently, followed by the trochlear nerve.[137]

The oculomotor nerve innervates three rectus (superior, inferior, and medial) and the inferior oblique muscles, the levator palpebrae superioris, and iris sphincter. Its paresis results in diagonal diplopia due to deviation of the eye down and out. This may be accompanied by ptosis and pupil dilation with anisocoria greater in the light. However, the pupil is often spared in diabetes-associated CN3 compromise, whereas mydriasis and pain are often found in paresis secondary to aneurysmal compression.

The abducens nerve controls the lateral rectus. When paretic, the patient will also experience diplopia, but it will be horizontal due to esotropia that is greater at a distance than at near. Sudden-onset CN6 palsy must be differentiated from giant cell arteritis, myasthenia gravis, medial wall fracture, intracranial hypertension and thyroid (restrictive) orbitopathy.

When the trochlear nerve is affected, the patient will experience diagonal diplopia, in this case due to involvement of the superior oblique muscle. CN4 palsy also results in small torsional rotation of the eye. Patients with this condition often learn to adopt a head-tilt to compensate. Differential diagnoses include multiple sclerosis, aneurysms, intracranial hypertension, head trauma and tumours.

Diagnosis of Ocular Complications of Diabetes Mellitus

In the provision of primary eye care, the optometrist plays a crucial role in detecting ocular manifestations of systemic disease, including diabetes. Particularly when the patient and optometrist have a long history together, changes in both ocular structure and ocular function can be observed over time. The following recommendations for the optometric examination of diabetic patients should facilitate the detection of potentially sight-threatening diabetic eye disease.

OPTOMETRIC EXAMINATION OF A PATIENT WITH DIABETES

When examining a patient with diabetes, optometrists should consider the following elements of the patient's medical history:[138]

1. Type and duration of diabetes: type 1, type 2, or gestational (self and family)
2. Current diabetes treatment (diet, oral medications, insulin type and dosage)
3. Blood sugar and glycemic control (including most recent fasting (spot) and A1c values)
4. Level of compliance with blood glucose control
5. History of diabetic retinopathy: date of diagnosis, level of severity, and treatments
6. Blood pressure and cholesterol/lipid status and treatment
7. Presence of co-existing kidney disease: note glomerular filtration rate (GFR)
8. Presence of peripheral or autonomic neuropathy

Optometrists should be active participants within a multidisciplinary health care team including, but not limited to, the primary care physician, diabetes educator, nutritionist, endocrinologist and nephrologist.

ENTRANCE TESTING

Habitual and best-corrected (or pinhole) visual acuities should be assessed, with special attention paid to any reduction in best-corrected acuity and refractive shifts that may be attributable to fluctuations in blood glucose. Pupil assessment may reveal sluggish responses, and ocular motility may be impacted by cranial nerve palsies involving CN3, CN4 and CN6. Confrontation visual field testing may reveal peripheral constriction, particularly if there is a history of panretinal photocoagulation.

ANTERIOR SEGMENT EXAMINATION

Slit lamp biomicroscopic examination of the anterior eye may reveal signs of dry eye syndrome or corneal defects indicative of poor wound healing. Careful examination of the iris is necessary to rule out neovascularization of the iris (NVI) and gonioscopy may be required if there is suspicion of new vessel growth involving the angle, raising the risk of neovascular glaucoma (NVG). Regular tonometry will reveal any changes in intraocular pressure. Examination of the crystalline lens is important, as patients with diabetes frequently develop posterior subcapsular, cortical, nuclear, and, more rarely, snowflake cataracts. Snowflake cataracts consist of gray-white opacities reminiscent of snowflakes.[139]

DILATED FUNDUS EXAMINATION

Stereoscopic slit lamp funduscopy through a dilated pupil is essential for the detection of diabetic retinopathy, including DME, which is the most common cause of vision loss in diabetes (see Section 3: Diabetic Retinal Disease). The use of mydriatic agents is generally safe unless contraindicated by a high risk of angle closure. The high magnification afforded by direct ophthalmoscopy may be helpful in the detection of NVD, but its clinical utility is

otherwise limited by the lack of stereopsis. Binocular indirect ophthalmoscopy is indicated, particularly when there is poor blood sugar control in patients with long-term diabetes due to concerns of peripheral ischemia.

RETINAL IMAGING

Digital fundus photography is key for documenting and monitoring diabetic retinal findings.[140,141] Ultra-widefield photography may be used as an ancillary imaging technique.[142,143] More recently, OCT has become important for detecting and quantifying retinal thickening, which is key in the diagnosis and assessment of DME. It is important to note that neither photography nor objective imaging should be viewed as a substitute for dilated fundus examination, but rather should serve as useful ancillary documentation, monitoring and educational tools. In remote and underserved communities with limited access to optometric or ophthalmologic services, telemedicine protocols may be established to aid in diagnosing DR. [144]

Intravenous fundus fluorescein angiography may be necessary to determine the extent of retinal ischemia, particularly in the presence of advanced nonproliferative retinopathy, any level of proliferative retinopathy, and DME. Ultra-widefield fluorescein angiography (UWFA) can also be a useful tool for detecting peripheral retinal ischaemia.[70,145]

SUMMARY OF EXAMINATION PROCEDURES [146,147]

Procedure	Potential diabetes-related ocular complications
Case history	Pertinent details and risk factors as noted above
Visual acuity: aided, pinhole	Decreased/shifted from normal/previous; fluctuating vision
Pupil reflexes	Sluggish light and near responses
Ocular alignment: cover test	Cranial nerve 3, 4, or 6 palsies
Extra-ocular motility testing	
Visual field testing	Loss of sensitivity Peripheral scotomas from panretinal photocoagulation
Tear film and ocular surface	Dry eye syndrome
Cornea	Reduced corneal sensitivity and wound healing ability
Iris	Neovascularization of the iris (NVI)
Lens	Early onset of nuclear, cortical and posterior subcapsular cataracts; more rarely, snowflake cataracts
Gonioscopy	Neovascularization of the angle (NVA)
Tonometry	Increased IOP (neovascular glaucoma and POAG)
Vitreous	Vitreous hemorrhage; vitreoretinal fibrosis
Retina • dilated fundus exam is required • digital fundus photography is recommended • OCT is recommended when clinical exam suggests DME or an unexplained change in visual acuity	DR and/or DME/CSDME

SUGGESTED TIMELINES

Patients with type 1 diabetes should have annual screenings for DR beginning 5 years after the onset of their disease. Patients with type 2 diabetes should be examined promptly at the time of diagnosis, and an annual recall schedule will help ensure they are not lost to follow-up.[148]

Women who develop gestational diabetes do not require an eye examination during pregnancy and do not appear to be at increased risk of developing DR during pregnancy. However, patients with diabetes who become pregnant should be examined early in the course of their pregnancy.[148]

At each exam, it is important to review glycemic control, blood pressure and lipid control, assess the patient for other non-ocular diabetes complications, provide counselling to the patient, and provide a report to the family physician and endocrinologist, if applicable.

If retinopathy is present, the stage of severity of retinopathy will establish appropriate monitoring intervals or trigger a referral for treatment (see Section 3: Diabetic Retinal Disease).

See the table in Appendix 1, which incorporates the diagnostic characteristics, recommended follow-up, and referral for different stages of DR.

DIABETIC MACULAR EDEMA AND CLINICALLY SIGNIFICANT MACULAR EDEMA

Diabetic macular edema (DME) can occur at any stage of DR. Clinical assessment includes the stereoscopic examination of the macular area through a dilated pupil using a hand-held lens and slit lamp (stereo fundus biomicroscopy) to detect retinal thickening with or without accompanying hard exudates.[149] OCT can assess macular thickness both qualitatively and quantitatively, and may assist in differentiating DME from other maculopathies (ischemic maculopathy, taut posterior hyaloid membrane, subfoveal serous detachment, etc.).[150,151,152,153]

As discussed in Section 3, clinically significant diabetic macular edema (CSME) is a strictly defined form of DME involving retinal thickening that encroaches on the fovea. The detection of CSME should trigger a referral to an ophthalmologist for consideration of treatment. A review should occur at least every six months following treatment once the patient is stable.

Optometrists should counsel patients on the importance of complying with follow-up eye care to aid in the early detection, and ideally prevention, of visual loss, and emphasize that micro-vascular changes like those detected within the eyes can also occur in other areas of the body. Patients with DR must recognize that they may have normal vision and visual acuity even in the presence of advanced levels of nonproliferative or proliferative retinopathy and/or ME. Providing brochures and website references may enhance compliance. An optometric report to the family physician and/or endocrinologist is essential for timely collaborative follow-up care of the patient with diabetes.

Management of Ocular Complications of Diabetes Mellitus

Treatment of the ocular complications of DM is largely dictated by the severity of the ocular disease, although consideration must be given to the age and wishes of the patient, the desired visual outcome, and systemic and ocular comorbidities. Important aspects of treatment include vigilant monitoring, education about improved blood glucose control and systemic health, and prompt referral to an ophthalmologist when medical or surgical treatment is indicated.

Ocular complications may be the presenting signs of diabetes, arising prior to the diagnosis of the disease itself. In such situations, the patient must be referred for systemic diagnostic testing while treatment of the diabetic eye disease begins. The following review of the management of diabetic eye disease will assume that the patient has either been previously diagnosed with diabetes or that the appropriate systemic diagnostic testing has been initiated.

MANAGEMENT OF RETINAL COMPLICATIONS

Monitoring and education:

In the case of mild to moderate NPDR without DME, examination by an optometrist should occur every 6 to 12 months, with careful scrutiny for progression. If the NPDR advances to a severe level or if DME is detected, the patient should be referred to an ophthalmologist.

Patient education regarding the effects of diabetes on ocular and systemic health and emphasizing the benefits of improved blood glucose control is imperative. Collaboration with the family physician and/or endocrinologist is essential to facilitate improved control of the diabetes and comorbidities.[148] A certified diabetes educator may also be an important part of the health care team.

Medical and surgical treatment:

1) Laser photocoagulation

a) Focal/grid photocoagulation
Focal/grid photocoagulation is used in the management of DME. Despite the risks, which include choroidal neovascularization, subretinal fibrosis, and iatrogenic visual field loss, focal photocoagulation remains an acceptable and effective treatment for DME, particularly if there is no centre/foveal involvement.[154,155]

b) Panretinal photocoagulation (PRP)
PRP is still used in eyes with proliferative retinopathy, particularly those that are considered to be at high risk based on the ETDRS (see Section 3: Diabetic Retinal Disease). While there are risks involved with PRP itself (most notably iatrogenic peripheral visual field loss and an increased risk of DME), PRP has been shown to reduce the risk of severe vision loss (Best corrected visual acuity (BCVA) of ≤5/200) by 50% in patients with high-risk PDR, defined as the presence of any three of the following:[88,91]

- Neovascularization of the disc (NVD)
- Neovascularization elsewhere (NVE)
- Severity of neovascularization
  - NVD > ¼ disc area in size
  - NVE > ½ disc area in size
- Preretinal or vitreous hemorrhage

2) Vitrectomy

a) Vitreous hemorrhage (VH)
In the case of a central vitreous hemorrhage, particularly if it is non-clearing or recurring, timely vitrectomy is recommended; delayed vitrectomy is associated with less satisfactory outcomes.[156]

b) Vitrectomy for DME
The vitreous is believed to contribute to DME through abnormally glycosylated and cross-linked vitreous collagen causing vitreomacular traction (VMT).[157] For this reason, vitrectomy (and consequent release of the VMT) may be considered in eyes with concurrent DME and VMT, and at least moderate vision loss.[156,157] Further, in patients with diabetes, the vitreous is known to contain exceedingly high levels of VEGF, essentially bathing the retina in VEGF and creating an optimal environment for breakdown of tight junctions at the inner and possibly the outer retinal barrier.[158] Research suggests that performing vitrectomy earlier gives more predictable results and less risk of complication than vitrectomy on eyes with PDR.[156,159] The primary risks associated with vitrectomy for DME are post-operative VH and retinal detachment.[157]

Of note, one study found no increased risk of peri- or post-operative hemorrhage following vitrectomy in patients on systemic anti-coagulant therapy. Patients undergoing vitrectomy should not have to discontinue use of anti-coagulants.[160]

3) Intraocular steroids

Intraocular steroids (most commonly triamcinolone, fluocinolone acetonide and dexamethasone) are another treatment option for DME. These steroids can be delivered through intravitreal injection, or implanted in a sustained-release format. While intravitreal injections of steroids can successfully reduce DME, their effect is short-lived, meaning that sustained-release implants may be a superior mode of delivery.[161] Sustained-release implants are injected through the pars plana as an outpatient procedure. The effects of the treatment last approximately 6 months.[162]

Complications can arise related to intravitreal steroids: increases in IOP and the development or progression of cataracts must be monitored closely. With sustained-release implants, the rates of these particular complications are particularly high: increased IOP is reported in 3 to 64% of patients (with lower rates when low-dose steroid implants are used) and cataracts requiring extraction within four years are found in 75 to 91% of patients.[161,163] Another serious complication is VH; less significantly, pruritis and an unusual sensation in the eye may be reported. Because of the complication rate, intraocular steroids may be best reserved for patients with recurrent or persistent DME. It has also been suggested that a focal or grid laser is preferred over triamcinolone injection since, while these treatments provide similar outcomes regarding visual acuity, the adverse effects are less significant with laser treatment.[164] Steroid treatment may also be used in conjunction with other treatment modalities (such as grid or focal laser, or PRP), rather than as a stand-alone treatment.[165]

4) Vascular endothelial growth factor inhibitors (anti-VEGFs)

VEGF is thought to be up-regulated by hypoxia and increased plasma glucose, and is found in higher concentrations in the retina and vitreous in patients with DR. VEGF increases the permeability of blood vessels and drives neovascularization. Anti-VEGFs decrease vessel permeability and reverse angiogenesis, and have become widely and successfully used in the treatment of DME and PDR.[166]

The anti-VEGFs most commonly used include:

- ranibizumab (Lucentis) – approved by Health Canada for treatment of DME
- bevacizumab (Avastin) – not approved by Health Canada, but often used off-label for the treatment of DME
- aflibercept (Eylea) – approved by Health Canada for treatment of DME

Intraocular injections of anti-VEGFs are now considered to be first-line treatment in eyes with DME. The initial treatment is typically every 4 to 6 weeks, then less frequently for a period of time determined by the treating ophthalmologist, typically guided by OCT-assessed retinal thickness and morphology.[167] Anti-VEGFs have also shown promise in the treatment of PDR. A recent randomized trial demonstrated that patients treated with ranibizumab had better central acuity and peripheral visual field sensitivity, and lower incidences of VH and DME than patients treated with PRP alone.[168]

Combined therapies for DME are gaining popularity. Pharmacotherapy has been shown to complement focal/grid laser photocoagulation in the management of DME,[169] and may reduce the treatment burden in these patients.[170] Additional large-scale, prospective, multi-centre, randomized, controlled trials for evaluating the role of combination therapy in DME are needed.[171]

MANAGEMENT OF NON-RETINAL OCULAR COMPLICATIONS

Refractive changes

Transient changes in refractive error associated with fluctuating blood glucose levels are commonly seen in patients with diabetes, and appropriate patient counselling is advised. A change in refractive correction may be required, as indicated by the patient's BCVA and visual requirements. However, it is recommended to defer prescribing refractive correction for patients with recently diagnosed diabetes or who are undergoing intensive glycemic control until normalization of blood glucose and stabilization of refractive error.[172,173] For the established diabetic, re-education on proper glucose control is important, while for the patient who has not been diagnosed with diabetes, a referral to their family physician for further investigation is indicated. In either case, once proper glycemic control is established, the refraction typically returns to its original state.[174]

Ocular-surface disease

Ocular-surface disease is more common in patients with diabetes, particularly in the presence of poor blood sugar control. Therefore, careful screening for dry eye disease (DED) in all patients with diabetes is recommended. Research shows that DED is associated with the duration of diabetes, A1c, and the presence of retinopathy; therefore, it may be beneficial to counsel patients on the benefits of glycemic control for the prevention of DED as well as retinopathy. [175,176]

Early diagnosis and treatment of DED is important for preventing secondary infection, corneal ulceration and scarring, and reduced quality of life. DED management in patients with and without diabetes is identical: the mainstays of management include artificial tears (AT), hot compresses and lid hygiene, topical anti-inflammatory agents (including corticosteroids and cyclosporine A), environmental modification, oral tetracycline derivatives, and punctal/lacrimal occlusion.[116,177] Oral omega-3 fatty acids have been shown to improve DED symptoms in patients with diabetes.[178]

Treatment of neurotrophic keratitis is aimed at achieving epithelial healing and preventing further corneal damage. Management involves treatment of underlying ocular-surface disease, often involving the use of preservative-free AT. Moderate presentations may require topical autologous serum AT, antibiotics, bandage contact lenses and/or collagen shields. Referral to an ophthalmologist may be required for more advanced neurotrophic keratitis; management options include the use of amniotic membrane, tarsorrhaphy, and conjunctival flap.[179]

Given the potential impact of diabetes on the ocular surface, some optometrists may have concerns about contact lens use. A review of the literature indicates that patients with diabetes can wear contact lenses as safely as patients without diabetes, provided there are no contraindications such as significant ocular-surface disease.[180]

Cataract

Careful assessment of refractive error and optimization of refractive correction is recommended for patients with cataract. If visual acuity cannot be improved sufficiently by refractive correction or if visualization of the retina is obscured by cataract, referral to an ophthalmologist for cataract extraction (CE) is recommended.

While visual improvement is achieved with CE in most patients with NPDR, improvement may be limited in patients with DME, PDR and/or poor pre-CE BCVA.[181,182] Careful pre-operative patient education regarding realistic surgical outcomes is advised.[183] Pre-operative treatment of severe NPDR or DME by photocoagulation or anti-VEGFs may result in better post-CE outcomes.[181,184,185]

Evidence regarding the progression of DR and development of macular edema following CE is mixed.[181,182,186,187,188]

While cataract surgery may be required once the patient's visual function starts to affect the activities of daily living, other treatment options to delay the need for surgical intervention have been investigated. Studies have shown that certain antioxidants (such as Vitamin B6 and N-acetylcysteine) can slow the oxidation that leads to early cataract formation. Another study found that high doses of Vitamin E combined with insulin helped reduce cataract formation in diabetic rats.[189] Delaying CE in the patient with DR provides some time to stabilize the condition. If the retinopathy is not controlled or is unstable, the risk of post-operative complications, especially ME, rises exponentially. CE before the presentation of proliferative disease is also of merit.[190]

Primary open angle glaucoma

While most POAG cases in patients with diabetes can be controlled with topical pharmaceutical agents, some patients require surgical intervention. Selective laser trabeculoplasty (SLT) has been found to be a safe and effective primary and adjunctive treatment for open-angle glaucoma.[191] However, there is contradictory evidence on its efficacy in the diabetic population.[192]

Rubeosis iridis and neovascular glaucoma

Neovascular glaucoma (NVG) is a complication of PDR that results from neovascularization of the iris (NVI) and anterior chamber angle. Early detection of NVI is critical, and necessitates immediate treatment with PRP, often accompanied by anti-VEGF injections to reduce the neovascular drive.[193] In addition to PRP and anti-VEGFs, management of NVG often involves medical and surgical treatment (typically the latter) to lower a markedly elevated IOP that results from secondary angle closure.[194] The visual prognosis is unfortunately quite poor.[195]

Diabetic papillopathy and anterior ischemic optic neuropathy

In patients with suspected diabetic papillopathy, other causes of disc edema must be ruled out to confirm the diagnosis.[196] While there is no generally accepted treatment for diabetic papillopathy and most cases resolve without sequelae over a few months, anti-VEGF injections or periocular steroids have been used for treatment.[197,198,199,200]

Patients with diabetes are at higher risk for developing non-arteritic anterior ischemic optic neuropathy (NAION),[132,201] one of the more common causes of acute optic nerve injury in individuals 50 years of age or older. There is currently no generally accepted treatment for NAION.[202]

Ocular ischemic syndrome (OIS)
Patients suspected of having OIS should be evaluated with carotid Doppler ultrasound to assess carotid patency, intravenous fluorescein or indocyanine green angiography to identify retinal ischemia and neovascularization, as well as a detailed anterior segment evaluation given the risk of NVI and NVG. Detection of underlying carotid occlusive disease is essential. While OIS arises from carotid stenosis, emboli from the carotid arteries can lead to retinal artery occlusion and ischemic optic neuropathy.[135] The prognosis for patients diagnosed with OIS is generally poor, and prompt patient referral for assessment by specialists in ophthalmology, internal medicine, cardiology and/or neurology is recommended.[203]

Cranial nerve palsies resulting in ocular movement disorders
As a result of the microvascular ischemia that accompanies diabetes, hypertension and hyperlipidemia, palsies of the third, fourth or sixth cranial nerves are relatively common. Consequently, patients with diabetes have a higher incidence of cranial nerve palsies than the general population.[204,205,206]

In the setting of cranial nerve palsy, it is important to rule out non-microvascular etiologies, which may require neuro-imaging such as magnetic resonance imaging (MRI).[205] If the underlying vascular disorder is addressed, the prognosis for cranial nerve palsy with confirmed microvascular etiology is good, with gradual resolution over 8 to 12 weeks.[207] Options for the management of diplopia prior to its spontaneous resolution include monocular occlusion or Fresnel prism.

MANAGEMENT OF COMORBIDITIES AND SYSTEMIC COMPLICATIONS OF DIABETES MELLITUS

Several issues need to be managed in patients diagnosed with DM, including glycemic control, blood pressure control, cholesterol levels, cardiovascular risks and weight management. While these matters are typically the purview of the family physician and/or endocrinologist, optometrists and other members of the patient's health care team may also play a role.

Concluding Remarks

People with diabetes are at risk for several ophthalmic complications, including diabetic retinopathy, many of which remain asymptomatic until quite advanced. Consequently, regular, ideally annual, comprehensive eye examinations are important for everyone with diabetes, as prompt diagnosis and timely treatment afford the best opportunity to prevent or minimize vision loss.

Optometrists who are familiar with the risk factors, diagnostic classification, follow-up schedules and referral criteria for these complications are well-positioned to provide accessible, quality eye care. As active participants on a multidisciplinary health care team, optometrists also play an integral role in patient education, by emphasizing the importance of optimal diabetes control and overall health management to reduce the risk of ophthalmic and other complications of the disease.

These guidelines are intended to assist optometrists with the complex decisions that characterize the care of patients with diabetes. They are informed by seminal and contemporary high-quality evidence and are the product of a guideline-development process that reflects good practice. Due to the ongoing evolution of our understanding of diabetes and DR, these guidelines should be considered a work in progress. Feedback is welcome and can be sent to the Canadian Association of Optometrists at info@opto.ca

Appendix 1: Diagnostic characteristics, recommended follow-up, and referral by stage of diabetic retinopathy

Suggested Frequency of Eye Examination for Patients with Diabetes *(subject to resource availability, specifically medical/surgical retinal specialists)*				
Stage of retinopathy	Diagnostic characteristics	Macular status	Frequency of Examination	Referral Timing and Treatment
No apparent retinopathy	No abnormalities	No DME	Every 12 months	No referral necessary
Mild NPDR	MA	No DME	Every 12 months	No referral necessary
		DME	Every 4 to 6 months	No referral necessary
		CSME	Every month	Within 1 month: consider focal laser, anti-VEGF
Moderate NPDR	MA IRH HE CWS	No DME	Every 6 to 12 months	No referral necessary
		DME	Every 3 to 6 months	No referral necessary: monitor carefully for CSME
		CSME	Every month	Within 1 month: consider focal laser, anti-VEGF
Severe or very severe NPDR	Any one of '4:2:1 Rule': 4: IRH (particularly dark-blot IRH) in 4 retinal quadrants 2: venous beading in 2+ quadrants 1: IRMA in 1+ quadrant Very severe NPDR: 2 or more features of severe NPDR	No DME	Every 2 to 6 months	If very severe, within 1 month: consider PRP Review at least every 6 months once stabilized
		DME	Every 2 to 4 months	If very severe, within 1 month: consider PRP Review at least every 6 months once stabilized
		CSME	Every month	Within 1-2 weeks: consider PRP, focal laser, anti-VEGF Review at least every 6 months once stabilized.
PDR	NVD NVE VH PRH	No DME	Every 2 to 4 months	Within 2 weeks: consider PRP Review at least every 6 months once stabilized
		DME	Every 2 to 3 months	Within 2 weeks: consider PRP Review at least every 6 months once stabilized.
		CSME	Every month	Within 1 week: consider PRP, focal laser, anti-VEGF Review at least every 6 months once stabilized
High-risk PDR	Severe NVD: larger than 1/4 to 1/3 disc area Severe NVE: larger than 1/2 disc area VH or PRH with fibrovascular proliferation or tractional RD	No DME	Every 2 to 3 months	Within 1 week: PRP and/or anti-VEGF Review at least every 6 months once stabilized
		DME	Every 1 to 3 months	Within 1 week: PRP and anti-VEGF; consider focal laser Review at least every 6 months once stabilized
		CSME	Every month	Within 1 week: PRP and anti-VEGF; consider focal laser Review at least every 6 months once stabilized
Diabetic macular edema (DME) is defined as: Retinal thickening or HE detected through stereoscopic examination of the posterior pole, but not within the criteria set for clinically significant macular edema (CSME). **CSME is defined as:** Retinal thickening at or within 500 microns of the centre of the macula; and/or HE at or within 500 microns of the centre of the macula with adjacent retinal thickening; and/orRetinal thickening of one disc-diameter in size, at least part of which is within one disc-diameter of the centre of the macula. Refer CSME to ophthalmology for immediate treatment (within 1-2 weeks if accompanied by more advanced retinopathy). Review at least every 3 to 6 months once stabilized.				
A patient with sudden severe vision loss or signs/symptoms of retinal detachment should be immediately referred to an ophthalmologist able to treat proliferative disease/CSME.				

Other abbreviations: CWS, cotton wool spots; DR, diabetic retinopathy; HE, hard exudates; IRH, intraretinal hemorrhages; IRMA, intraretinal microvascular anomalies; MA, microaneurysms; NPDR, nonproliferative diabetic retinopathy; NVD, neovascularization of the disc; NVE, neovascularization elsewhere; PDR, proliferative diabetic retinopathy; PRH, preretinal hemorrhage; PRP, panretinal photocoagulation; RD, retinal detachment; VEGF, vascular endothelial growth factor; VH, vitreous hemorrhage

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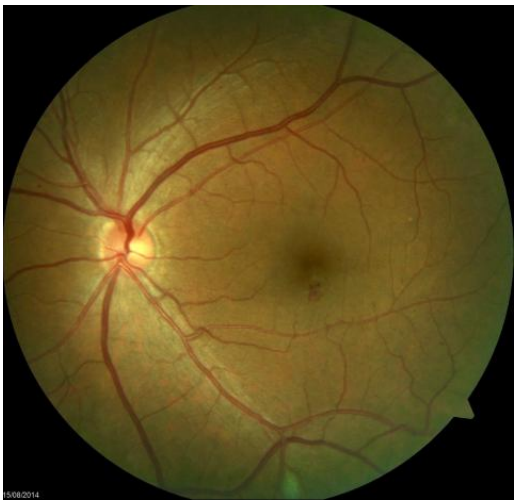
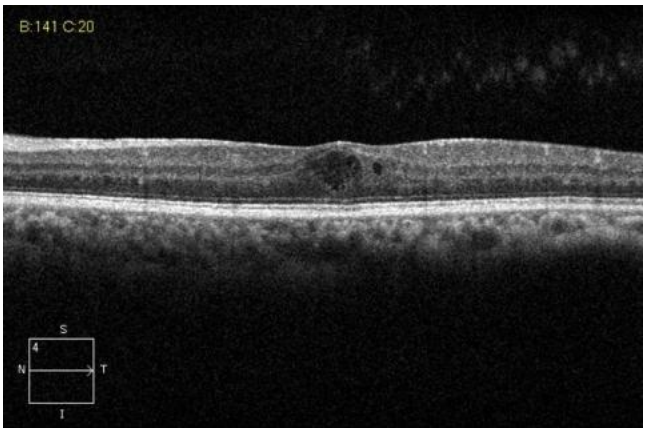
Clinically significant macular edema

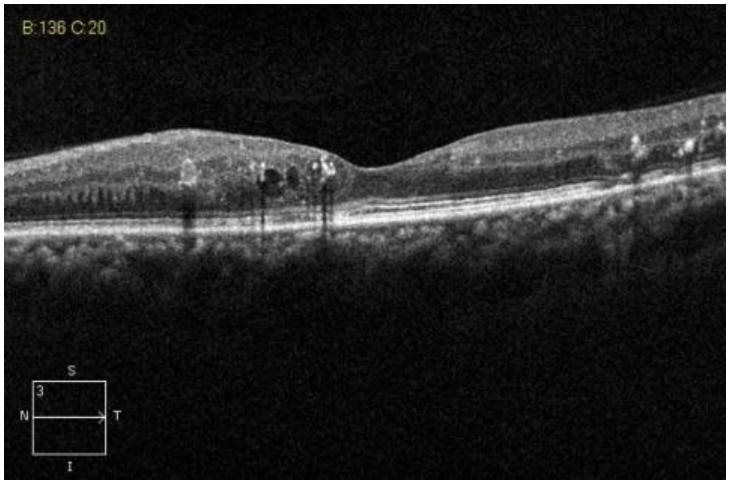
This 56-year old Guyanese man has intra-retinal hemorrhages/microaneurysms and retinal thickening just inferior to (within 500µm of) the fovea. Macular OCT shows speckled intra-retinal fluid and a small cyst at the level of the inner plexiform layer. The outer retina is unremarkable, and best acuity remains 6/6.





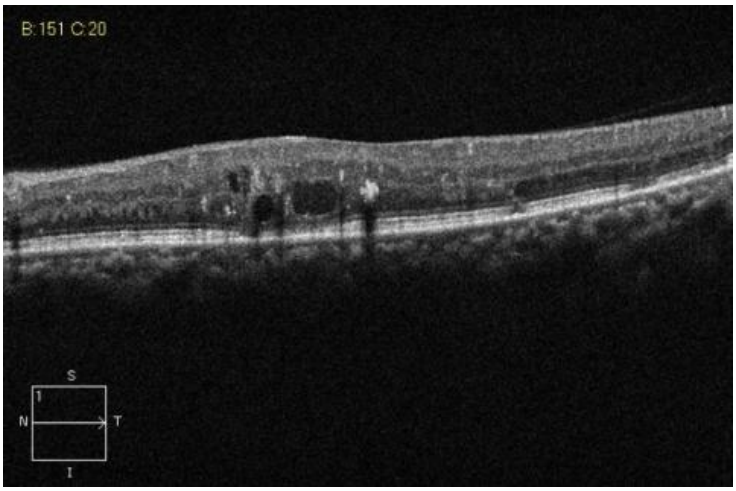
Early nonproliferative diabetic retinopathy and clinically significant macular edema

This 56-year old Indian man has prominent hard exudate (HE) accumulation and intra-retinal hemorrhaging with associated retinal thickening throughout the macula, and several inferior cotton wool spots. Macular OCT shows very hyper-reflective HE predominantly involving the inner and outer nuclear layers (note the deeper shadowing posterior to the hyper-reflective HE). A less hyper-reflective microaneurysm (margin more reflective than center) is present just nasal to the fovea. Speckled central intra-retinal fluid and outer retinal thickening are also present nasally (note the 'saw tooth' appearance of the outer plexiform layer). The ellipsoid zone is slightly irregular, although best acuity remains 6/6-.



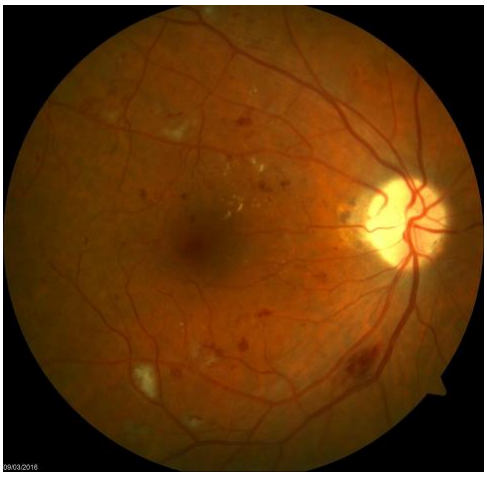
Early nonproliferative diabetic retinopathy and clinically significant macular edema, post-anti-VEGF treatment

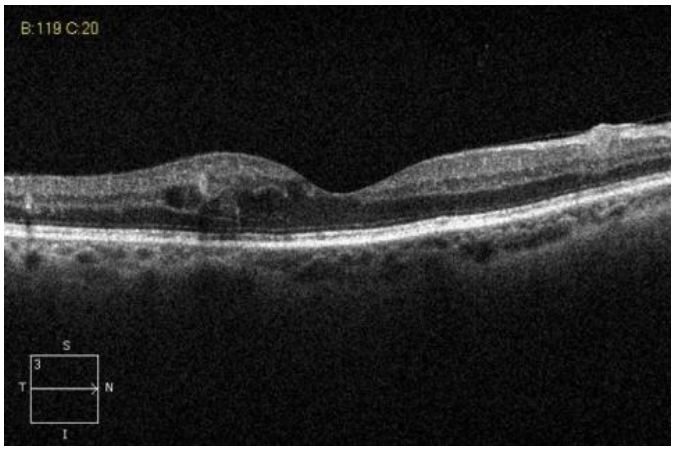
30 months post-anti-VEGF treatment, this now 58-year old Indian man shows a significant decrease in HE, and fewer intra-retinal hemorrhages and cotton wool spots. Macular OCT shows less hyper-reflectivity and secondary shadowing, but persistent (in fact, slightly increased) speckled IRF in the inner and outer nuclear layers. The ellipsoid zone remains irregular, more superior-nasal than central, with best acuity of 6/7.5.



Moderate nonproliferative diabetic retinopathy and clinically significant macular edema

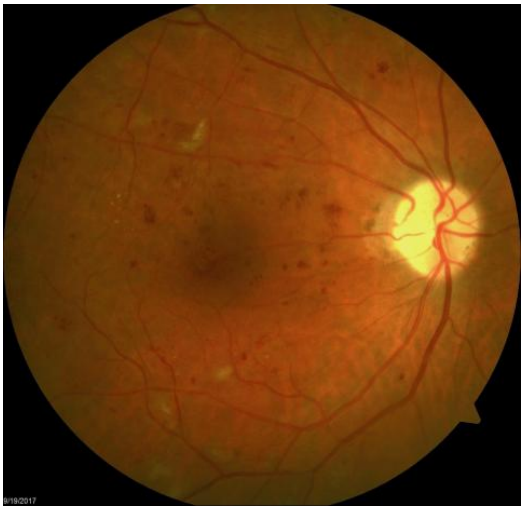
This 75-year old Caucasian man shows multiple intra-retinal hemorrhages and cotton wool spots, hard exudates in a circinate pattern superior to the fovea, and a retinal nerve fiber layer hemorrhage along the inferior arcade. Macular OCT shows speckled IRF and hyper-reflective hemorrhages/microaneurysms predominantly temporal to the fovea. Despite the macular edema, the ellipsoid zone remains intact with best acuity of 6/6. Referral for anti-VEGF therapy was recommended, but declined.

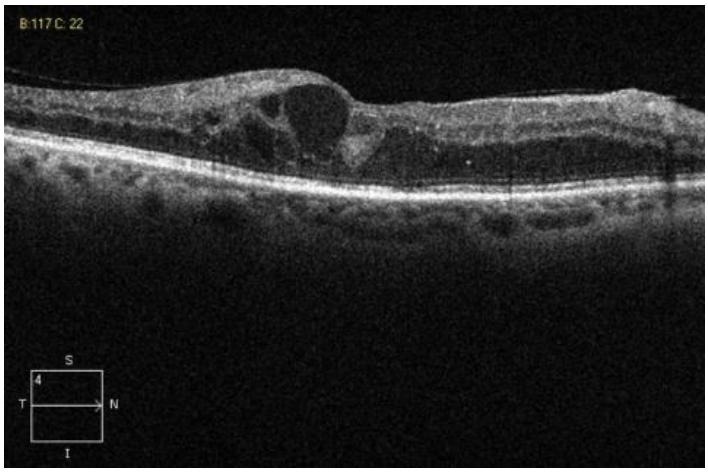




Moderate nonproliferative diabetic retinopathy and clinically significant macular edema (18 months post-initial presentation)

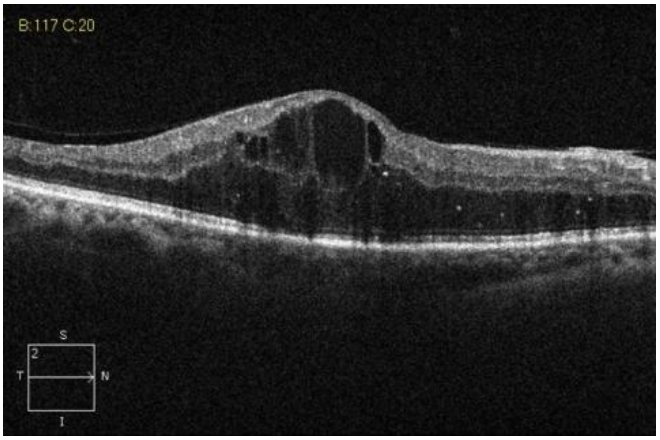
Eighteen months after initial presentation, this now 76-year old Caucasian man shows less intra-retinal hemorrhaging, HE, and cotton wool spot formation, and resolution of the retinal nerve fiber layer hemorrhage along the inferior arcade. Clinical macular exam suggested persistent thickening, particularly temporally. This was confirmed by OCT, which showed a significant increase in speckled IRF temporal to the fovea, and diffuse outer retinal thickening and hyper-reflective foci (the latter thought to represent activated inflammatory/microglial cells) nasal to the fovea. The ellipsoid zone remains intact with best acuity of 6/6. Referral for anti-VEGF consultation was again recommended, but again declined.





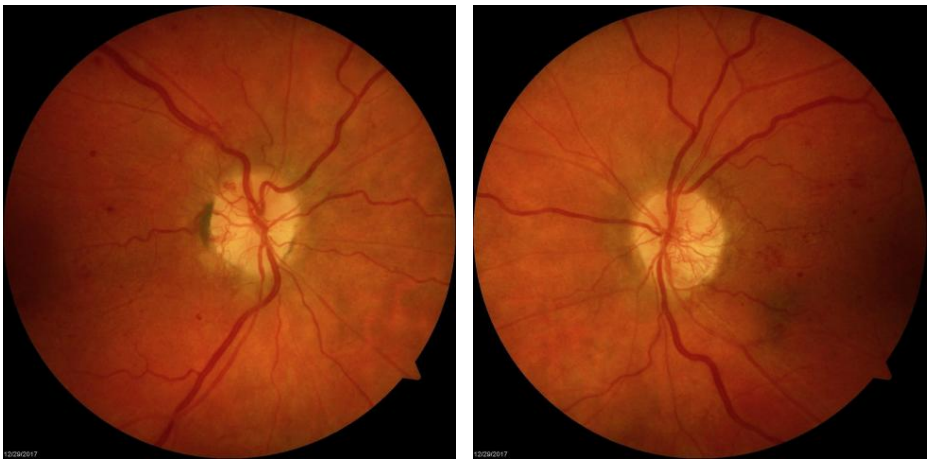
Moderate nonproliferative diabetic retinopathy and clinically significant macular edema (20 months post-initial presentation)

Within several months, this 76-year old Caucasian man returned with increasing blur, and best acuity had dropped to 6/18. Not surprisingly, macular OCT showed increased diffuse outer retinal thickening, more hyper-reflective foci, and much larger cystic cavities in the inner nuclear layer. At this point, referral was accepted: anti-VEGF treatment was initiated, and follow-up is ongoing.



Neovascularization of the disc

This 46-year old Caucasian woman with a history of gestational diabetes in her early 20s presented 15 years ago with signs suggesting diabetic retinopathy, and was subsequently diagnosed with type 2 diabetes mellitus. Blood sugar control was mediocre, and the patient developed bilateral diabetic macular edema and macular ischemia in the right eye. An additional oral hypoglycemic agent and weight loss led to a decrease in retinopathy; however, peripheral neuropathy and a poorly healing leg ulcer prompted the addition of insulin. The patient subsequently presented with moderate NPDR, CSME, and bilateral neovascularization of the disc. Despite this, best acuity remained 6/7.5 in both right and left eyes. Referral for consideration of anti-VEGF and/or pan-retinal photocoagulation was initiated, with follow-up pending.



Proliferative diabetic retinopathy

This 45-year old Caucasian woman with a 35-year history of type 1 diabetes underwent pan-retinal photocoagulation (PRP) in her early 40s following the development of NVD, which subsequently showed some regression. The retina exhibited scattered dot and blot hemorrhaging and ghost vessels, predominantly in the temporal macula, and peripheral laser scarring. Two years later, she developed a vitreous hemorrhage (VH) secondary to traction on several persistent neovascular fronds; her acuity remained good (6/6-) and her retinal specialist recommended observation as the hemorrhage cleared. Within several months, proliferative vitreoretinopathy with tractional retinal elevation and a smaller VH along the superior arcade was noted (see photo). Repeat retinal consult yielded the recommendation to continue observation: aside from a third small central VH that quickly resolved, the clinical picture and visual acuity have remained stable for the subsequent two years.