

Clinical & Refractive Optometry is pleased to present this continuing education (CE) article by Dr. Gay K. Tokumaru entitled **A Practical Guide to Diabetic Retinopathy**. In order to obtain a 1-hour Council of Optometric Practitioner Education (COPE) approved CE credit, please refer to page 40 for complete instructions.

A Practical Guide to Diabetic Retinopathy

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ABSTRACT

Diabetes mellitus is a major public health issue in Canada and the United States, and optometrists will frequently encounter patients with diabetes and diabetic retinopathy in clinical practice. This article reviews basic principles of diabetes and its systemic complications, in particular diabetic retinopathy. The pathophysiology as well as the clinical findings typical of nonproliferative and proliferative diabetic retinopathy and macular edema are discussed. The risk factors for the development of diabetic retinopathy are examined, and guidelines for the clinical management of patients with diabetic retinopathy are presented.

INTRODUCTION

Diabetes mellitus is a major public health issue in North America. There are approximately 1.4 million Canadians with diabetes, and this number is expected to reach 3 million by 2010. In the United States, 5.9% of the population, or 15.7 million people, have diabetes. Of those aged 65 years and older, approximately 10% of Canadians and 18.4% of Americans, have diabetes. An estimated one-third of all diabetics in Canada and the United States are undiagnosed.^{1,2}

Ocular manifestations of diabetes mellitus are common, and in particular diabetic retinopathy is a significant health issue. Epidemiologic data available from the United States indicate that 40% to 45% of diabetics have some degree of diabetic retinopathy, and about 15% have retinopathy that is severe enough to cause vision loss.² Optometrists frequently encounter diabetic patients, and it is essential that we possess a sound understanding of what diabetes is, how it affects the body and the eyes, what puts patients at risk for developing diabetic retinopathy, and how to manage diabetic retinopathy in clinical practice.

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Diabetes can be classified into two basic types. With insulin-dependent diabetes mellitus (IDDM, or type 1), the body is unable to produce insulin, so exogenous insulin is required to prevent ketoacidosis: very high sugar levels and accumulation of fat by-products in the blood. In this type, onset is usually abrupt, occurs prior to age 40, and is probably mediated by an autoimmune process.

Non-insulin dependent diabetes mellitus (NIDDM, or type 2), is the most common type of diabetes, comprising 75% to 90% of all cases.³ In this type, the body produces insulin but the tissues resist the action of insulin. In these patients insulin may be used as therapy, but they do not become ketoacidotic in the absence of insulin, thereby distinguishing them from type 1 diabetes mellitus. The onset of the disease is usually insidious, occurs after the age of 40, and is typically associated with obesity.

The systemic complications of diabetes can be broadly classified into two categories: macrovascular and microvascular. Macrovascular complications affect the large blood vessels of the body, and include coronary artery disease, peripheral vascular disease, and cerebrovascular disease. Coronary artery disease, in which the blood vessels of the heart are involved, includes angina, myocardial infarction, and heart failure. Peripheral vascular disease, or impaired circulation, can result in gangrene and nonhealing foot wounds, and may necessitate amputation of the toes, foot, or leg. Cerebrovascular disease includes stroke and transient ischemic attacks. Such macrovascular complications are two to four times more common in diabetics than in nondiabetics.

Microvascular complications affect the small blood vessels of the body and include nephropathy (kidney involvement) neuropathy (nerve involvement), and retinopathy.

Nephropathy, or kidney disease, can lead to end-stage renal disease (ESRD) or kidney failure, necessitating either kidney dialysis or a kidney transplant.

Neuropathy, or nerve damage, most commonly affects diabetics in the form of peripheral or sensory neuropathy. This results in the sensation of pain, burning, prickling, or tingling in the extremities, most commonly the feet and toes. Ultimately, a loss of sensation and numbness can result. Autonomic neuropathy is another

Table I Nonretinal complications of diabetes
<ul style="list-style-type: none"> • Reduced corneal sensitivity • Recurrent corneal erosions • Delayed corneal wound healing • Neovascularization of the iris (rubeosis iridis) • Sluggish papillary reflexes • Fluctuations in refractive error • Cataracts • Papillitis • Ischemic optic neuropathy • Cranial neuropathies: III, IV, or VI

form of nerve damage in which the autonomic nerves that control the bladder, intestinal tract, and genitals are affected. Damage to these nerves can result in paralysis of the bladder (predisposing to urinary tract infections); gastroparesis (difficulty moving food through the stomach, leading to vomiting and bloating), and impotence.

Retinopathy is also a form of microvascular involvement from diabetes. Although nonretinal complications can occur (Table I), retinopathy is the most common manifestation of diabetic eye disease.

PATHOPHYSIOLOGY OF DIABETIC RETINOPATHY

All the funduscopy abnormalities observed in diabetic retinopathy are the result of the primary pathologic changes that occur in the capillary bed of the retina. These changes involve either (1) closure of capillaries, leading to ischemia, or (2) abnormal vascular permeability, leading to edema. The most likely pathophysiologic mechanism of diabetic retinopathy is thickening of the basement membrane of the capillaries and loss of the pericyte nuclei. Pericytes are mesothelial cells that wrap around the capillary endothelial cells, and normal capillaries have a one-to-one ratio of pericyte nuclei to endothelial cells. In the diabetic eye, the basement membrane becomes thickened and vacuolized, and the pericyte nuclei become lost, leading to weakening and closure of the capillaries. These early, invisible changes in the capillary bed eventually lead to the funduscopy changes typical of diabetic retinopathy.

Diabetic retinopathy resulting from retinal ischemia can either be nonproliferative (NPDR) or proliferative (PDR). Damage to the capillary bed can also take the form of abnormal vessel permeability, leading to leakage of plasma proteins and water into the intraretinal space (retinal edema).

NONPROLIFERATIVE DIABETIC RETINOPATHY — CLINICAL FINDINGS RESULTING FROM ISCHEMIA

Nonproliferative diabetic retinopathy (NPDR) includes a constellation of clinical findings that reflect ischemia of the retina and includes the following:

Microaneurysms

Pathologically, microaneurysms are focal capillary dilatations that occur in areas weakened by pericyte dropout and are usually the earliest structural alterations of retinal disease that are visible ophthalmoscopically.

Intraretinal Hemorrhages

Intraretinal hemorrhages are probably caused by fragile capillaries or thin-walled microaneurysms that leak and bleed. If this bleeding occurs in the superficial layers of the retina, flame-shaped hemorrhages will be seen. If they occur deeper in the retina — usually at the level of the outer plexiform or inner nuclear layer — they will appear as dot and blot hemorrhages.

Cotton-Wool Spots or Nerve-Fiber Layer Defects

These fluffy yellow-white lesions with feathery borders occur following the occlusion of precapillary arterioles. The hypoxia that follows these occlusions interrupts the normal axoplasmic transport, which is highly oxygen-dependent, leading to an accumulation of axoplasmic debris and fluffy white opacification of the inner retinal layers.

Venous Abnormalities

Venous abnormalities result from dilation and thinning of the venous wall and include venous beading (localized increases in venous caliber), venous narrowing, and venous loops.

Intraretinal Microvascular Abnormalities

Intraretinal microvascular abnormalities (IRMA) are irregular, segmented dilatations of the capillary bed and represent either intraretinal neovascularization, or the dilation of pre-existing vessels (shunt formation) (Fig. 1).

Arteriolar Occlusions

The larger arterioles of the retina can become chronically occluded, resulting in extensive areas of nonperfusion and the appearance of a “featureless retina.” In this presentation, the retina appears atrophic, with a noticeable paucity of typical NPDR lesions and an absence or sclerosis of the smaller branches of the arterioles.

Ischemic Maculopathy

When there is nonperfusion of the small capillaries surrounding the fovea, there can be an enlargement of the normal foveal avascular zone (FAZ), with a resulting decrease in vision. Because this is the result of capillary closure, it cannot be detected by fundus examination, but must be diagnosed by fluorescein angiography.

NONPROLIFERATIVE DIABETIC RETINOPATHY — CLINICAL FINDINGS FROM

ABNORMAL VESSEL PERMEABILITY

When there is breakdown of the inner- and outer-blood retinal barriers (BRBs) and loss of the tight junctions



Fig. 1 Intraretinal microvascular abnormalities in a patient with non-proliferative diabetic retinopathy (NPDR)

between the endothelial cells of the retinal vessels, these vessels can become abnormally permeable. Plasma proteins and water can leak out of the vessels and accumulate in the extracellular spaces of the retina, creating edema or thickening of the retina. As the normal retina and retinal pigmented epithelium adjacent to these areas of leakage remove some of this fluid, a lipid-rich exudative residue or “bathtub ring” can be left behind. These hard or lipid exudates often demarcate an edematous from a nonedematous retina.

Clinically, edema of the retina is of concern when it involves the macula, and macular edema can either be focal or diffuse. Focal edema results from focal leakage of microaneurysms or intraretinal microvascular abnormalities, and presents clinically as localized areas of retinal thickening, often surrounded by a lipid ring. Diffuse edema is the result of more widespread retinal thickening caused by generalized leakage from abnormal capillaries throughout the posterior pole, and often presents with minimal lipid exudates, as the diffuse breakdown of the BRBs doesn’t allow passage of the larger lipoprotein molecules.

PROLIFERATIVE DIABETIC RETINOPATHY

Proliferative diabetic retinopathy (PDR) is the growth of new blood vessels on the surface of the retina, either on or within one disc diameter of the optic nerve head (neovascularization of the disc — NVD), or elsewhere on the retina (neovascularization elsewhere — NVE). The ischemic retina is believed to produce a vasogenic or angiogenic factor that acts locally as well as diffusing throughout the vitreous to other parts of the retina, disc, and anterior chamber (e.g., the iris) to stimulate new vessel growth.

Natural History of Proliferative Diabetic Retinopathy

Typically, growth of new vessels in PDR is characterized by cycles of proliferation and regression, with a highly variable rate of growth that can range from weeks to years. Initially, neovascularization consists of budding endothelial cells that grow into fragile new vessels that eventually become surrounded by fibrous tissue. As the new vessels go through their cycles of growth and progression, the fibrous tissue becomes increasingly opaque and these fibrovascular proliferations become adherent to the posterior surface of the vitreous. Contraction of the vitreous or of the growing fibrous tissue can lead to small subhyaloid, preretinal, or vitreous hemorrhages (Fig. 2). Eventually, as these fibrovascular proliferations continue to grow and form vitreo-retinal adhesions, the hemorrhages become larger, promoting more fibrous adhesions and traction. Eventually, large fibrovascular membranes develop that can exert enormous traction on the vitreous and retina, leading to traction retinal detachments, dragging of the macula, and full-thickness holes of the retina (Fig. 3).

Eventually, PDR can reach an involitional or burnt-out stage in which very little progression occurs because the vitreous has completely detached. This stage is characterized by more transparent fibrous tissue, minimal vitreous or retinal hemorrhages, sclerotic-appearing vasculature, and poor visual acuity as a result of severe retinal ischemia (Fig. 4).

RISK FACTORS FOR DEVELOPING DIABETIC RETINOPATHY

In managing diabetic patients, there are a number of factors that are helpful in determining an individual patient’s risk of developing retinal complications of diabetes.

Duration and Type of Diabetes

One of the best predictors of the development of diabetic retinopathy is the duration of diabetes, as well as the type. There is excellent epidemiological data from the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), which took place in the 1970s and 1980s, in which several thousand diabetics were followed to see who developed retinopathy. As can be seen in Table II, the younger-onset diabetics had the greatest incidence of any retinopathy; by 10 years, 89% had some retinopathy and 30% had PDR. The older-onset diabetics not on insulin had the least retinopathy; by 10 years 70% had some retinopathy and only 10% had PDR. The older-onset group using insulin fell between the two groups, with 79% having some retinopathy and 24% developing PDR.^{4,6}

Glycosylated Hemoglobin

Glycosylated hemoglobin (Hemoglobin A1C; HgbA1C) is a type of hemoglobin in red blood cells that becomes

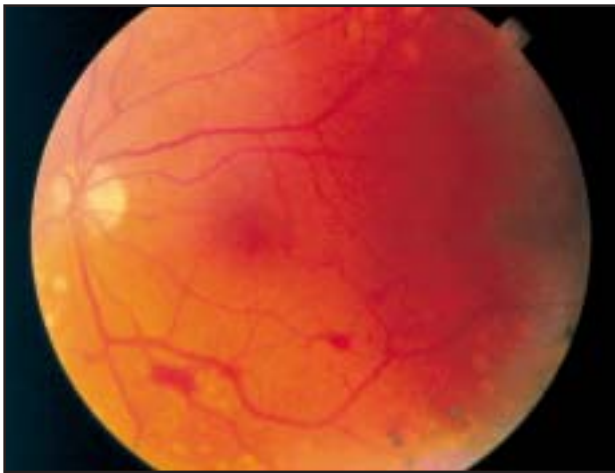


Fig. 2 Small preretinal hemorrhages in a patient with proliferative diabetic retinopathy

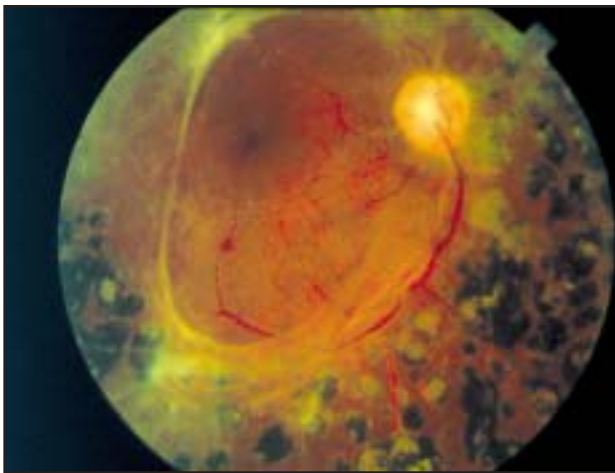


Fig. 4 Involutinal or burnt-out stage of proliferative diabetic retinopathy

glycosylated when exposed to circulating blood glucose. The amount of glycosylated hemoglobin bound to the red blood cells is directly proportional to the amount of glucose available to the red blood cell over its life span; therefore HgbA1C reflects the average blood sugar levels for the two- to three-month period before the test, and gives an overall measure of glycemic control rather than the “snapshot” of a single blood glucose reading. Normal HgbA1C levels vary by lab, but typically, a normal value is under 6.0%. An estimate of average daily blood glucose readings can be obtained from a single HgbA1C reading by multiplying the HgbA1C value by 30, then subtracting 60. Hence a reading of 6.0% roughly translates to an average daily blood glucose reading of 120 mg/dL. Numerous studies have demonstrated that glycosylated hemoglobin is one of the strongest risk factors for the

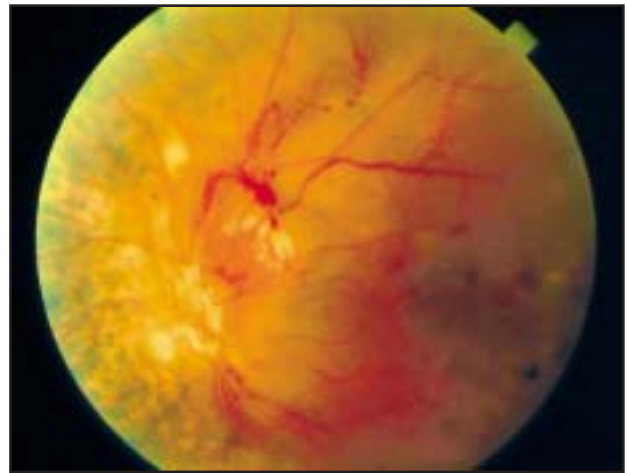


Fig. 3 Large fibrovascular neovascularization of the disc (NVD) with vitreous hemorrhage in a patient with proliferative diabetic retinopathy

Table II Four- and ten-year incidence of any retinopathy, improvement, progression of retinopathy, or progression to proliferative diabetic retinopathy by type of diabetes mellitus.

	Younger-onset		Older-onset (on insulin)		Older-onset (no insulin)	
	4-yr	10-yr	4-yr	10-yr	4-yr	10-yr
Incidence (%) of any retinopathy	59	89	47	79	34	70
Improvement (%)	7	10	15	21	20	26
Any progression (%)	41	76	34	69	25	53
Progression to PDR (%)	10	30	7	24	2	10
Number of subjects	891	765	485	251	502	282

incidence of any retinopathy, progression of retinopathy, and progression to PDR in all types of diabetics, independent of other factors such as age, duration, or type of diabetes.⁷

Blood Pressure

Recent studies of type 2 diabetics in England have demonstrated that tight blood pressure control reduces the risk and progression of diabetic retinopathy by 37% and the risk of visual loss by 47%. This benefit appears to exist regardless of the type of medication used to lower blood pressure (i.e., beta-blocker versus ACE inhibitor).^{8,9}

Lipid Profile (Total Cholesterol and Triglycerides)

Patients with elevated serum cholesterol (>240 mg/dL) are twice as likely as to have hard exudates than patients with normal serum cholesterol (<200 mg/dL). This translates to an increased risk of visual loss, as visual loss has been found to be associated with the presence and severity of hard exudates.¹⁰

Renal Disease

Kidney disease, as reflected by proteinuria (protein in the urine) and elevated blood urea nitrogen (BUN) and creatinine serum levels, are highly predictive of diabetic retinopathy.

Effect of Glycemic Control

The effect of glycemic control on the risk of developing diabetic retinopathy was definitively determined from the Diabetes Control and Complications Trial (DCCT), a major clinical trial involving over 1400 Type 1 diabetics at 20 centers followed for an average of 6.5 years.¹¹ The study was designed to determine whether intensive therapy (i.e., tight glycemic control) would prevent or delay the onset of retinopathy. The study found a 79% risk reduction in the cumulative incidence of retinopathy from five years onward for those patients who started out without retinopathy. For patients who started out with retinopathy, there was an average risk reduction (in the progression of retinopathy) of 76% after three years and continuing through the end of the study. Hence tight glycemic control does significantly reduce the risk of the development or progression of retinopathy, although there may be an initial worsening of retinopathy, and benefits may not be seen until after the first three or four years. Although this study was carried out on type 1 diabetics, a similar study of type 2 diabetics in the United Kingdom produced comparable results.¹²

Interestingly, these benefits of tight glycemic control appear to persist past the actual period of tight control. An observational follow-up study to the DCCT was carried out to determine if the benefits seen in the DCCT persisted once the study was over and study participants no longer followed the study guidelines.¹³ They found that the intensive-therapy group of the DCCT continued to have 72% to 76% lower rates of progression of retinopathy, a benefit that persisted despite the fact that once the study was over, the intensive-therapy group had gradually poorer glycemic control that approached that of the conventional therapy group at four years. In other words, the intensive therapy group appeared to enjoy a beneficial effect of that limited period of tight glycemic control that persisted for years after the actual period of such control, even as their control became less tight.

CLINICAL MANAGEMENT OF DIABETIC RETINOPATHY

Clinical management of diabetic patients and patients with diabetic retinopathy necessitates that clinicians carefully examine the retina stereoscopically through a dilated pupil, and that they possess a clear understanding of the guidelines and clinical significance of the grading of diabetic retinopathy.

Management of Nonproliferative Diabetic Retinopathy

Guidelines for grading the level of diabetic retinopathy, along with recommended follow up intervals, can be found in Table III. The significance of the level of diabetic retinopathy can be found in Table IV, which lists the risk of developing sight-threatening PDR as a function of the level of diabetic retinopathy. Since the proportion of patients with mild NPDR who will develop PDR within one year is very low (5%), a one-year follow up interval is acceptable. For patients with very severe NPDR, by contrast, where the proportion of patients who will develop PDR within a year is 45%, follow up within two to three months is necessary.

Management of macular edema. NPDR that takes the form of abnormal vascular permeability, or macular edema, can occur at any stage of diabetic retinopathy, and should be evaluated as a separate clinical entity. Macular edema is one of the leading causes of visual loss in diabetics, and is certainly the most significant cause of loss of vision in NDPR.

Macular edema is defined in terms of clinically significant macular edema (CSME). As defined by the Early Treatment of Diabetic Retinopathy Study (ETDRS),¹⁴ CSME involves:

- 1) thickening of the retina within 500 microns (approximately 1/3 of a disc diameter) of and including the foveal center, or
- 2) a large zone of retinal thickening (1 disc diameter or larger), any part of which is within 1 DD of the foveal center, or
- 3) lipid (hard) exudates, if associated with retinal thickening, within 500 microns of the center of the macula.

Patients with CSME who are treated by laser photocoagulation to the areas of leakage will experience a 50% reduction in the rate of visual loss after treatment.¹⁵ In the ETDRS, 30% of untreated eyes developed moderate visual loss (as defined by a doubling of the visual angle) at three years, as compared to 15% of eyes treated with photocoagulation.¹⁶ In cases where both CSME and PDR exist, treatment for the CSME should be addressed first, as treatment for PDR can exacerbate the CSME. In cases where a patient has both CSME and cataracts, if possible the CSME should also be treated first, since cataract surgery may exacerbate the CSME.

It is important to emphasize that the diagnosis of CSME requires the presence of retinal thickening, which is determined by a binocular examination of the macula with a funduscope lens, preferably a fundus contact lens. Once the diagnosis of CSME is made, a fluorescein angiogram is indicated to determine where to treat, but not whether or not to treat. Therefore, a careful stereoscopic examination of the macula is all that is required to

Table III Management guidelines for nonproliferative diabetic retinopathy (NPDR)		
	Clinical characteristics	Recommended follow-up
Mild NPDR	At least one MA and/or Hemorrhages/MAs < std photograph 2A (Fig. 5)	12 months
Moderate NPDR	Hemorrhages/MAs > std photo 2A and/or Soft exudates (NFLIs) and/or Minimal IRMA (< std photo 2A)	6-8 months
Severe NPDR	Hemorrhages/MAs > std photo 2A in all 4 fields (each field ~ 20 deg) or venous beading in > 2 fields or IRMA (> std photo 8A) in > 1 field (4-2-1 Rule)	3-4 months
Very Severe NPDR	2 or 3 of the above categories for severe NPDR	2-3 months

determine the presence of CSME, and subsequent referral for a fluorescein angiogram is warranted only on the basis of these examination findings.¹⁷

Management of Proliferative Diabetic Retinopathy

PDR is the presence of new blood vessels, either on the disc or by definition within 1 DD of the disc (NVD) or elsewhere on the retina (NVE). In most cases the presence of PDR warrants referral to a retinal specialist for evaluation for “scatter” or panretinal photocoagulation (PRP). PRP can significantly reduce the risk of visual loss from PDR. Treatment with PRP decreases the risk of “significant visual loss” (defined as 5/200 or worse visual acuity on two consecutive visits) by at least 50% at two years and at four years.¹⁸ Although the exact mechanism is unclear, PRP is believed to reduce the growth of new vessels by destroying some of the ischemic retina, thus reducing the production of the angiogenic factor that promotes neovascularization.

There are certain clinical findings or factors in PDR that increase the risk of developing severe visual loss. Eyes with three or more of these findings are at a much higher risk of visual loss than those with two or less. These factors are: (1) the presence of vitreous or preretinal hemorrhage, (2) the presence of new vessels, (3) the location of new vessels on or near the disc, and (4) the severity of new vessels (i.e., NVD that involves at least 1/3 of the disc, or NVE of at least 1/2 DD in size). When three or more of these factors are present, the eye is known to possess high-risk characteristics — conferring an added risk for visual loss and therefore when observed clinically, warrants immediate referral for treatment with PRP.¹⁹

Table IV Clinical significance of level of NPDR: risk of developing PDR as a function of level of NPDR			
Level of NPDR	Proportion with any high-risk PDR within 1 yr	Proportion with high-risk PDR within 1 yr	Proportion with high-risk PDR within 5 yrs
Mild	5%		15%
Moderate	27%		33%
Severe	52%	15%	60%
Very severe	75%	45%	

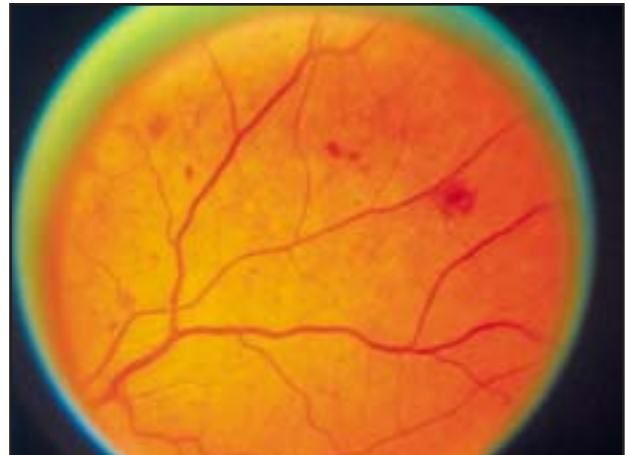


Fig. 5 Standard photograph 2A with intraretinal hemorrhages — used in grading nonproliferative diabetic retinopathy (NPDR) (See Table III)

CONCLUSION

Patients with diabetes mellitus are encountered frequently in clinical practice, and it is incumbent upon optometrists to have a clear understanding of the disease and its impact upon the body, particularly the eyes. Diabetic retinopathy can have a significant visual impact upon patients with diabetes, hence a sound knowledge of the risk factors for developing diabetic retinopathy and its clinical management is essential for eye care providers. □

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