DIABETIC RETINOPATHY

AUTHOR

Steven Ferrucci: Southern California College of Optometry

CONTRIBUTING AUTHOR

Michele Madigan: University of New South Wales

PEER REVIEWER

Richa Verma: Deakin University

CHAPTER CONTENTS

INTRODUCTION

Diabetic retinopathy is the leading cause of blindness in adults aged 20-74. It accounts for nearly 12% of all new cases of blindness, and a patient with diabetes is approximately four times more likely to become blind versus a patient without diabetic retinopathy.

However, many studies show that early diagnosis and treatment of diabetic eye-related disease can decrease vision loss by as much as 50-65%. However, despite this, many patients still do not see their eye care provider regularly to receive the timely eye care that is essential to the preservation of vision.

WHAT IS DIABETES?

Diabetes is a chronic disease that occurs when the pancreas does not produce enough insulin, or when the body cannot effectively use the insulin it produces. Hyperglycaemia, or raised blood sugar, is a common effect of uncontrolled diabetes and over time leads to serious damage to many of the body's systems, especially the nerves and blood vessels.

Type 1 diabetes: Due to destruction of insulin-producing cells in the pancreas; typically begins in childhood or early adulthood, though can develop at any age. Treated with insulin injections or a continuous infusion of insulin through an insulin pump.

Type 2 diabetes: Characterized by reduction in the production of insulin and inability of the body to respond fully to insulin. It typically develops after age 40 yrs, but can occur in younger adults, even adolescents. Treated with lifestyle change, tablets or insulin injections (usually later on).

Gestational diabetes: diabetes first identified during pregnancy. It typically disappears after childbirth, BUT there is a high risk of the mother developing type 2 diabetes in the next 10-15 years. (T1 more common than T2 – for now; T1 = early-onset)

COMPLICATIONS OF DIABETES

Microvascular

- retinopathy
- nephropathy (high blood glucose damages blood-filtering capillaries in the kidney)
- neuropathy (peripheral, autonomic, proximal, focal neuropathies)

Macrovascular

- heart disease
- stroke
- peripheral arterial disease

DIABETIC RETINOPATHY

There are several factors which influence the development of diabetic retinopathy. First and foremost is the duration of the disease. Simply put, the longer you have diabetes the more likely you are to develop diabetic retinopathy. This has been confirmed in several studies.

The second factor which influences the development of retinopathy is the control of blood sugar. The United Kingdom Prospective Diabetic Study (UKPDS) demonstrated that in Type 2 diabetes, for every 1% reduction in HGBA1c there is a 35% reduction in risk for retinopathy.

Diabetic retinopathy can be broken down into two major categories, non-proliferative and proliferative. Non-proliferative can then be further divided in mild, moderate, or severe (as well as very severe) based on certain characteristics.

Proliferative diabetic retinopathy can be further broken down to include high risk.

This classification system has evolved from the previous classification system which utilized the terms background, pre-proliferative and proliferative diabetic retinopathy.

It is encouraged that all practitioners learn and use the most recent classification system when evaluating patients as well as for sending referrals to retinal specialists or general physicians in consultation.

NON-PROLIFERATIVE DIABETIC RETINOPATHY (NPDR)

NPDR is caused by loss of retinal capillary pericytes which line the walls of the vessels within the retina. This in turns weakens the capillary walls, allowing blood and other fluids to leak through. It also begins the cascade that leads to non-perfusion in the capillary beds and hypoxia. As mentioned earlier, it can be divided into mild, moderate and severe (as well as very severe).

MILD NPDR

Mild NPDR is characterized by microaneurysms and dot/blot haemorrhages mild to moderate in number, in fewer than 4 quadrants. Microaneurysms (MA) appear as bright red spots, most often located in the vicinity of occluded capillaries, and are thus often the first sign of retinopathy. They can range in size from 12 to 100 µm in size, although only those larger than 30 µm are clinically visible. MAs can occur at any level between the superficial and deeper retinal capillary networks, or even from the choroidal circulation itself. Classically, one can appreciate more MAs angiographically than clinically, since the smallest ones are often only appreciated with fluorescein.

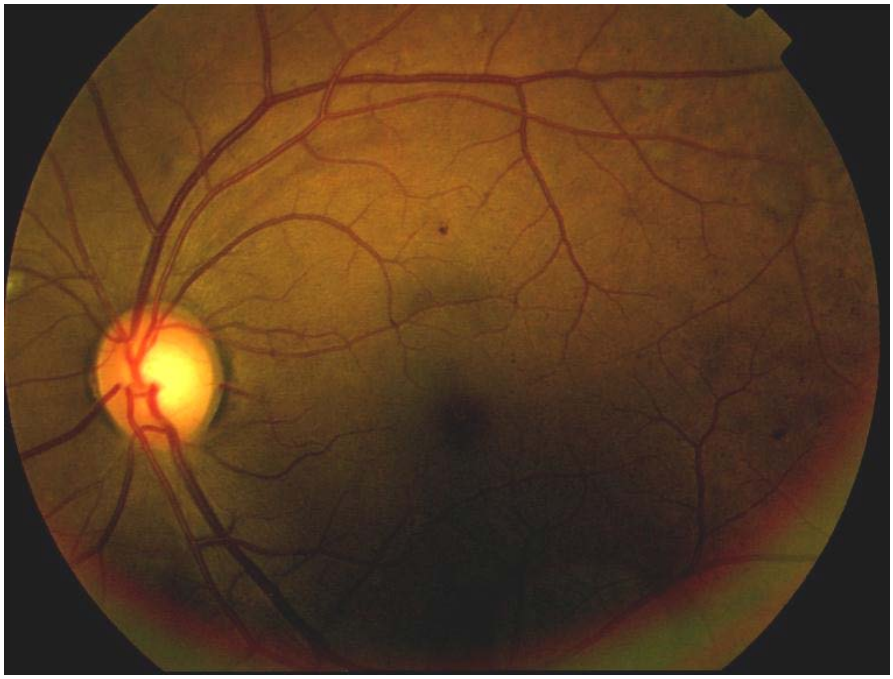

Figure 1: *Central blot haemorrhage and dot haemorrhages temporally*

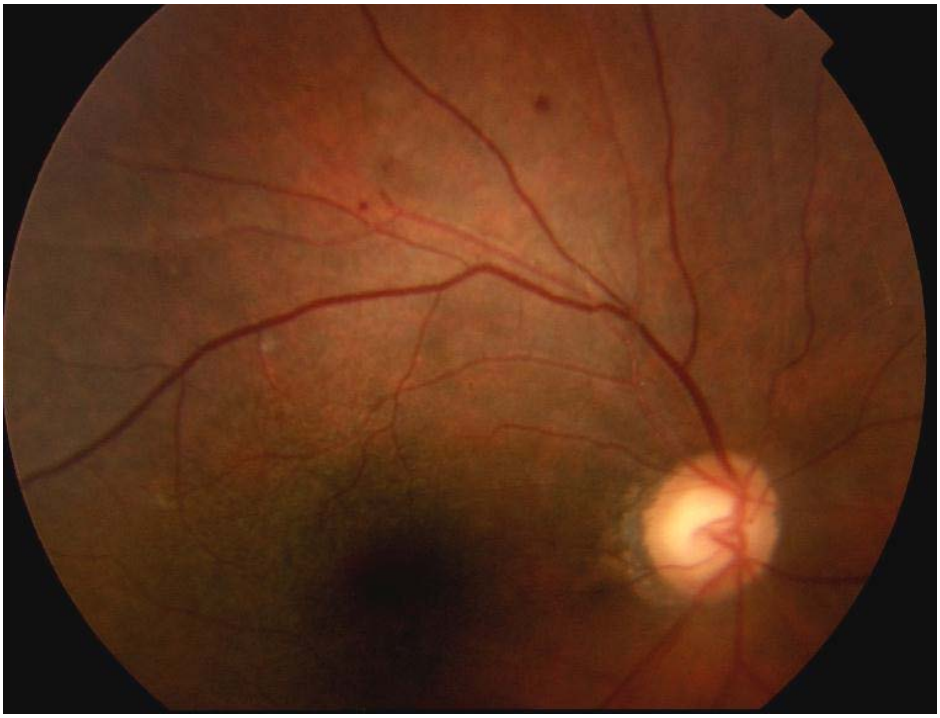

Figure 2: *Few blot haemorrhages superior temporally*

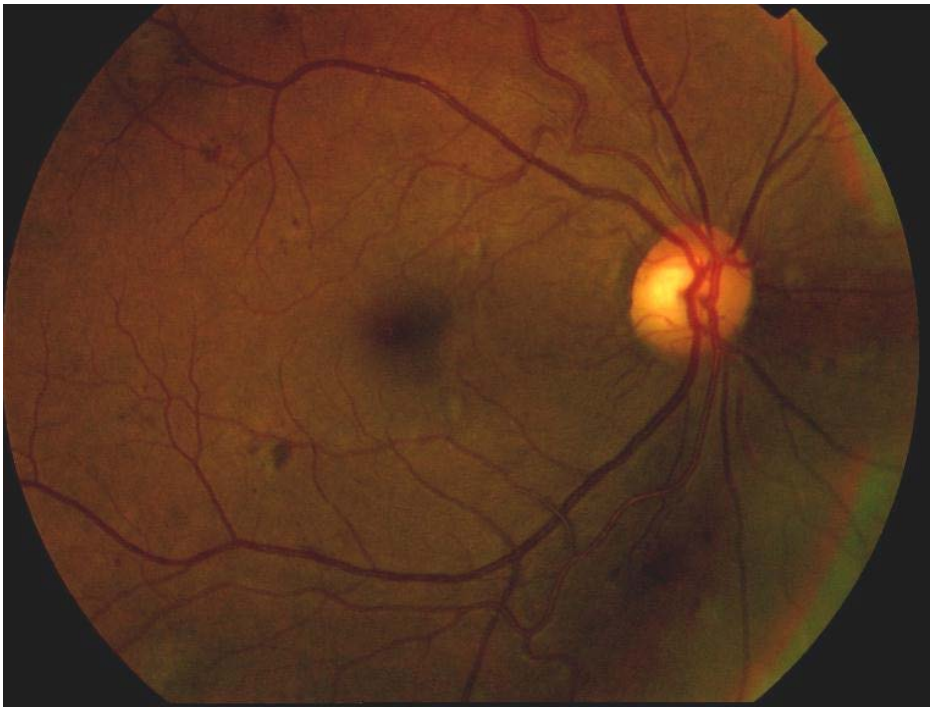

Figure 3: *Blot, dot haemorrhages and some microaneurysms*

Dot/blot haemorrhages by contrast are intraretinal haemorrhages that appear secondary to ruptured microaneurysm, capillary or venule. Their shape is due to their deeper location within the retinal layers, generally within the outer plexiform and inner nuclear layers. Dot haemorrhages have very distinct borders and blot haemorrhages tend to have more fuzzy or blurred borders classically, but this distinction has no clinical relevance. Dot/blot haemorrhages can be distinguished from MAs on FA, where MAs tend to appear hyperfluorescent, and dot/blot hemes block fluorescein and tend to hypofluoresce. Again, clinically the distribution between haemorrhages and MAs is somewhat irrelevant, as both represent the early signs of diabetic damage to the retinal microvasculature.

The haemorrhages are typically scattered through the posterior pole, but can be anywhere. However, if seen only peripherally other aetiologies such as ocular ischemia syndrome should be considered. Dot/blot haemorrhages may resolve within 3-4 months, without any visual obscurations.

Follow-up for patients with mild NPDR is every 6-12 months, depending on severity (NHMRC, Guidelines for the Management of Diabetic Retinopathy, 2008). Fundus photography is a useful tool to document baseline characteristics, but is not essential. FA or laser is not indicated at this time. Further, patient education regarding the presence of early diabetic changes as well as appropriate blood sugar control should be undertaken.

MODERATE NPDR

Moderate NPDR is characterized by marked haemorrhages or microaneurysms, cotton-wool spots (CWS), venous beading (VB), and intraretinal microvascular abnormalities (IRMAs), to a mild degree. Cotton-wool spots appear as fluffy, soft white spots often with striations, and represent small infracts within the nerve fiber layer. They typically resolve in 2-3 months, although they may be present for longer, as much as 1 year. CWS, however, are not pathognomonic for diabetes, and may be seen in other diseases such as vein occlusion, hypertensive retinopathy, anemia and cytomegalovirus retinitis.

Venous beading (VB) represents focal areas of dilatation with apparent thinning of the venous wall. VB represents areas of capillary non-perfusion and retinal ischaemia, and many researchers feel they are correlated with an increased probability of progression to proliferative disease.

Intraretinal microvascular abnormalities, or IRMAs, represent changes that occur in diseased capillary beds and refer specifically to telangiectatic changes that occur between diseased arterioles and venules. They occur within areas of capillary non-perfusion, and appear as fine, tortuous blood-filled vessels. They are often difficult to differentiate from early neovascularization clinically, and FA may be a helpful tool to help make this differentiation. On FA, IRMAs typically display little to no leakage, as compared to frank neovascularization which often demonstrates profuse leakage. Similar to VB, IRMAs also represent a retina that is at increased risk of developing proliferative disease.

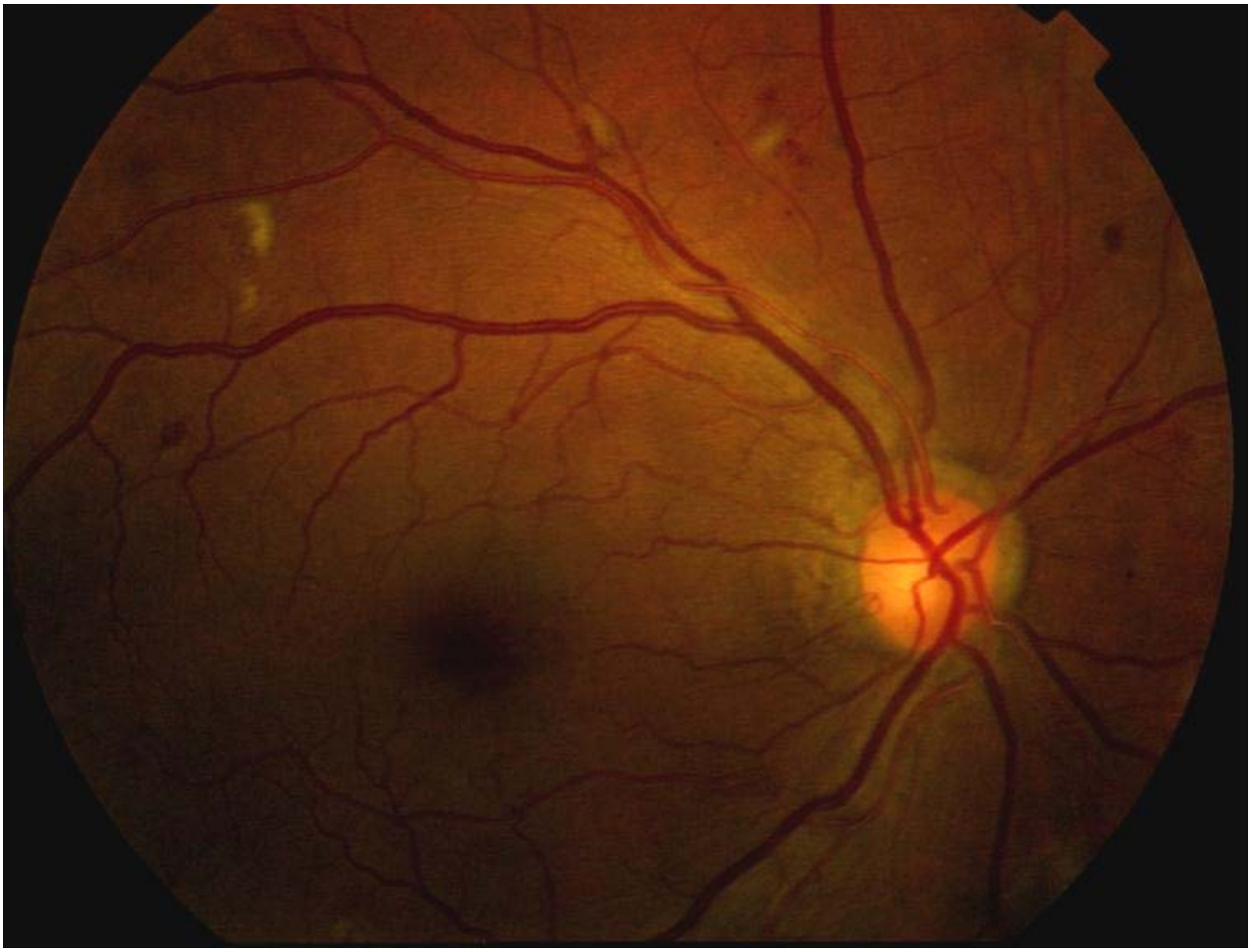

Figure 4: *Cotton-wool patches and more extensive blot haemorrhages*

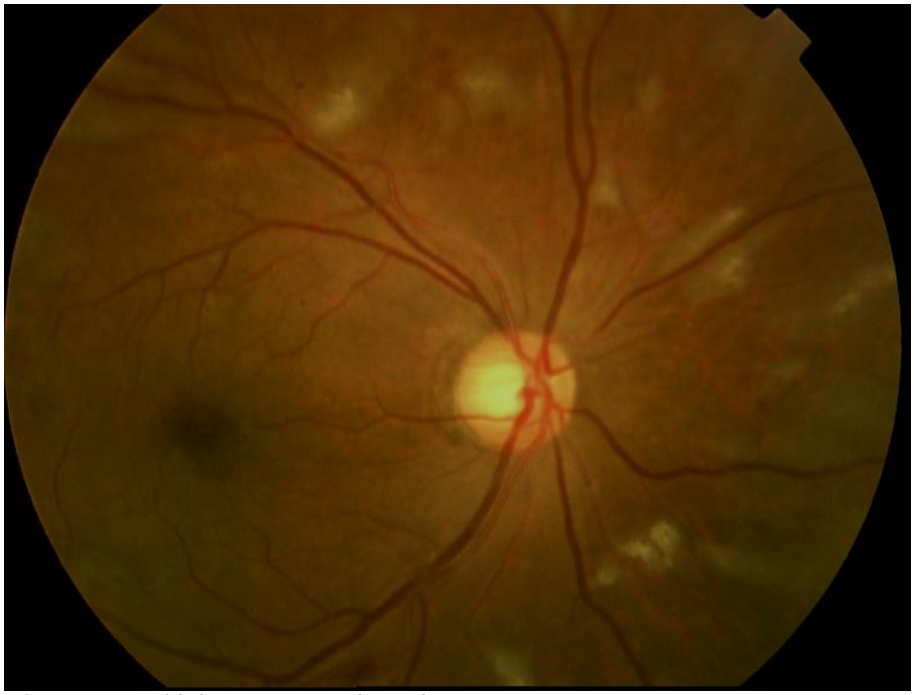

Figure 5: *Multiple cotton-wool patches*

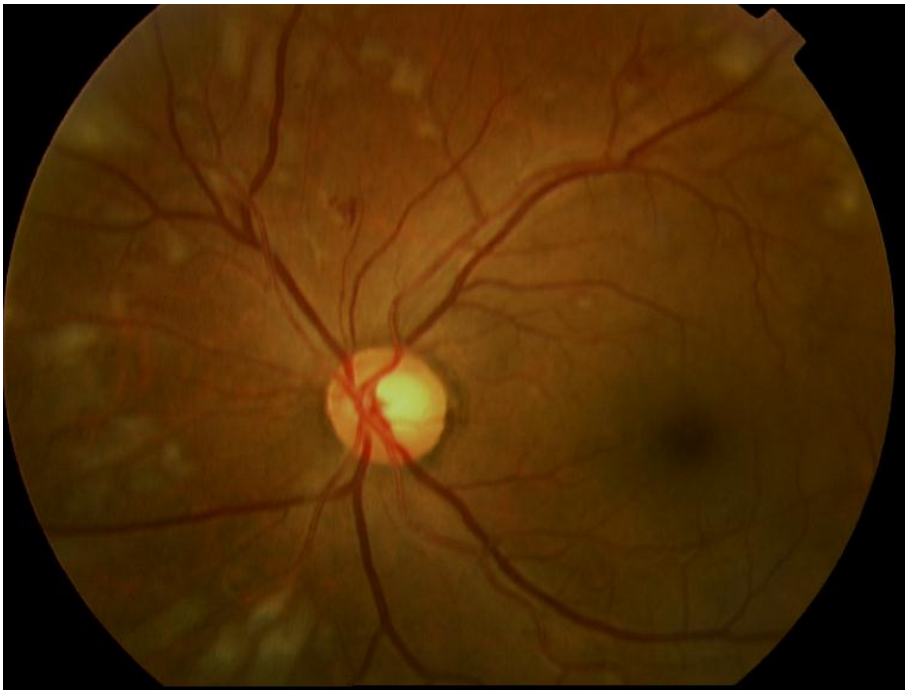

Figure 6: *Multiple cotton-wool patches and flame haemorrhages*

Follow-up of patients with moderate NPDR is generally every 6 months. Studies show that as many as 16% of patients with moderate NPDR can progress to proliferative disease within 4 years, so these patients should be educated about the importance of proper compliance. Fundus photography is useful to document the extent of retinopathy and to evaluate changes at subsequent visits. FA is not indicated in all patients, but may be useful if attempting to differentiate IRMA from true neovascularization.

SEVERE NPDR

Severe NPDR is characterized by the 4-2-1 rule. That is if any one of the following criteria is met, the patient is diagnosed with severe NPDR (NHMRC, Guidelines for the Management of Diabetic Retinopathy, 2008).

- More than 20 intraretinal haemorrhages in each of 4 quadrants
- Definite venous beading in 2+ quadrants
- Prominent intraretinal microvascular abnormalities in 1+ quadrant AND no signs of proliferative retinopathy

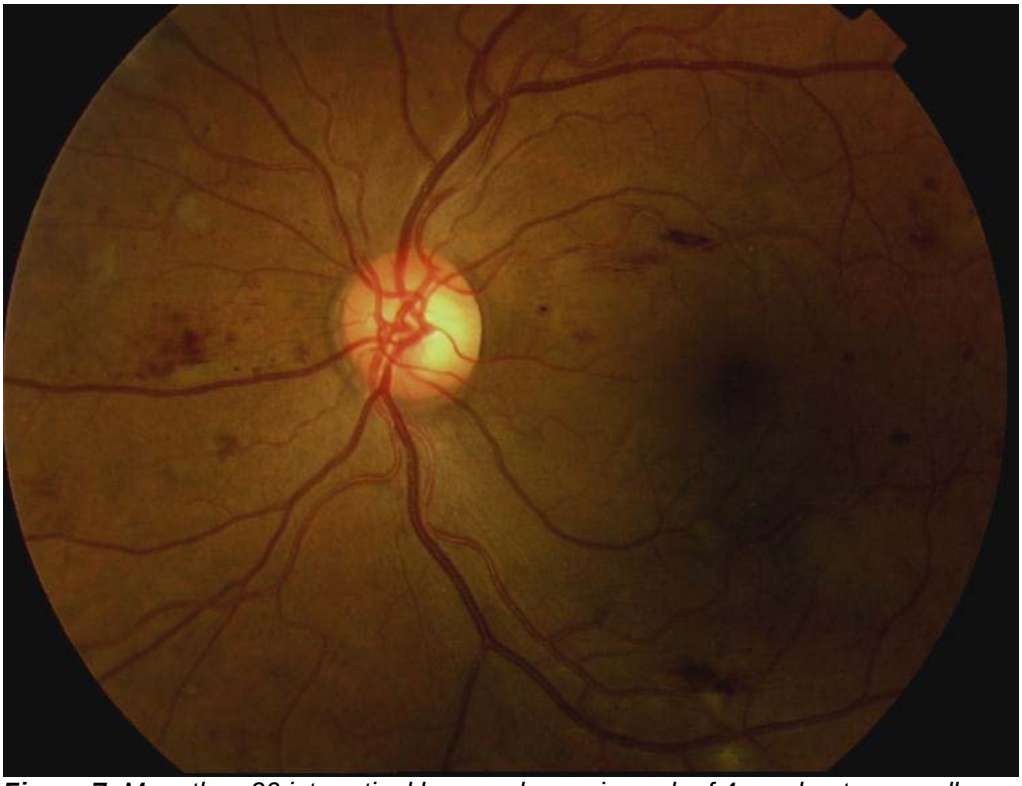

Figure 7: *More than 20 intraretinal haemorrhages in each of 4 quadrants, as well as cotton-wool patches*

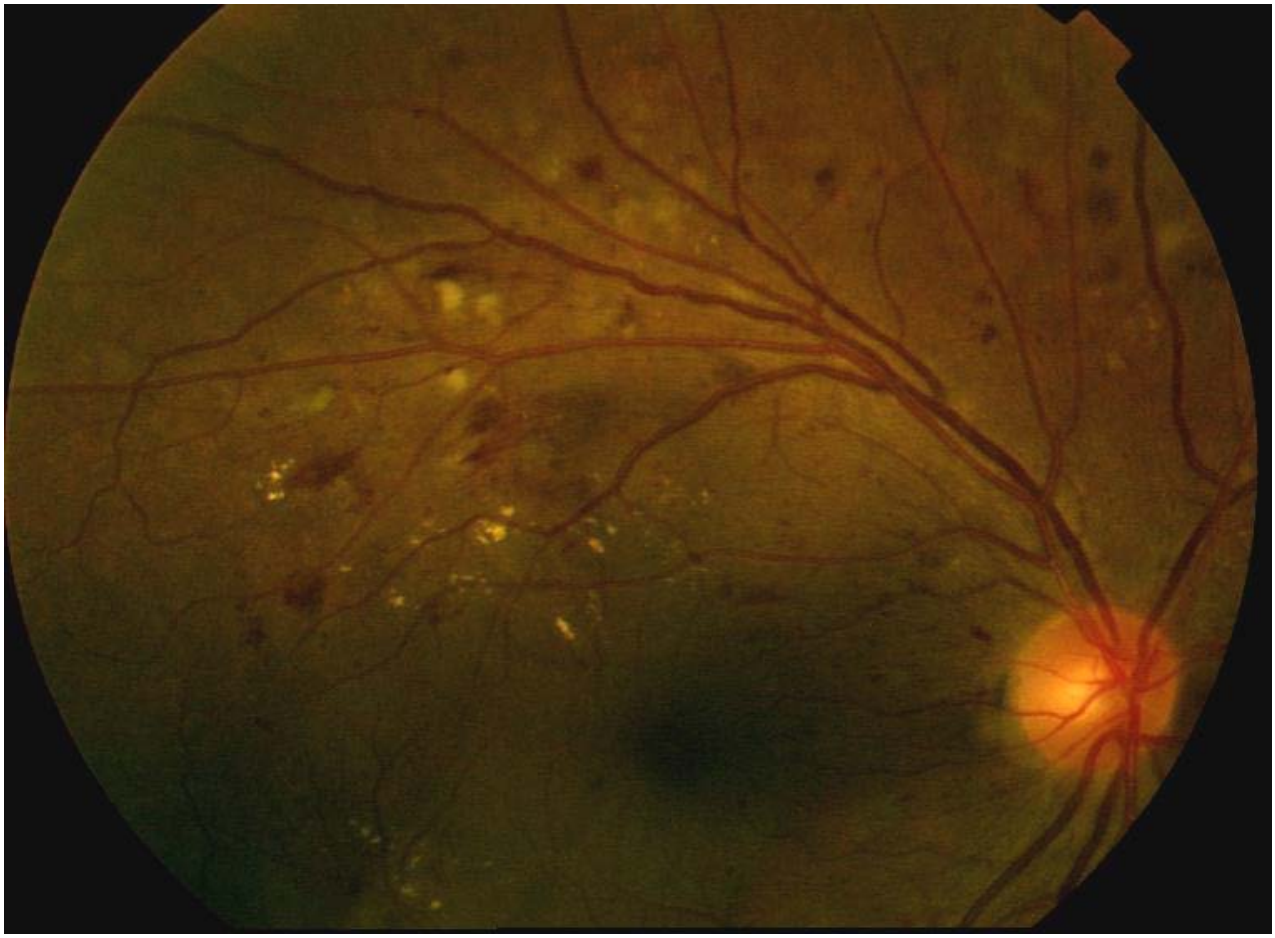

Figure 8: *More than 20 intraretinal haemorrhages in each of 4 quadrants. Note the VB on the superior arcade and hard exudates*

These patients should be re-examined in 3-4 months. Studies show that between 10 and 50% of patients at this level will progress to PDR within 1 year. FA is generally not indicated although it may be useful in select cases to determine the presence or absence of non-perfusion and areas of occult neovascularization. Some retinal specialists advocate laser intervention in the form of PRP in these patients. Therefore, at this level of retinopathy, a referral to a retinal specialist is not incorrect, and may often be warranted.

PROLIFERATIVE DIABETIC RETINOPATHY (PDR)

The hallmark of PDR is neovascularization, new vessels that arise from the retina and optic disc in response to ischaemia from advanced capillary closure. Other factors, such as vasoproliferative growth factors, also play a role in neovascular development.
Neovascularization can be divided into 2 groups: NVD, neovascularization of the disc, is new vessels growth on or within 1 disc diameter of the optic disc. All other is termed neovascularization elsewhere or NVE. These neovascular vessels tend to be weak and fragile, and are easily ruptured.

NVD appears as fine wisps or strands of blood vessels on or near the optic disc. They are best observed with careful inspection of the disc with a 78 or 90 D hand-held lens at the slit-lamp. NVE appears as a wheel-like network of fine vessels, typically arising from the retinal veins or capillaries. They are best appreciated with either indirect binocular ophthalmoscopy or hand-help slit-lamp lenses. With FA, both NVD and NVE will leak dye profusely, and IRMAs will not.

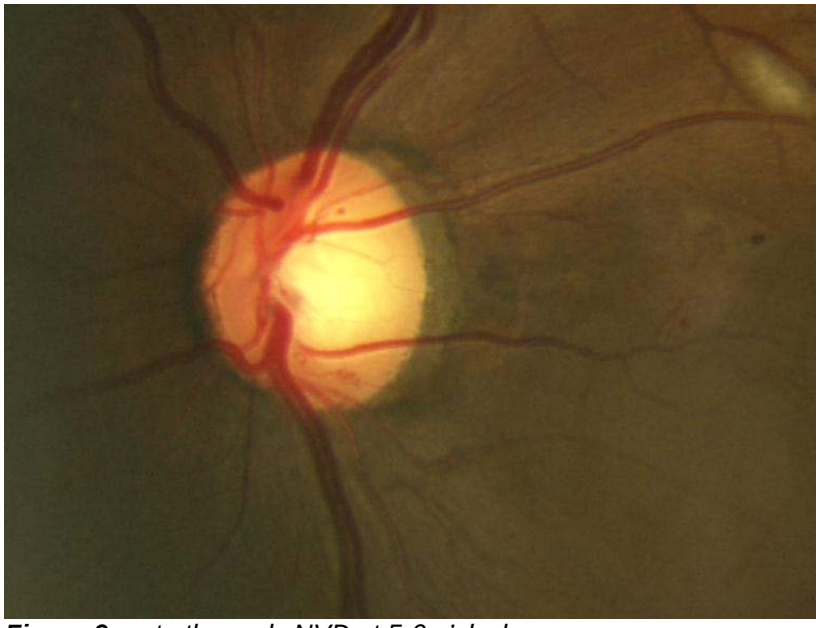

Figure 9: *note the early NVD at 5-6 o'clock*

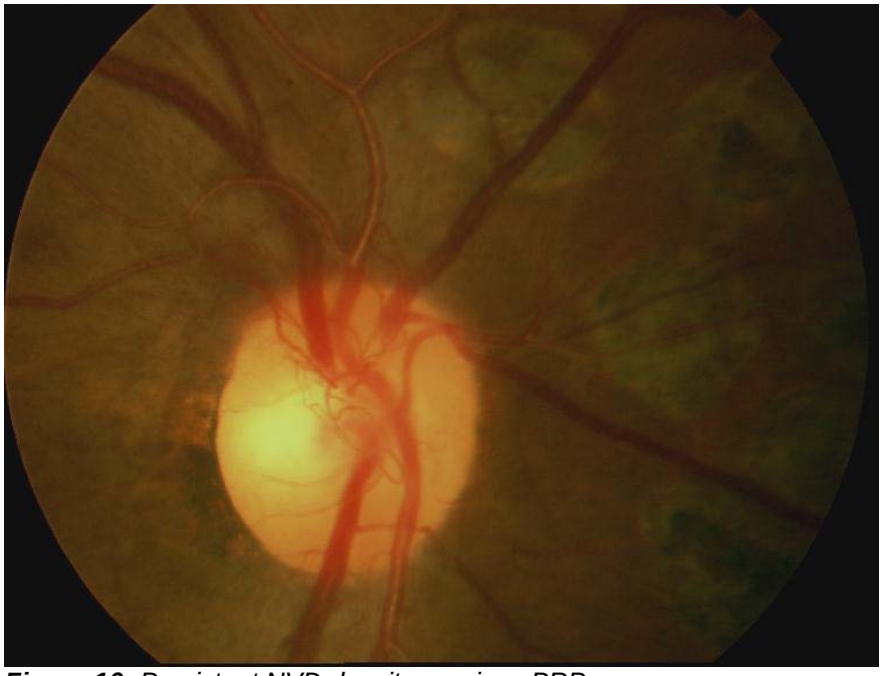

Figure 10: *Persistent NVD despite previous PRP*

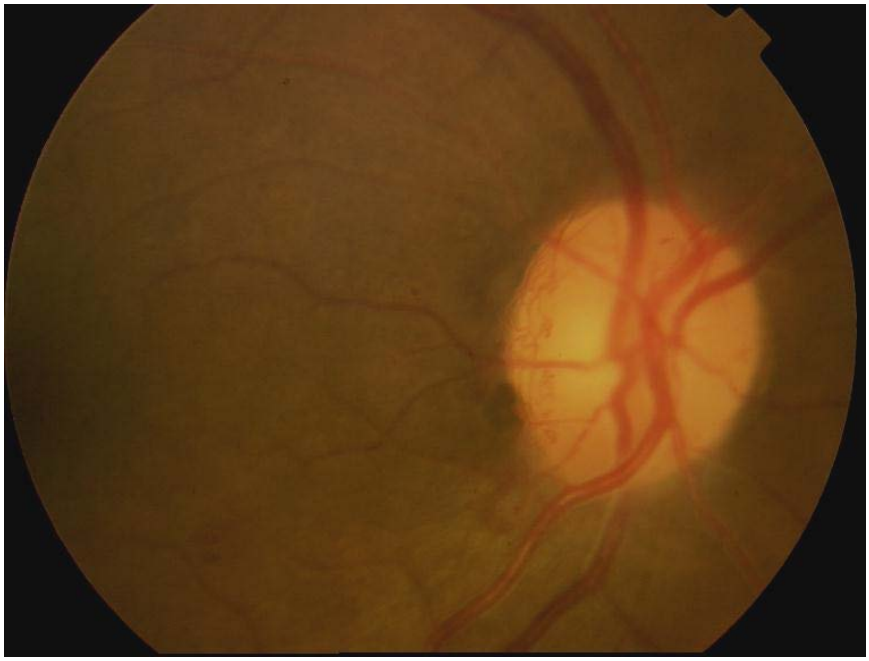

Figure 11: *NVD from 7-12 o'clock*

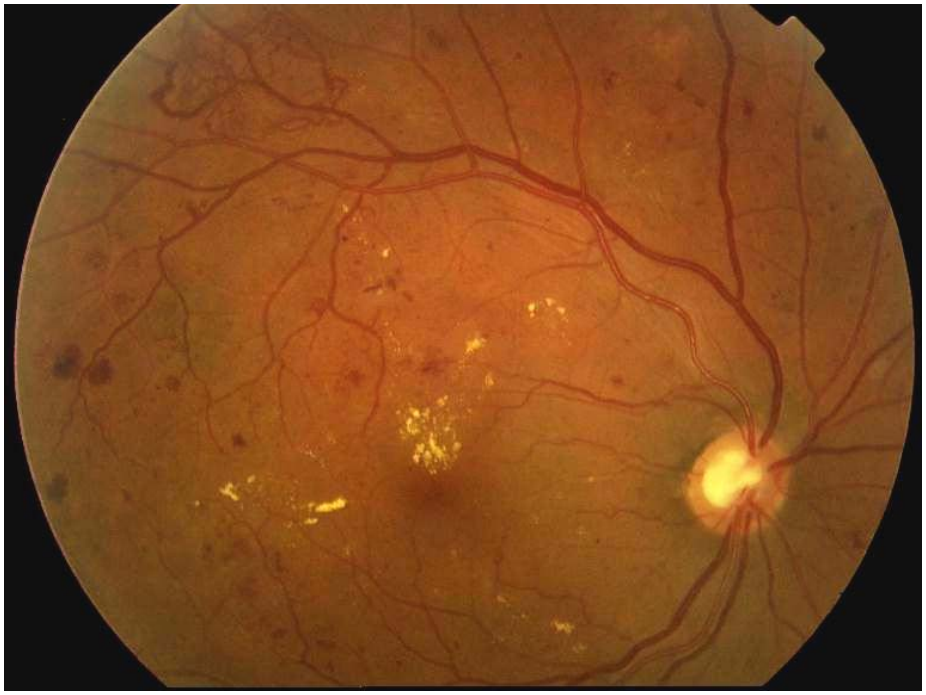

Figure 12a: *NVE superior arcade, right eye*

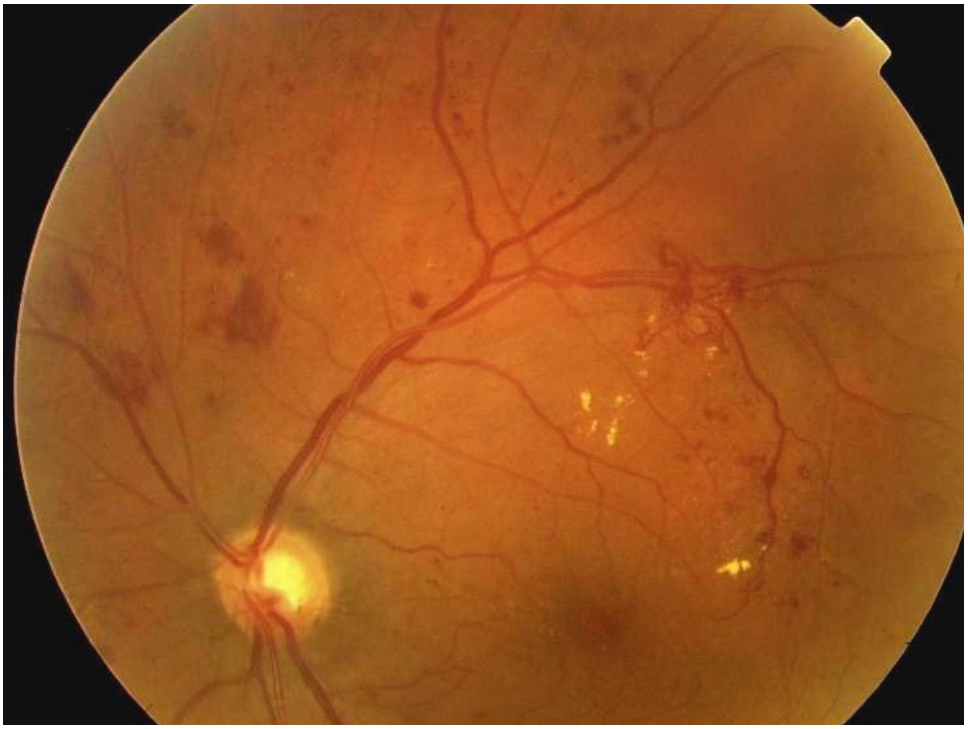

Figure 12b: *NVE superior arcade, left eye*

These patients should receive prompt referral for consultation with a retinal specialist, generally within 2 weeks, as most clinicians advocate PRP at this stage due to lower risk of vision loss and vitrectomy. If laser is not recommended for some reason, the patient should be followed closely, every 2 to 3 months to evaluate for progression.

An FA is not always indicated, but may be useful to differentiate between NV and IRMA if clinically uncertain. Fundus photos are helpful so one can look for regression of the NV following appropriate treatment.

HIGH-RISK PDR

High-risk PDR is characterized by the following:

- NVD > 1/4 to 1/3 disc area
- Any NVD with a preretinal or vitreous haemorrhage
- Moderate to severe NVE with a vitreous or preretinal hemorrhage

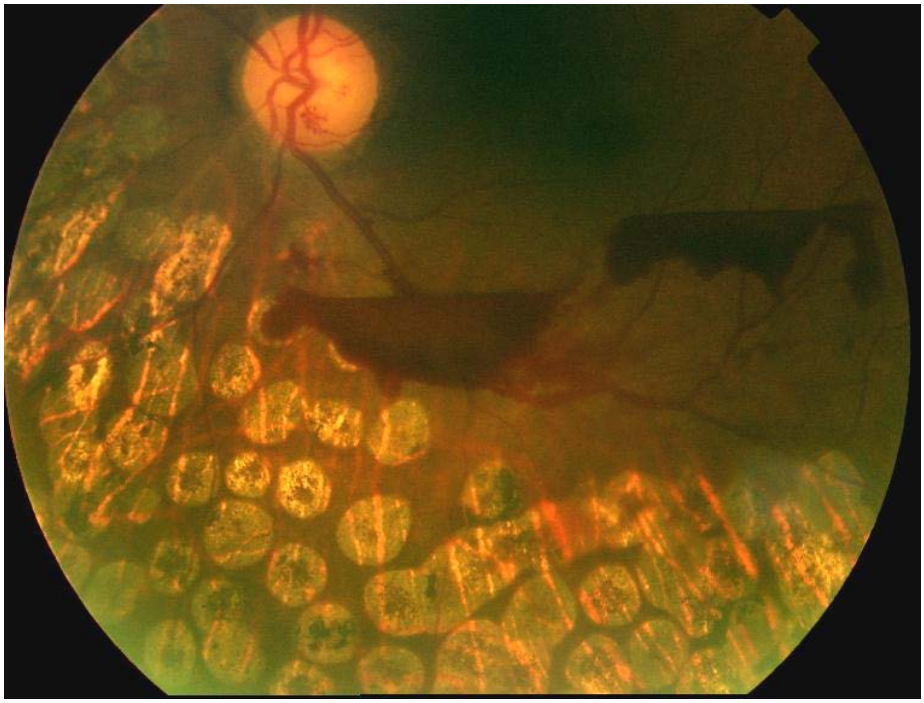

Figure 13: *High-risk PDR due to NVD with PRH*

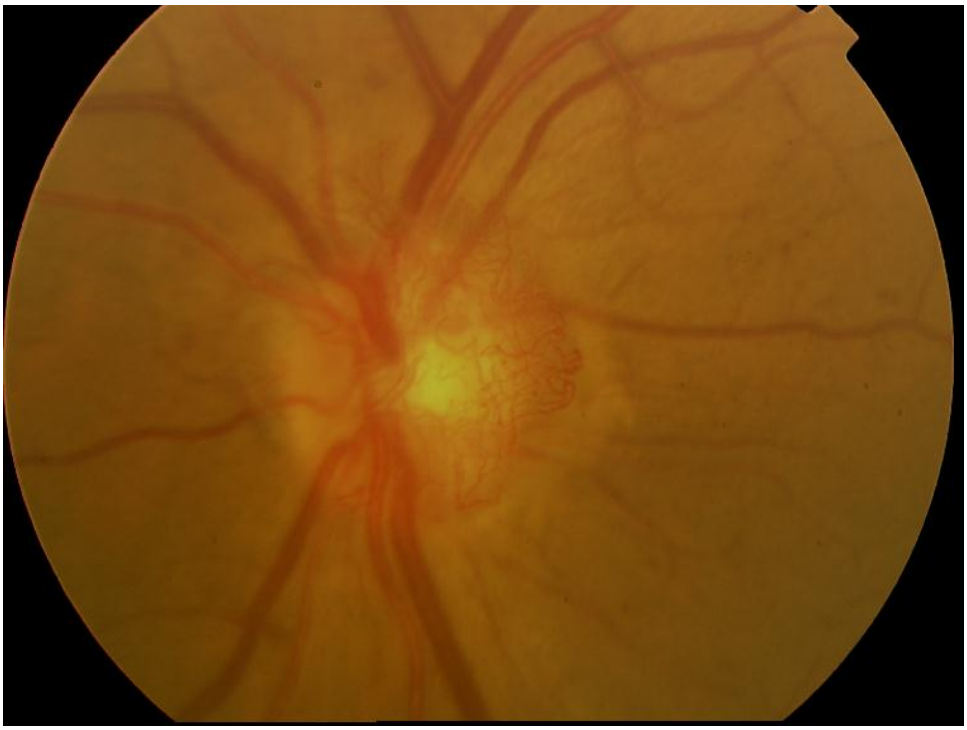

Figure 14: *High-risk PDR due to NVD > 1/3 disc diameter*

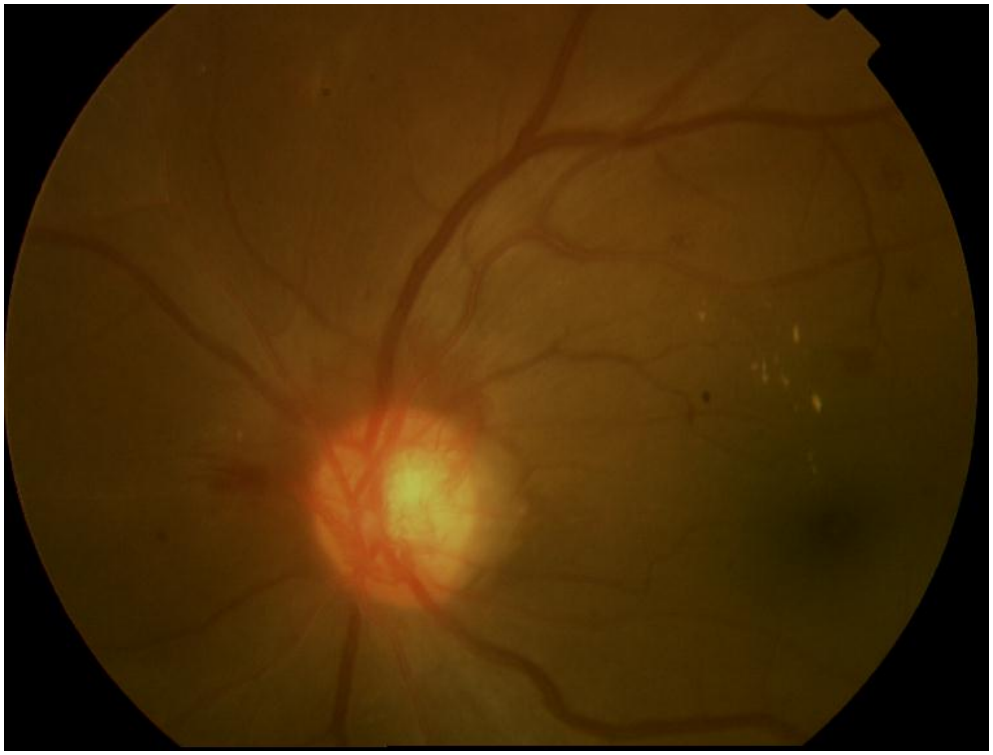

Figure 15: *High-risk PDR*

These patients are at very high risk for severe vitreous haemorrhage and vision loss within 2 years if appropriate treatment is not given. Immediate retinal consultation is advised, in 24-48 hours, and prompt PRP is indicated.

As with PDR, FA is not needed, except in select cases, but fundus photography is useful to document the extent of the damage and to help gauge the response to treatment. If PRP is unsuccessful in these patients, a vitrectomy may be required.

PAN-RETINAL PHOTOCOAGULATION (PRP)

Pan-retinal photocoagulation (PRP) is the treatment for proliferative disease. Essentially the laser is systematically applied to the retina, destroying parts of the tissue. This destruction eliminates the need for oxygen, thereby reducing the vasoproliferative stimulus. The elimination of hypoxia in turn leads to regression of new vessel growth. PRP is not without complications however, as side effects may include decreased peripheral vision, decreased night vision, and cystoid macular oedema (CME). Failure for regression with one treatment is possible and several treatments may be needed to achieve the desired therapeutic effect.

Two separate studies (The Diabetic Retinopathy Study and Early Treatment Diabetic Retinopathy Study) showed the benefit of PRP in patients with NV, especially those with high-risk characteristics. In short, the studies showed an overall reduction rate of severe vision loss (5/200 or less) by approximately 50% in treated vs. untreated eyes.

Newer studies are looking at the role of anti-VEGF treatment along with or instead of PRP. While some small studies and case reports have shown positive results, PRP still remains the mainstay of treatment at this time.

MACULAR OEDEMA

Macular oedema is an accumulation of intraretinal fluid in the macular area with or without hard exudates. Macular oedema is the leading cause of moderate vision loss in all diabetics, especially in Type 2. It can occur at any stage of retinopathy, but its prevalence and incidence increases with both duration of diabetes and the overall level of retinopathy.

Patients with macular oedema should be evaluated every 3 months, to see if they develop clinically significant macular edema (CSME), at which point a retinal consult for treatment is indicated.

Clinically Significant Macular Edema (CSME) occurs when:

Retinal thickening is present at or within 500 microns (1/3 disc diameter) of center of the macula
Hard exudates are present at or within 500 microns (1/3 DD) if associated with thickening of adjacent retina
Thickening is present greater than 1DD in size, part of which is within 1DD of center of the macula

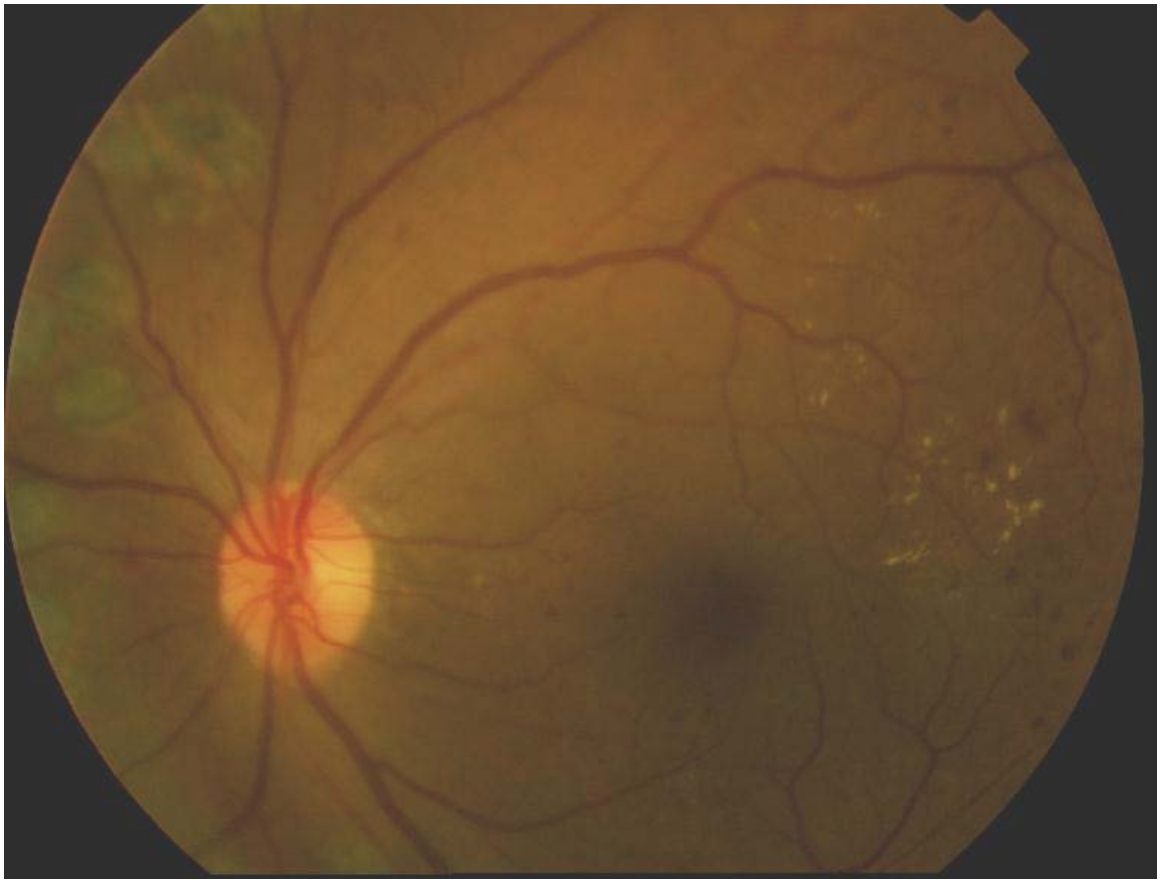

Figure 16: *Area of exudates and retinal thickening temporally that does not meet criteria for CSME*

Figure 17: *Borderline CSME with area of thickening almost one DD in size approximately 1 DD from center of macula*

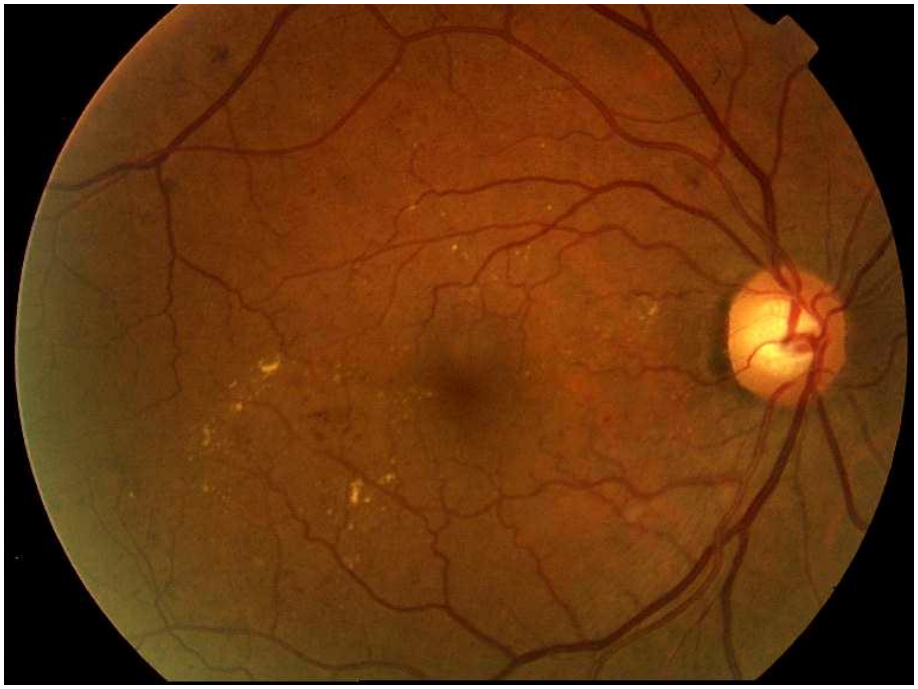

Figure 18: *CSME with area of thickening within 500 microns from the center of the macula*

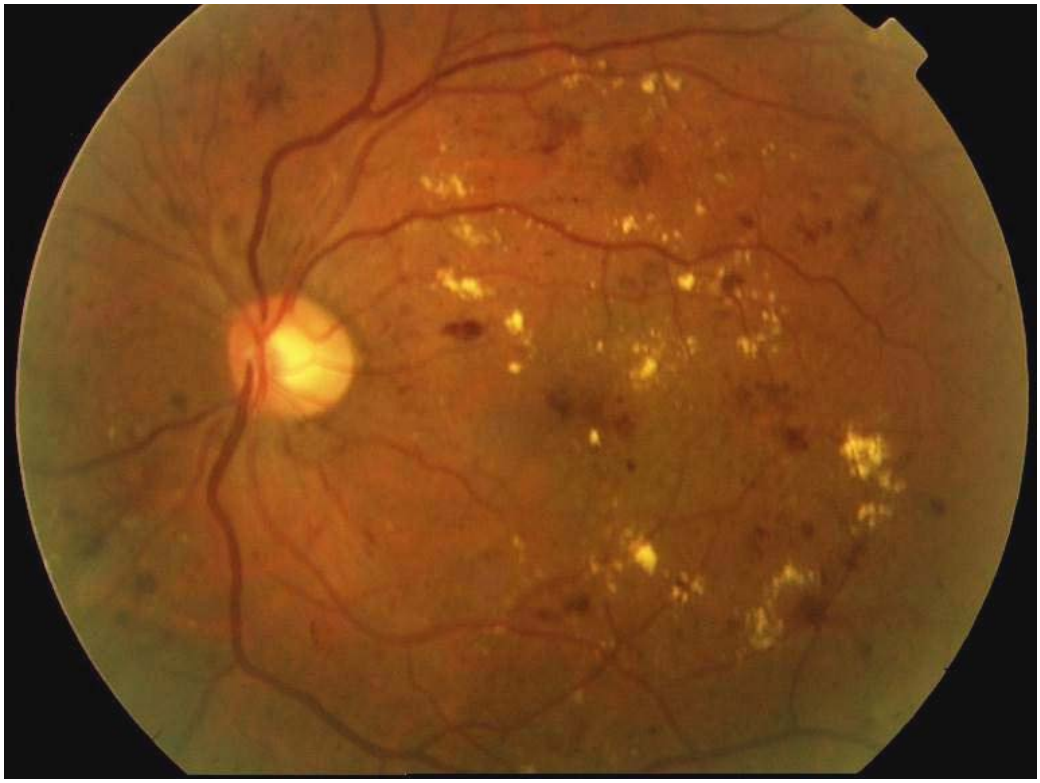

Figure 19: *Frank CSME*

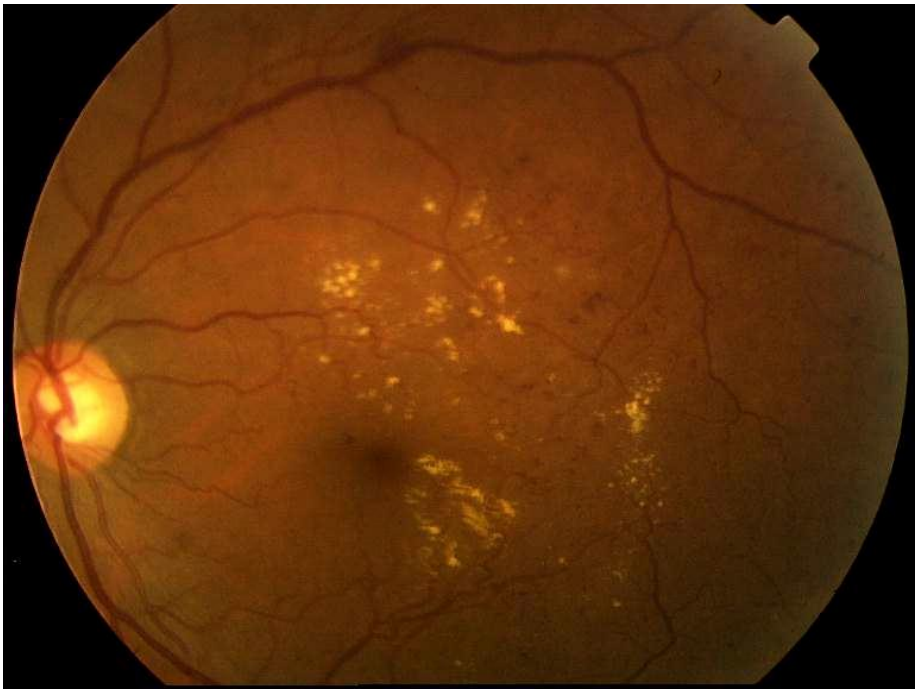

Figure 20: *Frank CSME*

If these characteristics are met, the patient should be sent for a retinal consultation to consider FML (Focal macular laser) within 2 weeks.

FA is not needed to diagnose CSME, as the diagnosis is based on examination by slit-lamp biomicrosopy with a stereo view using hand-held lenses. However, FA is helpful once the diagnosis has been made to help the retinal specialist guide the treatment. Fundus photography is also useful, even without a FA, to help document the response to treatment.

FOCAL MACULAR LASER (FML)

The treatment for CSME is FML. Numerous clinical studies have reported the efficacy of laser photocoagulation in the treatment of diabetic macular oedema. For example, the Early Treatment Diabetic Retinopathy Study (ETDRS) demonstrated that prompt photocoagulation of CSME reduces the risk of moderate vision loss by 50%. However, it is important to note that the goal of the treatment is to prevent further vision loss, not to improve vision already lost. As such, a patient needs to be advised of this prior to initiation of treatment.

Resolution of oedema following treatment is generally rather slow, and patients should be reexamined 3-4 months after treatment to evaluate its effect and to see if additional treatment is indicated. Side effects, although rare, include para-central scotomas, risk of CNVM, and immediate vision loss due to misplaced laser shot.

Intravitreal triamcinolone (IVT) has been used for treatment of CSME especially in those cases that do not respond to laser. Recent studies however indicated that IVT is in fact no better than FML, and FML should still be considered the gold standard for care of CSME.

CONCLUSION

Patients with diabetes need to be seen periodically and examined for any signs of diabetic retinopathy. All diabetics are urged to get annual dilated retinal examinations, even in the absence of symptoms, as signs of damage often precede visual complaints. If any damage is seen, timely intervention and referral to a retinal specialist is advised.

Patients need to be advised as to the possible ocular side effects of diabetes, and to report any ocular symptoms associated with their diabetes as soon as possible. Lastly, they should be reminded that better diabetic control can help prevent retinopathy and its associated vision loss.