REVIEW ARTICLE

Diabetic Retinopathy

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Abstract

***Introduction**: To provide a review of the current standard of care in diabetic eye management. **Methods**: A non-systematic evidence-based review utilising available data and consensus statements on the subject matter. **Results**: Diabetes mellitus affects some 9.0% of Singaporeans, and more than 60% of patients with diabetes in this population remained undiagnosed. Diabetic retinopathy is an important complication among diabetic patients and adverse visual outcome associated with this condition can be reduced by more than 95% by taking measures including good glycaemic control, timely and appropriate laser therapy, and vitrectomy surgery when indicated. An important aspect of management is the accurate disease classification which is essential for prognostication, appropriate follow-up schedule, and timing of therapeutic intervention purposes. **Conclusion**: Diabetic retinopathy will remain a significant problem if the current trend in diabetes among Singapore residents prevails. As the severe visual impairment associated with diabetic retinopathy can be largely prevented with appropriate and timely intervention, the major challenge to the health care providers today is the identification and education of patients with diabetes, and the enrollment of these patients in a life-long comprehensive ophthalmic management programme in order to minimise visual morbidity.*

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Key words: Classification, Diabetes mellitus, Diagnosis, Management, Ocular complications

Introduction

Diabetes mellitus affects some 9% of Singaporeans.[1,2] Studies had shown that virtually all insulin dependent diabetes mellitus (Type 1) and 85% of non-insulin dependent diabetes mellitus (Type 2) patients would develop retinopathy after 20 years of disease.[3,4] Diabetic retinopathy is the chief cause of acquired vision loss in developed countries, as it is in Singapore. Blindness had been estimated to be 25 times more common in the diabetic population as compared with the non-diabetic population.[5,6]

The impact of blindness on the Singapore economy from diabetes is unknown. The 1998 Singapore National Health Survey revealed that more than 60% of patients with diabetes,[1] or about 210,000 people with diabetes mellitus remained undiagnosed. Among those diagnosed with diabetes, more than half had poor blood sugar control as determined by HBA1c measurements. The onset and progression of retinopathy was shown to be influenced by glycaemic control.[7,8] Given that three-quarters of the diabetic patients residing in Singapore did not achieve good glycaemic control, the burden of retinopathy-related morbidity would be significant. The Diabetic Retinopathy Study (DRS) and Early Treatment Diabetic Retinopathy Study (ETDRS) (to be further discussed later) had demonstrated that, in the absence of laser intervention, the risk of severe visual loss (vision of 5/200 or worse in 2 consecutive visits 4 months apart) from advanced stages of diabetic retinopathy and risk of moderate visual loss (doubling in visual angle) from macular oedema were about 30% after 2 and 3 years respectively.[9,10] These risks were reduced by 50% with laser treatment. Moreover, when treatment is instituted as the retinopathy is approaching or just reaching high risk characteristics, the risk of severe visual loss can be reduced by greater than 90%.[11]

As progression of diabetic retinopathy and its visual complications can be significantly reduced with timely and appropriate medical and surgical interventions,[12,13] diabetes-related visual impairment burden on the state and society can be largely avoided. Therefore, it is crucial for the healthcare provider to be familiar with both the diabetic eye complications and the current standard of care in diabetic eye management.

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Pathophysiology

Diabetes mellitus is a condition characterised by a state of chronic hyperglycaemia due to absolute deficiency of, or relative tissue insensitivity to insulin. The chronic state of hyperglycaemia results in macrovascular and microvascular abnormalities, translating into increased morbidity and mortality associated with conditions such as atherosclerosis, ischaemic heart disease and renal failure. Important microvascular-related morbidity in the diabetic patient includes retinopathy, neuropathy, dermatopathy and nephropathy.

The earliest effect of diabetes mellitus in the eye is an abnormality of retinal blood flow autoregulation.[14-17] Early specific histopathological responses are also noted, such as decrease in retinal pericytes, thickening of vascular endothelium basement membrane and mural endothelial cell proliferation.[18-20] With increasing dropout of retinal pericytes, the altered retinal vasculature walls can develop outpouchings (microaneurysms), become more fragile, and disruption of the blood retinal barrier may ensue, causing abnormally increased vascular permeability.[21,22] The leakage of blood and serum from the retinal vasculature results in retinal haemorrhages, retinal oedema and hard exudates. Clinically, these microaneurysms and small retinal haemorrhages are usually not readily distinguishable and primarily manifest as red dots and blots, while retinal nerve fibre layer haemorrhages are 'flame' shaped. Moderate visual loss will follow if the fovea is affected by the leakage.

Additional rheologic changes in diabetic retinopathy include increased platelet aggregation tendency, sclerosis and narrowing of the retinal vessels, decrease in vascular perfusion, and ultimately complete obliteration of the capillaries and small vessels causing retinal ischaemia.[23,24] Angiogenic growth factors are produced within the eye in response to the retinal ischaemia and these factors stimulate the development of new vessels.[25] New vessels have a tendency to grow around regions of strong vitreous adhesions to the retina, and the posterior face of the vitreous serves as scaffold for the growth of the arborising, abnormal vessels. Thus, new vessels are often seen at or around the optic disc, the vascular arcades, and also at the junctions between perfused and non-perfused retina. When the retina is very severely ischaemic, the concentration of angiogenic growth factors may reach sufficient concentration in the anterior chamber to cause abnormal new vessel proliferation on the iris and the anterior chamber angle. Uncontrolled anterior segment neovascularisation will result in rubeotic glaucoma as the fibrovascular proliferation in the angle of the eye causes blockage of aqueous outflow through the trabecular meshwork. Several angiogenic growth factors have been isolated from eyes with diabetic retinopathy, and these include insulin-like growth factors (IGF), basic fibroblast growth factor (bFGF), hepatocyte growth factor (HGF) and vascular endothelial growth factor (VEGF).[26-29]

VEGF is thought to be the main diffusable growth factor responsible for the development of diabetes retinopathy.[28-30] It is present in high concentrations in eyes with proliferative disease, including new vessels associated with other retinal vasculopathies.[28,29] Its expression is inducible by experimental retinal hypoxia.[31] In addition to the potent angiogenic property, VEGF increases retinal vasopermeability and blood flow.[32,33] All these properties are observed in diabetic retinopathy. Furthermore, these effects on vasopermeability and angiogenesis in the experimental animal models are reversed/blocked with VEGF antagonists.[33,34]

The abnormal new vessels in diabetic retinopathy have a tendency to bleed, causing preretinal and vitreous haemorrhages. While the presence of large amount of blood in the preretinal space or vitreous cavity *per se* is not damaging to the retina, these intraocular haemorrhages often cause prolonged significant visual loss. Surface membranes can develop on the retina causing wrinkling and/or traction on the retina as the blood is organised. The development of new vessels will eventually enter a quiescent state and, in the process, organisation and contraction of the fibrous component associated with new vessel complexes may cause severe traction on the retina, leading to tractional retinal detachment and retinal tears.

In short, retinal ischaemia (when the fovea is affected), significant macula oedema near or in the fovea, preretinal and/or vitreous haemorrhages, and retinal detachment can threaten the vision in a patient with diabetic retinopathy. Indirect effects that may also affect vision include retinal vessel occlusion and/or embolic phenomenon secondary to accelerated atherosclerotic disease progression in diabetic patients, and uncontrolled glaucoma secondary to anterior segment neovascularisation.

Classification

Broadly, diabetic retinopathy can be classified into non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR).[12,35] Macula oedema may co-exist with either group, and is not used in the classification of level of retinopathy. The historical nomenclatures for non-proliferative diabetic retinopathy, i.e. 'background retinopathy' and 'pre-proliferative retinopathy' have been replaced. They are too non-specific and do not reflect the risk stratification of the prognostically important subgroups in NPDR.[12] As will be explained later, NPDR is further subclassified into 4 categories that have important prognostic implications.

The current classification of diabetes is derived from 2 important trials on diabetic retinopathy conducted in the United States, namely the DRS and ETDRS.[35,36] Several clinical features of retinopathy are used in the classification, and the criteria are summarised in Table I. In the classification of diabetic retinopathy, haemorrhages and/or microaneurysms (H/Ma) are not individually distinguished. It was found, using fluorescein angiography, that the distinction of these lesions is of little clinical importance, as substantial predictive power for providing guidelines in management of NPDR can be obtained by clinical grading of the combined lesions alone.[37] The other important classifying lesions are intraretinal microvascular abnormalities (IRMA); venous beadings (VB); presence, location, severity of new vessels; and presence of preretinal or vitreous haemorrhages. IRMAs are thought to be either abnormally dilated or proliferation of pre-existing intraretinal capillaries in response to retinal ischaemia. Venous calibre abnormalities are usually seen in eyes with increasing retinal hypoxia. The manifestations of these venous abnormalities include venous dilatation, beading and loop formation.

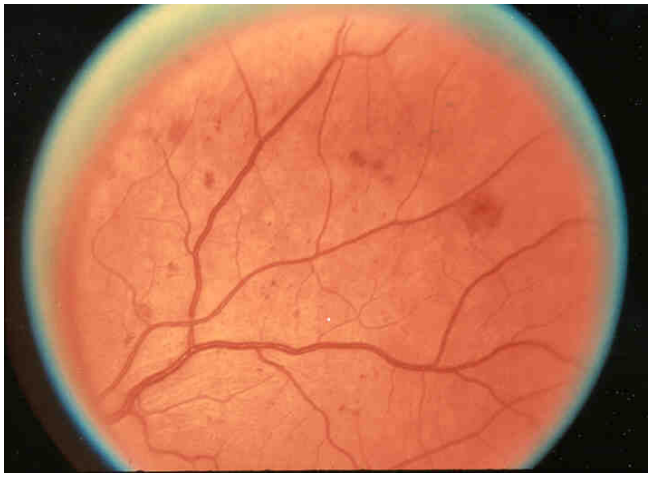
Several standard photographs are used in the DRS and ETDRS studies, and these serve as reference for comparison to the level of severity of the lesions employed in disease classification.[38] The key photographs, namely Standard Photographs 2A, 8A and 10A may be obtained by contacting the Fundus Photograph Reading Center, Department of Ophthalmology and Visual Sciences, University of Wisconsin in Madison, USA (http://wieyemd.ophth.wisc.edu).

The ETDRS data revealed that patients with severe to very severe NPDR had a very high risk of progression to PDR within a year (Table II).[36] Fortunately, classification of such severe levels of NPDR can be made clinically. From the ETDRS data, a '4-2-1' rule was established, which is very useful in determining which NPDR patients are at risk. The presence of any one of the following three criteria denotes severe NPDR, namely:

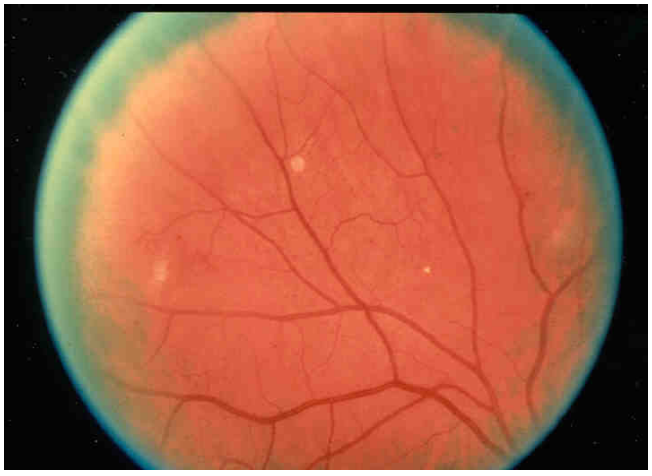
4 retinal quadrants of H/Ma equal to or more severe than Standard Photo 2A;
2 or more retinal quadrants of venous beading;
1 or more retinal quadrant of IRMA equal to or more severe than Standard Photo 8A.

The presence of 2 or more of above lesions denotes very severe NPDR.

Results from the ETDRS also showed that hard exudates and cotton wool spots (soft exudates), which represent disrupted axonoplasmic flow in the nerve fibre layer due to ischaemia, are not critically important in the classification of non-proliferative retinopathy level.[36] In fact, a weak inverse relationship between such lesions and the progression to proliferative retinopathy was found.



Standard Photo 2A. Reprinted with permission from the Association for Research in Vision and Ophthalmology (Ref. 38).



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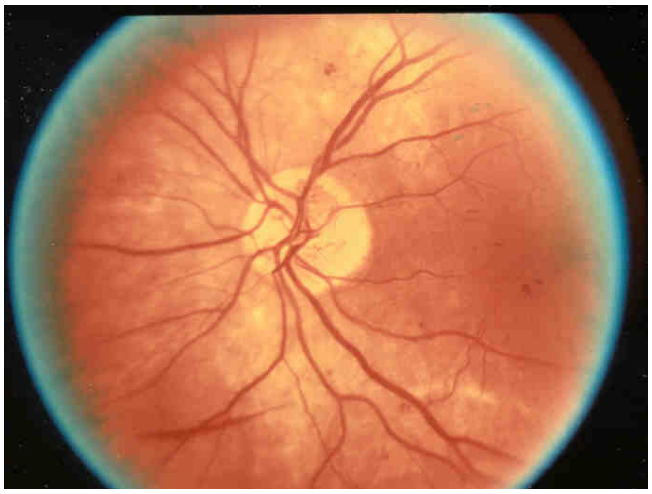

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TABLE I: CLASSIFICATION OF DIABETIC RETINOPATHY

Non-proliferative Diabetic Retinopathy
Mild: H/MA only
Moderate: H/MA, hard exudates and cotton wool spots, IRMA and venous beading definitions not met for more severe levels
Severe: (any one of the following)
4 retinal quadrants of H/Ma equal to or more severe than Standard Photo 2A;
2 or more retinal quadrants of venous beading;
1 or more retinal quadrant of IRMA equal to or more severe than Standard Photo 8A.
Very Severe: two or more of the above
Proliferative Diabetic Retinopathy: Presence of new vessels
Without high risk characteristics: criteria not met for high risk characteristics
With high risk characteristics: (any of the following)
New vessels on the disc with evidence of preretinal or vitreous haemorrhage
New vessels on the disc equal to or more severe than Standard Photo 10A (1/3 to ¼ disc area of new vessels)
New vessels elsewhere larger than ½ disc area and evidence of preretinal or vitreous haemorrhage
Macular oedema: retinal thickening within 3000 μm (2 disc diameter) of fovea
Clinically significant macular oedema: retinal thickening threatening central vision
Any of the following:
Retinal thickening within 500 μm of fovea
Hard exudate with adjacent area of retinal thickening within 500 μm of fovea
Zone of hard exudate with adjacent area of retinal thickening 1 disc area or larger any part of which is within 1 disc diameter of the fovea.

H/MA: retinal haemorrhages and/or microaneurysms
IRMA: intraretinal microvascular abnormalities

Adapted from Early Treatment in Diabetic Retinopathy Study Group

Diabetic retinopathy is classified as proliferative when there is presence of new vessels. New vessels can be found on/near the optic disc or elsewhere in the retina and the descriptions are commonly abbreviated as NVD (new vessels on the disc) and NVE (new vessels elsewhere). For definition purposes, all new vessels found within one-disc diameter from the optic disc are classified as NVD. PDR can further be classified as high risk or non-high risk based on the criteria set in Table I. The risk of severe visual loss is high when high risk characteristics are present and therefore, full scatter laser should be initiated promptly in such patients.[39]

Macular oedema (ME) refers to thickening of retina within 3000 μm, or two disc diameters, of the fovea. The macula oedema is termed clinically significant (CSME) if it threatens the central vision.[10] The criteria for CSME are defined in Table I and CSME is diagnosed when any one of the three criteria is present. CSME is essentially a clinical diagnosis and best evaluated using a slit lamp with a hand-held or contact fundus lens.[10] Visual acuity is not part of CSME diagnosis.

TABLE II: RISK OF PROGRESSION TO PROLIFERATIVE RETINOPATHY (PDR) BY LEVELS OF SEVERITY IN NON-PROLIFERATIVE DIABETIC RETINOPATHY (NPDR)

Retinopathy level	% developing PDR in 1 year	% developing high risk PDR in 5 years
Mild NPDR	5	15
Moderate NPDR	12-27	33
Severe NPDR	52	60
Very severe NPDR	75	75

Data from ETDRS Group[11]

Role of Fundus Fluorescein Angiogram (FFA)

As the diagnosis and classification of diabetic retinopathy and macula oedema are clinical, there is no role for the routine use of fluorescein angiogram in diabetic retinopathy classification.[12] However, FFA is fundamental in the identification of treatable lesions in cases of CSME.[40] It may also be employed to confirm macular ischaemia as a cause of visual loss in selected patients. Although extensive retinal capillary non-perfusion documented on FFA is correlated with progression of NPDR to PDR, the clinical grading of retinopathy levels according to ETDRS give similar prognostic prediction.[37] Thus, FFA is not routinely used in the diagnosis of diabetic retinopathy.

Important Interventional Studies in Diabetes Retinopathy

Five major prospective clinical trials in diabetic retinopathy have influenced the modern management of diabetic retinopathy. They are the DRS, ETDRS, Diabetic Retinopathy Vitrectomy Study (DRVS), Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS). Briefly, the DRS was designed to investigate the role of photocoagulation (xenon arc and argon laser) in preventing severe visual loss (defined as best corrected vision of <5/200 or worse on two consecutive visits 4 months apart) in patients with NPDR and PDR. Both photocoagulation methods showed a benefit in reducing severe visual loss, with the overall risk reduced by 60% from 37% to 17% after 6 years.[9]

The ETDRS was performed to investigate the most opportune time for pan retinal photocoagulation laser intervention in diabetic retinopathy; to investigate the timing and role of laser treatment in macular oedema; and assess the role and effects of aspirin in retinopathy. Aspirin was found to have no effect in diabetic retinopathy.[41] With timely laser intervention, i.e. applied just as the eye develops

PDR with high risk characteristics, the risk of bilateral severe visual loss was reduced by 97% after 3 years.[11] Further evaluation of ETDRS data revealed that among Type 2 patients (but not Type 1), a beneficial reduction in disease progression (to PDR with high risk characteristics), need for vitrectomy, and risk of severe visual loss were observed when scattered laser was initiated even earlier (i.e. treatment initiated when the eye has severe to very severe NPDR or PDR without high risk characteristics).[42] The risk of severe visual loss or need for vitrectomy was reduced by 50% in Type 2 patients receiving laser treatment prior to high risk characteristics while no additional benefit was observed in Type 1 patients.

The DRVS was initiated to study the role of early vitrectomy in severe PDR with severe vitreous haemorrhage and to determine whether vitrectomy improved visual prognosis for patients with very severe PDR and visual acuity of 10/200 or better. This study showed that early vitrectomy in vitreous haemorrhage was beneficial in Type 1 patients but not in Type 2 patients.[43] However, as the study was performed in the 1970s where intraoperative endolasers were not available and given that the vitrectomy instrumentation has been markedly refined since, this study must be interpreted with caution as the outcomes may be considerably different today.[12]

The DCCT, a multicentre trial involving 1441 patients, showed that intensive glycaemic control in Type 1 diabetes was effective in delaying the onset of retinopathy and in slowing the progression of NPDR.[7] Similarly, the UKPDS, a 20-year study in the United Kingdom studied the impact of intensive glycaemic and blood pressure control on progression of microvascular and macrovascular complications in Type 2 diabetic patients.[8] This study demonstrated that improved glycaemic or blood pressure control reduced the risk of significant visual impairment by nearly 50%. In both DCCT and UKPDS, the most important side effect of tight glycaemic control was a 3-fold increased risk of hypoglycaemia.

Management and Recommendation

The most important step in the prevention of diabetic complications is tight blood sugar control. Patient education is paramount in achieving this end and thus it cannot be overemphasized that patients need to be taught the nature, natural history and the options available to control their disease. All health care providers within the multi-disciplinary team that manages the diabetic patient have an important role to play in this regard.

Although the primary care physician's role is pivotal in the long-term management of the diabetic patient, the ophthalmologist plays a central part in the management of diabetic ocular complications. Only the eye care provider can provide the skills and instrumentation necessary for a comprehensive eye examination which at the very minimum should include tonometry, slit lamp evaluation of the iris and the angles, state of crystalline lens, biomicroscopic examination of the posterior pole, and indirect binocular ophthalmoscopy.

It is recommended that all Type 1 diabetic patients should have their retina evaluated within 3 to 5 years after

TABLE III: RECOMMENDED OPHTHALMIC EXAMINATION SCHEDULE IN DIABETIC RETINOPATHY

Diabetes type	First examination	Minimum follow-up†
Type 1 (or younger than 30 years*)	Within 5 years of diagnosis once patient is 10 years or older	Yearly
Type 2 (or 30 years and older)	At time of diagnosis	Yearly
Pregnancy in established DM patients	Prior to conception and 1st trimester	At physician's discretion

† more frequent follow-up required in abnormal findings (see Table IV)
* age at diagnosis of diabetes

Recommendation based on Aiello et al[12]

TABLE IV: RECOMMENDED MANAGEMENT IN DIABETIC RETINOPATHY

Retinopathy level	Laser treatment strategy	Follow-up (mo)
Mild NPDR		
No ME	none	12
ME < CSME	none	4-6
CSME	focal/grid	2-4
Moderate NPDR		
No ME	none	6-8
ME < CSME	none	4-6
CSME	focal/grid	2-4
Severe NPDR		
No ME	may consider PRP in Type 2	3-4
ME < CSME	may consider prior to PRP	2-3
CSME	focal/grid	
	may consider PRP in Type 2	2-3
Very severe NPDR and non-high risk PDR		
No ME	may consider PRP in Type 2	2-3
ME < CSME	may consider prior to PRP	2-3
CSME	focal/grid	
	may consider PRP in Type 2	2-3
High risk PDR		
No ME	PRP	2-3
ME < CSME	may consider prior to PRP	2
CSME	focal/grid and PRP	2

CSME: clinically significant macula oedema; ME: macula oedema; NPDR: non-proliferative diabetic retinopathy; PDR: proliferative diabetic retinopathy; PRP: panretinal photocoagulation

Adapted from Aiello et al[52]

diagnosis, or age 10 is reached, whichever is later.[12] (Table III). Severe diabetic eye complication is virtually never encountered in pre-pubescence state. Thereafter, the follow-up period should be decided according to the state of the retina, as summarised in Table IV.[12]

In Type 2 patients, an ophthalmological consult should be obtained within the first few months after diagnosis, as it is well known that the development of retinopathy in this group of patient is not well correlated with the duration of disease. This is because many patients with Type 2 disease will have had a considerable period of chronic hyperglycaemia prior to diagnosis of diabetes mellitus. Therefore, it is not unusual for the newly diagnosed Type 2 diabetic patient to have visually threatening diabetic retinopathy at time of diabetes diagnosis. Suggested follow-up schedule in Type 2 patients is similar to that applicable to the Type 1 patients.

There are several medical and physiological conditions that may exacerbate diabetic retinopathy. Apart from puberty, pregnancy too will cause acceleration in disease progression.[44] Therefore, patients should be informed of this risk and it is imperative that diabetic retinopathy is brought under control prior to conception. An ophthalmic evaluation should be scheduled in each trimester, and more frequently if necessary. However, patients who developed gestational diabetes are not at increased risks of developing diabetic retinopathy and hence comprehensive diabetic eye examinations are unnecessary.[12]

Hypertension, fluid retention and elevated serum lipids appear to have negative influence on retinopathy, especially the effects on diabetic macular oedema in the latter two conditions.[45,46] Extraction of cataract in a diabetic patient, especially surgery complicated by posterior capsule rupture, can also exacerbate diabetic retinopathy and macula oedema.[47]

Laser treatment has been shown to be effective in reducing the risk of visual loss in proliferative diabetic retinopathy with high risk characteristics.[9] Scattered laser treatment may also be considered in Type 2 patients that are approaching high risk, i.e. severe to very severe NPDR or PDR without high risk characteristics. This recommendation is based on re-evaluation of ETDRS data, which revealed that the risks of severe visual loss and retinopathy progression were reduced by 50% in this subgroup when earlier treatment was instituted.[42] Provided close follow-up can be maintained, scatter laser treatment is not recommended in Type 1 patients who are approaching high risk characteristics as such a benefit of early treatment is not observed.[12,42] Scatter laser is not recommended in mild to moderate NPDR.

Eyes with CSME should receive focal or grid laser treatment. The ETDRS had found that treatment for CSME can reduce moderate visual loss (doubling of visual angle on two consecutive visits 4 months apart) by 50% after 3 years.[10] Fluorescein angiogram is particularly useful in guiding the placement of laser treatment in this respect. When a patient who requires scatter treatment also has concurrent CSME, focal treatment should be performed first as scatter photocoagulation can exacerbate the macular oedema. Because of the negative effects of cataract extraction on progression of macula oedema, it is prudent to manage such patients vigilantly and pre-treat any CSME prior to cataract surgery if this is possible. Otherwise, focal laser treatment should be instituted shortly after cataract operation if the cataract precluded adequate initial view of the fundus.

Vitrectomy surgery is important in restoring vision in eyes with non-clearing vitreous haemorrhage in all diabetic patients. A reasonable waiting time to allow the spontaneous clearance of vitreous haemorrhage in Type 2 patients is 3 to 6 months. However, results from DRS showed that immediate vitrectomy surgery was advantageous in Type 1 patients with recent vitreous haemorrhage causing severe visual loss.[43] Early vitrectomy may be employed in patients with vitreous haemorrhage and poor vision in the fellow eye, in order to hasten visual recovery. It is important to attempt laser treatment to ensure that the patients with severe PDR or vitreous haemorrhage received scatter laser as far as possible prior to vitrectomy, since the result of vitrectomy favours patients who have had scattered laser prior to surgery.[48]

The role of vitrectomy in patients with extensive active fibrovascular proliferation despite adequate laser photocoagulation is less well defined. However, if such patients had tractional retinal detachment involving or threatening the macula, vitrectomy and membrane dissection is beneficial. Expanding indications for vitrectomy in diabetes mellitus, although not yet evaluated in controlled trials, include persistent diffuse macula oedema associated with an attached and thickened posterior hyaloid, massive premacular haemorrhage, progressive retrolenticular fibrovascular proliferation, haemolytic glaucoma and macular heterotopia.[49-51]

Conclusions

Diabetic retinopathy is a major cause of visual impairment in Singapore and will continue to be significant if the current trend in diabetes among Singapore residents prevails. As most morbidity with diabetes can be prevented or delayed with appropriate glycaemic control, the most important challenge for health care providers today is the identification of patients with diabetes. Upon diagnosis, the patient needs to be educated of the disease, and enrolled in comprehensive diabetic management programme, with joint secondary or tertiary care involvement when

appropriate. With timely ophthalmic intervention, most of the visual impairment related to diabetes can be minimised and therefore it is imperative for both the patient and the health care provider to be aware of the necessity of a rigorous and life-long ophthalmic evaluation.

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