
# Guidelines for the

# Management of Diabetic Retinopathy

**Prepared by the Australian Diabetes Society for the Department of Health and Ageing**

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The NHMRC provided support to this project through its Guidelines Assessment Register (GAR) process. The GAR consultants on this project were Ms Tracy Merlin and Professor Janet Hiller of Adelaide Health Technology Assessment - Adelaide Research and Innovation Pty Ltd. These guidelines were approved by the Chief Executive Officer of the NHMRC under Section 14A of the *National Health and Medical Research Council Act, 1992* on 8th June 2008.

## Disclaimer
This document is a general guide to appropriate practice, to be followed subject to the clinician's judgement and the patient's preference in each individual case.

The guidelines are designed to provide information to assist decision-making and are based on the best evidence available at the time of compilation (up to 31 August 2007). They are not meant to be prescriptive.

These guidelines can be downloaded from the National Health and Medical Research Council website: www.nhmrc.gov.au/publications.

# Table of Contents

# Tables

# Foreword

The National Health & Medical Research Council developed *Clinical Practice Guidelines for the Management of Diabetic Retinopathy*, published in 1997[1]. This information has now been updated to include literature that has been published up to September 2007. The objective of these guidelines is to assist practitioners in making decisions about the appropriate health care of patients with diabetes.

Considerable evidence now shows that diabetes is becoming a more frequent problem in our community so that detecting diabetic eye disease is critically important, since there are well-developed and proven strategies to prevent visual loss.

One of the earliest randomised controlled clinical studies to show the success of a particular treatment investigated photocoagulation therapy for diabetic retinopathy. Findings from the Diabetic Retinopathy Study were reported in 1976, showing that appropriate laser treatment would dramatically reduce the risk of blindness.

Further major prospective trials have now shown that the control of diabetes, and more recently, the control of hypertension in patients with diabetes, will reduce the risk of visual loss from diabetic eye disease.

The period since 1997 has witnessed the introduction of newer modalities to investigate patients with diabetic eye disease, such as Optical Coherence Tomography and newer treatments such as intravitreal triamcinolone. A variety of agents aimed at inhibiting pathways leading to diabetic retinopathy (e.g. protein kinase C) or the induction of retinal angiogenesis (e.g. vascular endothelial growth factor) are also being evaluated in clinical trials at this time.

Each of the guidelines has been linked to measures of the quality of the evidence available on that subject.

Changes in the attitudes and practices of optometrists and ophthalmologists following the release of the 1997 *Guidelines*[1], were documented in a series of reports by the Working Group on Evaluation of NHMRC Diabetic Retinopathy Guidelines[2-5]. Although well distributed and apparently well received, there appeared to be few changes in the referral pattern by optometrists[3;4]. However, the proportion of persons with known diabetes examined with dilated fundoscopy by optometrists reportedly increased[4]. There were also few changes in ophthalmic practice documented as a result of the *Guidelines*. Some change in accordance with recommendations was apparent in the co-management of macular oedema and cataract[5] and in fluorescein angiography[3;5]. These evaluations, however, were conducted one to three years after release of the *Guidelines*. Longer-term analysis of changes in practice[6] will be important and are planned in association with these revised Guidelines.

This background research work was undertaken in Professor Paul Mitchell's University of Sydney department of ophthalmology at Westmead Hospital in Sydney. The information provided in these guidelines was submitted for public consultation and the Committee has examined all these submissions before producing the final document. The Committee feels that this is an important review of a disease becoming progressively more common, yet still a major cause of avoidable blindness and visual impairment in Australia.
*Associate Professor Justin O'Day*
June 2008

## Guidelines Review Process

The review, conducted between 2004 and August 2007, updates the 1997 Guidelines with additional literature from 1996 to the end of August 2007.

The literature review was designed to answer specific questions relating to the management of diabetic retinopathy put by a Panel of the Retinopathy Subcommittee of the Australian Diabetes Society, headed by A/Prof Justin O'Day; members of this committee are listed in Appendix 1.

The questions, modified and supplemented from those used for the original Guidelines document, are listed on Page 8.

Medline (PubMed), Embase and the Cochrane Database were used to conduct the literature search. Selected unpublished Australian data (AusDIAB Study, Blue Mountains Eye Study, etc) have been incorporated where appropriate. Literature searches were limited to English language publications. Studies were selected on the basis of pre-determined inclusion criteria for specific research questions. Studies that addressed the research questions were classified according to the NHMRC dimensions of evidence.

**Evidence dimensions**

| ***Type of evidence*** | *Definition* |
|---|---|
| Strength of the evidence | |
| Levels of evidence | The study design was used as an indicator of the degree to which bias has been eliminated by design |
| Quality | The methods used by the investigators to minimise bias within a study design |
| Statistical precision | The *p*-value or, alternatively, the precision of the estimate of the effect. It reflects the degree of certainty about the existence of a true effect. |
| Size of the effect | The distance of the study estimate from the "null" value and the inclusion of only clinically important effects in the confidence interval |
| Relevance of the evidence | The usefulness of the evidence in clinical practice, particularly the appropriateness of the outcome measures used |

In all parts of this literature review, we attempted to comment on the levels and quality of evidence of the articles used according to NHMRC established guidelines. The NHMRC 'additional levels of evidence and grades of recommendations' approach (available at http://www.nhmrc.gov.au/consult/index.htm) is currently undergoing a second stage of consultation and pilot testing. This approach was introduced midway during the development of these Guidelines and so has not been applied. The systematic literature review instead included appraisal of the evidence using the established NHMRC levels of evidence hierarchy (NHMRC, 1999)[7-10].

**Levels of evidence**

Levels of evidence were appended to the Guidelines that were developed to address the questions pertaining to interventions, such as the treatment/management of diabetic retinopathy and diagnostic accuracy studies. For other research questions, such as risk of retinopathy or diagnostic accuracy of screening tools, the study design itself has been appended to the Guideline in order to indicate the quality of the evidence underpinning the recommendation.

| *Level of evidence* | *Study Design for Interventions* |
|---|---|
| I | Evidence obtained from a systematic review of all relevant randomised controlled trials |
| II | Evidence obtained from at least one properly designed randomised controlled trial |
| III-1 | Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method) |
| III-2 | Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group |
| III-3 | Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group |
| IV | Evidence obtained from case-series, either post-test or pre-test/post-test |

Source: NHMRC (1999)

Where appropriate, we discussed or provided information on potential biases arising from study design or analyses, an estimate of effect including statistical precision or confidence intervals, and commentary on the relevance of the study results to clinical practice.

NHMRC recommendations on preparing clinical practice guidelines[8-12] were used in the literature appraisal and in developing key points, consensus good practice points, and evidence-based guidelines.

The study selection criteria and search terms used in this systematic literature review are provided in Appendix 2.

In developing this revision of the Guidelines for Management of Diabetic Retinopathy, liaison has occurred with the NHMRC representatives (Mr Chris Gonzales and Ms Janine Keough) and the appointed Guideline Assessment Register (GAR) consultants (Prof Janet Hiller and Ms Tracy Merlin). The process for development of the guidelines, including public consultation, is provided in Appendix 4.

# A. Questions Set by the Committee

All of these questions were addressed in developing this report, but its structure may differ in the order in which questions are addressed.

### 1. Epidemiology of diabetic eye disease

1.1 What is the epidemiology of diabetes in Australia and worldwide and what trends are emerging over time?
1.2 What are the prevalence and incidence of diabetic retinopathy in Australia and worldwide and what trends are emerging over time?
1.3 What is the effect of duration of diabetes on the development and progression of diabetic retinopathy?
1.4 Is there any difference in the risk of diabetic retinopathy for the different types of diabetes?
1.5 What are the risk factors associated with diabetic retinopathy?
1.6 What is the prevalence of significant cataract in people with diabetes?

### 2. Grading of diabetic retinopathy

2.1 Identify and report on current grading systems for diabetic retinopathy.

### 3. Detection of diabetic retinopathy

3.1 What are the sensitivity and specificity of screening tests/examinations to detect diabetic retinopathy?
3.2 What is the sensitivity of the use and interpretation of non mydriatic retinal photography in screening for diabetic retinopathy?
3.3 When should the pupil be dilated and what are the potential adverse affects of pupil dilation?
3.4 What costs are associated with screening tests/examinations?
3.5 What are the criteria for referral to an ophthalmologist?
3.6 What is the most appropriate timing and/or frequency of eye examinations in people with diabetes?

### 4. Management of diabetic retinopathy

4.1 What is the timing of, patterns of, and follow-up after, laser treatment (or photocoagulation) for diabetic retinopathy?
4.2 What is the role of fluorescein angiography in the management of diabetic retinopathy? What are its risks and complications?
4.3 Are there any new modalities for assessing the severity of diabetic retinopathy?
4.4 What is the role of vitrectomy in managing diabetic eye disease?
4.5 What evidence is there to support alternative therapies for diabetic retinopathy?
4.6 Is there any benefit or risk from using anticoagulants in people with diabetic retinopathy?
4.7 What is the visual outcome from cataract surgery in people with diabetes?

### 5. Management cost and care for diabetic retinopathy

5.1 What is the cost to the Australian community for diabetic retinopathy and its management?
5.2 What approaches to co-ordinated care for patient detection and management are effective in people with diabetic eye disease?
5.3 What are the cost implications of these approaches?
5.4 Are there any special groups that need consideration in the management of diabetic retinopathy?

# B. List of Acronyms Used

| | |
|---|---|
| ADA | American Diabetes Association |
| AGE | Advanced glycation end products |
| ATSI | Aboriginal and Torres Strait Islander people |
| AusDiab | Australian Diabetes, Obesity and Lifestyle Study |
| BP | Blood pressure |
| BMES | Blue Mountains Eye Study |
| CSME | Clinically significant macular oedema (oedema abbreviated as 'E' as in U.S. literature) |
| CWS | Cotton wool spot |
| DCCT | Diabetes Control & Complications Trial |
| DM | Diabetes mellitus |
| DME | Diabetic macular oedema (oedema abbreviated as 'E' as in U.S. literature) |
| DN | Diabetic nephropathy |
| DR | Diabetic retinopathy |
| DRS | Diabetic Retinopathy Study |
| DRVS | Diabetic Retinopathy Vitrectomy Study |
| ETDRS | Early Treatment Diabetic Retinopathy Study |
| FA | Fluorescein angiography |
| H/Ma | Haemorrhages/microaneurysms |
| $HbA_{1C}$ | Haemoglobin $A_{1C}$ (glycosylated haemoglobin) |
| Hex | Hard exudates |
| HRC | High risk characteristics |
| IRMA | IntraRetinal microvascular abnormalities |
| Ma | Microaneurysms |
| ME | Macular oedema (oedema abbreviated as 'E' as in U.S. literature) |
| MVIP | Melbourne Visual Impairment Project |
| NPDR | Non-proliferative diabetic retinopathy |
| NVD | New vessels on the (optic) disc |
| NVE | New vessels elsewhere |
| OCT | Optical coherence tomography |
| PDR | Proliferative diabetic retinopathy |
| PRP | Panretinal photocoagulation |
| PSC | Posterior subcapsular cataract |
| RCT | Randomised controlled trial(s) |
| STR | Sight threatening retinopathy |
| T1DM | Type 1 diabetes mellitus |
| T2DM | Type 2 diabetes mellitus |
| UKPDS | UK Prospective Diabetes Study |
| VB | Venous beading |
| WESDR | Wisconsin Epidemiologic Study of Diabetic Retinopathy |

# C. Summary of the Guidelines

Table 1 summarises guidelines contained in this document. Readers should consult the relevant section of the document for further details and a presentation of the evidence for each guideline. Guidelines regarding intervention or treatment are accompanied by a Quality of Evidence rating (Levels I-IV). A Level I rating indicates that the guideline is based on the highest quality evidence, whereas a Level III or IV rating indicates that the statement or recommendation is based on lower quality evidence.

## Table I: Summary of guidelines for the management of diabetic retinopathy with level I to IV evidence

| *Guidelines* | *Evidence Level* |
|---|---|
| **I. Diabetes and diabetic retinopathy** | |
| 1. Undertake a multidisciplinary approach in all patients with diabetes to achieve optimal glycaemic control (target $HbA_{1c}$ levels 7.0% or lower) and to adequately manage blood pressure (target systolic blood pressure less than 130 mmHg) and serum lipids (target LDL cholesterol of less than 2.5 mmol/L and a target triglycerides of less than 2.0 mmol/L). | **I (glycaemic control)[13;14]; II (blood pressure control)[14-16]; II (blood lipid control)[17-19]** |
| **II. Screening for diabetic retinopathy** | |
| 2. Ophthalmologists, optometrists and other trained medical examiners should use dilated ophthalmoscopy or slit lamp biomicroscopy with a suitable lens (e.g. 78 D), to detect presence and severity of DR and DME, with adequate sensitivity and specificity. | **Systematic review of diagnostic accuracy studies[20] (dilated ophthalmoscopy) and individual diagnostic accuracy study (slit lamp biomicroscopy)[21]** |
| 3. In the absence of a dilated fundus examination by a trained examiner, use non-mydriatic (or mydriatic) photography with adequate sensitivity, specificity and low technical failure rate to detect presence of DR. | **Systematic review of diagnostic accuracy studies[20] and individual diagnostic accuracy studies[22-26]** |
| 4. Ensure that all people with diabetes have a dilated fundus examination and visual acuity assessment at the diagnosis of diabetes and at least every 2 years. | **I[14;27]** |
| 5. Screen children with pre-pubertal diabetes for DR at puberty. | **IV[27]** |
| 6. Examine higher-risk patients (longer duration of diabetes, poor glycaemic control, blood pressure or blood lipid control) without DR at least annually. | **I[14]** |
| 7. Examine patients with any signs of NPDR annually or at 3- to 6-monthly intervals, depending on the DR level. | **IV[27]** |
| 8. Refer to an ophthalmologist urgently (within 4 weeks) if there is any | **IV[27;28]** |

| | | |
|---|---|---|
| | unexplained fall in visual acuity, or if there is any suspicion of DME or PDR. | |
| 9. | All cases of mild or moderate NPDR, should be followed closely to detect signs of sight-threatening retinopathy. | **IV**[29;30] |
| 10. | Conduct comprehensive eye examinations on pregnant women with diabetes during the 1st trimester and follow women with DR throughout their pregnancy. | **IV**[31] |
| 11. | Women with gestational diabetes do not need ophthalmic surveillance after delivery, unless diabetes persists. | **IV**[31] |
| 12. | Perform FA if diffuse DME is present, and use the angiogram to identify sources of perimacular leakage and non-perfusion, to guide focal and grid laser treatment. | **II**[32-34] |
| 13. | Use FA to assess signs of likely macular ischaemia. | **II**[35;36] |
| **III.** | **Management of diabetic retinopathy** | |
| **Laser treatment** | | |
| 14. | For high-risk PDR, perform PRP as soon as possible. | **II**[37] |
| 15. | For earlier PDR stages, commence PRP after any maculopathy is stabilised | **II**[37] |
| 16. | Consider PRP for severe NPDR, particularly if there is T2DM, poor follow-up compliance, impending cataract surgery, renal disease, pregnancy, severe disease in the fellow eye or evidence of retinopathy progression. | **II**[38] |
| 17. | For less severe retinopathy, balance benefits of laser against the small risk of damage to vision from laser treatment. | **II**[37] |
| 18. | For all eyes with CSME, apply standard focal/grid macular laser treatment to areas of focal leak and capillary non-perfusion. | **II**[37;39] |
| 19. | For DME not meeting CSME criteria, consider either laser treatment or deferral, depending upon progression of signs, the status of the fellow eye, or ability to follow closely, and warn patients of potential risks. | **II**[37;39] |
| 20. | For eyes with both PDR and CSME, but without high-risk PDR, delay PRP until focal or grid macular laser treatment is completed. | **II**[37;39] |
| 21. | Review patients closely after completion of laser treatment. If high-risk characteristics do not regress or re-develop, perform additional laser treatment. | **II**[37] |
| 22. | Warn patients about the adverse effects of laser treatment. | **II**[37;39] |
| **Vitrectomy** | | |
| 23. | Consider vitrectomy within 3 months for T1DM patients with severe vitreous haemorrhage in eyes suspected to have very severe PDR. | **II**[40-42] |
| 24. | Also consider early vitrectomy for eyes with severe PDR, not responding to aggressive and extensive PRP. | **II**[40;42] |
| 25. | Consider vitrectomy to relieve macular or other retinal traction in | **IV**[42-44] |

| | | |
|---|---|---|
| | advanced PDR cases, in an attempt to salvage some vision. Such cases, if left untreated, will mostly develop severe visual loss or blindness. | |
| 26. | Consider vitrectomy in eyes with chronic or diffuse DME that is non-responsive to laser treatment, or if related to vitreomacular traction. | **III-1**[45-48] |
| 27. | Warn patients about the adverse effects of vitrectomy surgery. | **II**[40;49] |
| **Medical and Ancillary Therapies** | | |
| 28. | Strive to achieve optimal glycaemic control ($HbA_{1c}$ levels less than 7%) in all patients with diabetes in order to reduce the development and progression of DR | **I**[13;14] |
| 29. | Consider adjunctive blood-pressure-lowering therapy in patients with DR. Any lowering of systolic and or diastolic blood pressure is beneficial. In patients with DR, aim to keep systolic BP <130 mm Hg. | **I**[50-53] |
| 30. | Consider lowering blood lipids to reduce diabetes macrovascular complications and to reduce progression of DME. | **II**[18;54] |
| 31. | Consider lowering blood lipids in patients with extensive hard exudate deposition. | **III-3**[55-57] |
| 32. | Consider using intravitreal triamcinolone (IVTA) for DME that persists after focal/grid laser treatment. | **II**[58] |
| 33. | Also consider IVTA for cases of extensive macular hard exudate deposition, or as an adjunct to PRP for PDR. | **III-3**[59-64] |
| 34. | Warn patients having IVTA about the high incidence of secondary intraocular pressure rise, development of posterior subcapsular cataract, risk of intraocular infection, and the need for treatment of these adverse effects, as well as recurrence of the DME. | **II**[58] |
| **Management of Cataract** | | |
| 35. | Carefully assess DR in patients with significant cataract. Attempt to treat any DME with focal/grid laser, before cataract surgery, if possible. | **III-3**[65] |
| 36. | Once DR is stable, consider cataract surgery to improve vision in diabetic patients. If cataract is moderate to advanced, consider surgery to adequately assess need for laser or to permit laser. | **IV**[66-68] |
| **Special Groups** | | |
| 37. | Conduct annual screening for Aboriginal or Torres Strait Islander groups with diabetes. | **IV**[69] |

## Table II: Summary of consensus good practice points for the management of diabetic retinopathy

| *Good Practice points* |
|---|
| **II Screening for diabetic retinopathy** |
| 1. Always assess visual acuity at the time of DR screening |
| 2. Apply DR severity scales to determine need for referral, follow-up and treatment. |
| 3. Use FA in selected patients with PDR, or after PRP therapy for PDR to assess response |
| **III Management of diabetic retinopathy** |
| **Laser treatment** |
| 1. Complete as much PRP as possible before considering vitrectomy surgery, in order to minimise post-operative complications. |
| **Vitrectomy** |
| 2. Use OCT to confirm the presence and severity of DME and to monitor its response to treatment. |
| **Management of Cataract** |
| 3. Consider delaying cataract surgery until DR and DME signs are stabilised |
| **IV Costs and co-ordinated care for diabetic retinopathy** |
| 7. Screen for DR as part of the systematic and integrated care of people with diabetes, where possible. |

## Table III: Summary of key points in the management of diabetic retinopathy

**Diabetes**

- There are two common types of diabetes, type 1 (T1DM) and type 2 (T2DM) with some overlap in age at onset, together with intermediate forms.

**Epidemiology and Trends for Diabetes in Australia and Worldwide**

- The global prevalence of diabetes among adults aged ≥ 20 years was estimated in 2000 to be around 171 million (2.8% of the world's population), and is expected to rise to 366 million (4.4% of the estimated world population) by the year 2030.
- Asia is expected to be home to 61% of the total global projected number of people with diabetes by 2010, not only because it is the most populous continent on earth, but also because of increased urbanisation and improved life expectancy. India, China and the U.S.A. are expected to have the highest numbers of people with diabetes in 2030.
- In 2002, the AusDiab group reported a diabetes prevalence of 8.0% in adult men and 6.8% in adult women from an Australian nationwide cross-sectional survey. These data reveal that the prevalence of diabetes has more than doubled since 1981. An additional 16% of adults had impaired glucose tolerance or impaired fasting glucose.
- Diabetes is around twice as prevalent in Aboriginal as in non-Aboriginal Australians. One report indicated that the prevalence of diabetes in the Aboriginal population increased from 12% to 21% between 1983 and 1997.

**Diabetic Retinopathy, Definition and Types**

- Diabetic retinopathy (DR) is defined as the presence of typical microvascular signs in a person with diabetes; these signs are non-specific and may also be seen frequently in people without diabetes.
- DR is categorised as 'non-proliferative' (NPDR) or 'proliferative' (PDR). The latter stage is associated with a high risk of visual loss. Diabetic macular oedema (DME) represents thickening near the foveal area, can occur in either stage and is a very frequent cause of impaired vision.

**Prevalence and Incidence of Diabetic Retinopathy in Australia and Worldwide**

- Overall, between 25 and 44% of people with diabetes have some form of DR at any point in time. A recent large meta-analysis pooling data from 8 population-based studies of older groups reported an overall DR prevalence of 40%. The prevalence of sight-threatening retinopathy (PDR or CSME) varies principally with the known duration of diabetes, with some influences from age and type of diabetes.
- Projections from these data indicate that around 300,000 Australians have some DR and that 65,000 have sight-threatening retinopathy (PDR or CSME).
- From earlier reports from the WESDR study to more recent reports from the UKPDS, Liverpool DR Study, and the BMES, the prevalence and incidence of DR appear to have decreased.
- The most recent Australian DR prevalence data derive from the AusDiab Study, which found an overall DR prevalence of 25.4%, with PDR in 2.1%.
- Few Australian DR incidence data are available, with recent (2004) annual incidence lower at 4.5% in the BMES compared to 8.0% in the 1985 Newcastle study.
- Typical retinopathy lesions are also found in older persons without diabetes (possibly due to hypertension and other conditions), with the prevalence varying from 7.8% (BDES) to 9.8% (BMES).

**Pathogenesis of Diabetic Retinopathy**

- Many biochemical pathways link the altered glucose metabolism seen in diabetes directly to development and progression of DR.
- DR has a multifactorial pathogenesis, involving many pathways linked to glycaemia (aldose reductase, protein glycation, protein kinase C activation, angiotensin enzyme expression, vascular endothelial growth factor expression, and others). New therapies may target these pathways.
- These biochemical changes are accompanied by increased blood retinal barrier permeability and initially by increases in retinal blood flow.
- Widened venular calibre is a marker of retinopathy severity.

**Risk Factors associated with Diabetic Retinopathy**

- All people with diabetes are at risk of developing retinopathy.
- Duration of diabetes is the strongest factor determining DR prevalence.
- The most important systemic factors associated with increased risk of DR are:
- Other documented risk factors include:
    - Glycaemic control – evidence from RCT (DCCT, UKPDS) and large cohort studies (WESDR); any lowering of HbA1c will assist in reducing the development and progression of DR. For patients with DR, the target for HbA1c levels should be 7.0% or lower.
    - Blood pressure – evidence from RCT (UKPDS) and cohort studies (WESDR); any lowering of blood pressure will assist in reducing the development and progression of DR. For patients with DR, the target for systolic blood pressure should be less than 130 mmHg.
    - Blood lipids – evidence from both RCT (ETDRS) and cohort studies (WESDR). Normalising blood lipid levels may reduce cardiovascular risk and also DR, particularly DME.
- The DR risk associated with hyperglycaemia and hypertension is continuous, with no evident glycaemic or blood pressure threshold.
- Other documented risk factors include:
    - Renal impairment
    - Pregnancy
- Candidate genes (ALR2, RAGE, TGF-beta1, VEGF, eNOS, MTHFR, IGF-1 and vitamin D receptor genes) – evidence from case-control studies.

**Grading of Diabetic Retinopathy**

- The modified Airlie House classification (Wisconsin system) has become the basis for detailed grading of DR and was used in all the major studies of risk factors and trials of laser and other treatments, including the DCCT, UKPDS, DRS and ETDRS studies. It was based on grading seven 30˚ stereoscopic fields. Newer cameras now mostly utilise wider fields, so that two- to four-field photography is likely to be sufficient to document DR in current clinical practice.
- The ETDRS study quantified the risk of retinopathy progression associated with the severity of individual lesions from masked photographic grading.
- The presence of IRMA, H/Ma and VB were strong predictors of progression from NPDR to PDR.
- The ETDRS classified DR into the following categories: None, Minimal NPDR, Mild NPDR, Moderate NPDR, Severe NPDR, PDR, High-Risk PDR.
- The International Clinical Diabetic Retinopathy and Diabetic Macula Edema Disease Severity Scale proposes five levels for grading of DR, based on risk of progression: None, Mild NPDR, Moderate NPDR, Severe NPDR or PDR. Presence and severity of DME is classified separately. The World Health Organisation grading system stresses referral urgency: STR

requiring immediate referral, lesions needing referral as soon as possible, and lesions that could be reviewed in a few months.

- It is important to detect DME in the assessment of DR, as this is the most frequent cause of decreased vision from retinopathy. Both macular oedema (ME) and clinically significant macular oedema (CSME), defined by proximity of these signs to the foveal centre, are best assessed using slit lamp biomicroscopy or by grading stereoscopic macular photographs.
- Optical coherence tomography may be also used to provide valuable confirmation and quantification of the clinical grading for DME.

**Examinations, Sensitivity and Specificity in Detecting Diabetic Retinopathy**

- Stereoscopic seven-field fundus photography by a trained grader is the gold standard method of detecting DR. It is mainly a research tool and is rarely performed in routine practice.
- Clinical examinations to detect DR may use slit lamp biomicroscopy, ophthalmoscopy or retinal photography. Pupils should normally be dilated. An exception is non-mydriatic photography with adequate photographic quality and sensitivity.
- Dilated slit lamp biomicroscopy is used in routine clinical practice to assess the presence and severity of DR.
- The level of sensitivity needed by the examination or screening test cannot be defined unequivocally. Screening examinations or tests should aim for a sensitivity of at least 60% (as defined in earlier studies), though higher levels are usually achievable. It is considered that mild DR missed at one visit would likely be detected at the next. Specificity levels of 90-95% and technical failure rates of 5-10% are considered appropriate for both measures.
- Dilated direct or indirect ophthalmoscopy by ophthalmologists, optometrists, or other trained medical examiners, or fundus photography by trained personnel, generally meet screening sensitivity guidelines.
- Clinical assessments to screen for DR should include measurement of visual acuity and a dilated fundus examination. Examiners need adequate sensitivity and specificity in performing assessments. Alternately, retinal photographic screening (which may be non-mydriatic) with adequate sensitivity should be performed. Technical failure, however, should prompt a referral for clinical assessment.
- Non-mydriatic digital retinal photography is increasingly used in screening DR. Its usefulness may be limited by reduced sensitivity for screening and detecting DR and by technical failure with ungradeable photographs caused by small pupils and media opacities. Adequate training of staff is very important. DME may be difficult to detect using this method when few exudates are present.
- Patients should be referred promptly for dilated fundus examination if non-mydriatic photographs cannot be graded.
- Digital photography has allowed screening services to reach rural and remote areas via tele-ophthalmology.
- People with diabetes present to a variety of examiners, including general practitioners, general physicians, endocrinologists, optometrists and ophthalmologists. All are potentially able to screen for DR.

**Safety of Pupil Dilation**

- Pupil dilation using 0.5 to 1.0% tropicamide is safe and markedly increases the sensitivity of DR screening, so should be considered mandatory in performing ophthalmoscopy or slit lamp biomicroscopy.
- Two large Australian population studies (MVIP and BMES) showed high levels of patient acceptance for pupil dilation. These and other population studies have also confirmed the safety of pupil dilation.
- Although practitioners should be aware of the potential to induce acute angle closure glaucoma from use of mydriatic drops, its incidence is rare (1 to 6 per 20,000 people) and

tropicamide alone has not been reported to cause this.

**Frequency of Examinations and Referral**

- A large, multicentre RCT has shown that timely laser treatment will prevent vision loss from PDR and DME.
- Early detection of sight-threatening retinopathy by regular eye exams is the key to reducing visual loss and blindness from DR.
- Persons with diabetes should have a dilated fundus examination by a trained examiner, with adequate sensitivity and specificity, at the time of diagnosis of diabetes and at least every two years thereafter, if no DR is found.
- Alternately, retinal photographic screening, that may be non-mydriatic, with adequate sensitivity, should be performed. Technical failure should prompt referral for a dilated fundus examination.
- Once DR is detected, further examinations should be conducted annually or at 3-12 monthly intervals depending on the level of DR. Any visual symptoms should prompt a further referral.
- It is important to measure the visual acuity of both eyes, at the time of DR screening.
- Children with pre-pubertal diabetes onset should be screened at puberty, unless other considerations indicate the need for an earlier examination.
- Women with diabetes who become pregnant should have a comprehensive eye examination in the first trimester and, if DR is found, they need close follow-up throughout pregnancy. This does not apply to women who develop gestational diabetes.
- Referral to an ophthalmologist should be urgent (within 4 weeks) if DME or PDR is suspected or if an unexplained fall in visual acuity is recorded.

**Role of Fluorescein Angiography in Assessing Diabetic Retinopathy**

- Fluorescein angiography (FA) is not appropriate to screen for DR.
- Routine use of FA should be guided by clinical experience, as there is little evidence to provide firm guidelines.
- The presence of CSME is the principal justification for FA in DR patients. It may not be needed to guide treatment if DME is occurring from a well-defined ring of hard exudates or from focal maculopathy. Nevertheless, FA should be performed whenever diffuse macular oedema is present, in order best to identify sources of perimacular leakage and non-perfusion, guiding focal and grid laser treatment.
- FA can determine presence of macular ischaemia.
- FA may be warranted in selected cases of severe NPDR to assess severity of retinal ischaemia, to detect subtle NVE or in assessing patients with PDR before PRP. It may also be warranted in certain cases to determine adequate regression of DR after laser treatment.
- FA has a small risk of significant side effects. Frequent adverse reactions include mild transient reactions that require no medical management such as nausea (5-10%), vomiting (1.3%), dizziness (0.6%), and itching (0.5%). Moderate adverse reactions, defined as transient but requiring some medical intervention, include urticaria, syncope, thrombophlebitis or local tissue necrosis from extravasation of injected fluorescein and occur rarely. Severe adverse reactions, such as anaphylaxis or cardiac arrest, were reported in 1:20,000 FA procedures. Deaths occurred in 1:50,000-200,000 FA procedures. A number of FA-related deaths have been reported in Australia.
- It is important to have resuscitation equipment and medications readily available wherever FA is performed.

**New Modalities to Assess the Severity of Diabetic Retinopathy**

- Ophthalmoscopy, slit lamp biomicroscopy, fundus photography and fluorescein angiography (FA) have traditionally been used to assess the severity of DR.
- Optical Coherence Tomography (OCT) provides an effective qualitative and quantitative method of examining the eye, particularly in detecting early macular thickening, and also in following progression or regression of macular oedema over the course of treatment. OCT has good reproducibility and accuracy for the measurement of retinal thickness with an axial resolution in the order of 10μm or better with newer instruments. OCT also correlates reasonably with both biomicroscopic examination and FA in CSME.
- Heidelberg Retinal Tomography (HRT) and the Retinal Thickness Analyzer (RTA) are two other modalities that have the potential to provide an indirect measure of retinal thickness in order to quantify diabetic macular oedema. Both techniques have acceptable reproducibility and an axial resolution of around 150μm and 50μm respectively.
- All three new imaging modalities are disadvantaged by image degradation from ocular media opacities such as significant cataract (particularly posterior subcapsular or cortical cataracts, the types seen in diabetes) or vitreous haemorrhage, and by difficulties with small pupils and the relatively high cost of the currently available equipment. To date, all have been assessed only in case series.
- The electroretinogram (ERG) may possibly detect abnormalities at the retinal level before overt DR is evident. As with other imaging instruments, severe media opacities can also interfere with some standard ERG measures, although bright-flash ERG techniques can overcome this to some extent.

**Laser Treatment (Photocoagulation) for Diabetic Retinopathy**

- Multiple RCT, including the DRS and ETDRS, have shown that panretinal photocoagulation (PRP) significantly reduces the risk of severe vision loss (best corrected visual acuity <5/200) from PDR by at least 50%, and that focal or grid laser photocoagulation reduces the risk of moderate vision loss (doubling of the visual angle) from CSME by at least 50%.
- Recommendations of the type and pattern of laser photocoagulation have not changed since the ETDRS reported guidelines in 1987:
    - Apply PRP using 200- to 500-micron burns placed approximately one-half burn width apart, from the posterior fundus to the equator.
    - Apply focal laser photocoagulation using 100-micron laser burns to areas of focal leakage (i.e. leaking microaneurysms) and areas of capillary non-perfusion in the peri-macular region.
    - Apply grid laser photocoagulation using 50-100 micron burns in a grid pattern to areas of diffuse leakage and non-perfusion at the macula.
    - Although treatment is ideally guided by fluorescein angiography, this may not be needed to treat many cases with focal DME. Treatment is unlikely to be beneficial in the presence of significant macular ischaemia.
- ETDRS results were achieved by rigorous application of laser recommendations and close follow-up with re-treatment, as needed.
- Mild, diffuse macular grid laser was shown to have no benefit over routine focal/grid laser, reducing DME and OCT macular thickness less than standard treatment, so is not recommended.
- The following timing of laser treatment is recommended:
    - Patients should be seen at follow-up visits every 1-4 weeks during the course of PRP and then every 2-4 months thereafter until stable.
    - Follow-up of patients with DME should also occur every 2-4 months until stable.

**Role of Vitrectomy in Managing Diabetic Retinopathy**

- The Diabetic Retinopathy Vitrectomy Study (DRVS) was a multi-centre RCT that evaluated indications and timing of pars plana vitrectomy for management of advanced DR.
- The indications and rationale for vitrectomy established by the DRVS still guide therapy, but the thresholds for performing surgery are lower as a consequence of improved surgical results, improvements in vitreoretinal instrumentation and technique, and the introduction of ancillary modalities or modified techniques.
- Early vitrectomy for treatment of vitreous haemorrhage secondary to DR was found highly cost-effective in a cost-utility analysis using DRVS results.
- The benefits of early vitrectomy for non-resolving severe vitreous haemorrhage were less for type 2 diabetes.
- Vitrectomy was found in small RCT to benefit chronic or diffuse DME.
- OCT is valuable to confirm and quantify DME, and to confirm traction and its response to surgery.
- Vitrectomy, possibly combined with inner limiting membrane peeling, in selected eyes with thickened or taut posterior hyaloid has been found to facilitate more rapid resolution of DME and improvement in visual acuity.
- Combined cataract surgery (phacoemulsification and insertion of a posterior chamber intraocular lens) with vitrectomy has been shown to result in earlier visual rehabilitation by avoiding need for later cataract surgery.
- Complications from vitrectomy include recurrent vitreous haemorrhage, endophthalmitis, glaucoma, retinal tear or detachment, rubeosis iridis, and premature development of cataract.

**Medical Therapies for Diabetic Retinopathy**

- Trials of blood-pressure-lowering therapy in diabetes suggest the importance of hypertension/ blood pressure as a major modifiable risk factor for DR. It is unclear from the trials whether a threshold exists beyond which further lowering of blood pressure no longer influences DR progression.
- Benefits on DR may also be seen from the use of anti-hypertensive agents in people with diabetes and normal blood pressure levels.
- The renin-angiotensin system and angiotensin converting enzyme (ACE) are expressed in the eye, may independently affect VEGF expression, and are involved in the pathogenesis of DR. ACE inhibitors, used in managing blood pressure, have been evaluated for effects on DR.
- Lisinopril was shown to reduce DR progression in a 2-year RCT (Level II evidence). Other larger trials are ongoing. The UKPDS, however, did not find an ACE inhibitor superior to a beta blocker in its effect on DR. Blood pressure reduction alone may be the important parameter in determining progression of DR.
- Disordered blood lipids may increase the risk of macular hard exudate deposition and CSME. Fenofibrate reduced the need for laser treatment in a large diabetes cardiovascular trial. Studies to date suggest a potential role for fibrates or statins in managing DR, particularly in patients with extensive hard exudate deposition.
- ETDRS data showed that aspirin did not increase the risk of vitreous haemorrhage or exacerbate the severity or duration of vitreous or preretinal haemorrhage.
- Protein kinase C (PKC) plays a major role in hyperglycaemia-induced microvascular dysfunction in diabetes and DR. One PKC inhibitor, ruboxistaurin, has been the subject of 3 large RCT. Two trials showed benefit in reducing risk of moderate visual loss, but not on progression of DR or progression to DME. The third trial failed to demonstrate a reduced need for laser with this drug. Further trials are ongoing. Overall, there is insufficient evidence to recommend use of ruboxistaurin.
- A pathogenic role for aldose reductase in DR is likely. However, trials of aldose reductase inhibitors (ARIs) to reduce severity or progression of retinopathy have not shown benefit and have been limited by toxicity of the agents tested.

- Elevated growth hormone levels have been associated with accelerated DR. A small trial of a somatostatin analogue (Octreotide) compared to conventional therapy showed a reduced need for PRP laser and progression. Use of this therapy may be limited by its high maintenance cost.
- A pathogenic role for advanced glycation end-products (AGEs) in DR is likely. AGE inhibitors such as aminoguanidine are currently being evaluated in trials.
- Human trials have shown benefits from use of steroid agents in treating DME. Because of the transience of most steroid agents (e.g. cortisone), depot steroid agents such as triamcinolone, have been used.
- Intravitreal triamcinolone (IVTA) is widely used in managing DME that persists despite focal/ grid laser treatment. A small 2-year Australian RCT demonstrated benefit from IVTA on OCT macular thickness and visual acuity . Repeated injections are frequently needed, at around 6-monthly intervals.
- IVTA may also be used in treating patients with massive hard exudates deposition or as an adjunct to PRP for PDR.
- Frequent adverse ocular effects from IVTA include elevated intraocular pressure and glaucoma and development of posterior subcapsular cataract, often needing surgery.
- Unresolved issues include the ideal triamcinolone dosage, need for additional post-IVTA focal/grid laser, duration of repeat therapy, and concerns regarding the formulation in current use.
- Anti-Vascular Endothelial Growth Factor (VEGF) drugs, administered by repeat intravitreal injection, offer great promise in managing both PDR (including iris new vessels) and DME. Their use is accompanied by acceptably low rates of serious adverse ocular effects (less than from IVTA). Repeated applications are needed, and their long-term safety is not known.
- For PDR, anti-VEGF agents (particularly bevacizumab) are currently widely used as an adjunct to laser treatment and prior to vitrectomy surgery. For these two indications, RCT evidence is lacking. For DME, there is accumulating RCT evidence of benefit.
    - Pegaptanib (Macugen) has been shown to reduce OCT macular thickness and visual loss due to DME.
    - Bevacizumab (Avastin) is currently the most widely used anti-VEGF agent for DR; it reduces OCT macular thickness, and PDR activity and severity, and improves visual acuity. There are unresolved concerns regarding its systemic safety.
    - Ranibizumab (Lucentis) may have similar effects
- Ovine hyaluronidase (Vitrase) has been shown to accelerate the clearing of vitreous haemorrhage in PDR.

**Management of Cataract**

- Diabetes is associated with an increased risk of both cataract (particularly cortical and posterior subcapsular cataract) and cataract surgery.
- Vitrectomy in diabetic patients is associated with earlier onset of cataract and need for cataract surgery.
- Cataract surgery may be needed to adequately assess need for laser and to permit laser treatment to be completed.
- Cataract surgery may also lead to substantial visual improvements in diabetic patients.
- The visual outcome after cataract surgery in people with diabetes depends on the severity of pre-operative DR and presence of DME. Asymmetric retinopathy progression can occur in the operated eye, and the risk of rubeosis iridis or neovascular glaucoma increases after cataract surgery.
- Pre-operative DME and active PDR are strong predictors of a poor visual result.
- Although modern cataract surgical techniques show consistently improved visual outcomes in diabetic patients, a systematic review of case series and clinical trials consistently demonstrated worse visual results from cataract surgery in persons with than without DR.

- Progression of DR after cataract surgery is correlated with diabetic control at the time of surgery and the presence of T2DM and PDR at baseline.
- While no RCT have examined timing of laser treatment in relation to cataract surgery, current opinion recommends that adequate laser treatment of significant DR be completed before cataract surgery.
- Current opinion suggests that consideration of intravitreal triamcinolone (or bevacizumab) may be considered on the same day as cataract surgery in patients with DME to reduce progression.
- Diabetic patients develop posterior capsule opacification (PCO) earlier and with greater magnitude than do non-diabetic patients; but no correlation has been found between PCO and stage of DR, duration of diabetes, or HbA1c level.
- In relation to visual acuity or DR progression, no important differences exist between phacoemulsification and extra-capsular cataract extraction (ECCE).

**Consideration of Special Groups in Managing Diabetic Retinopathy**

- The prevalence of diabetes in Aboriginal and Torres Strait Islander communities is between 2- and 4-fold higher overall than in non-Aboriginal communities.
- Australians in rural and remote communities experience considerably higher hospitalisation due to diabetes than in metropolitan areas, which demonstrates the need for improved diabetes care services.

**Costs of Diabetic Retinopathy and Its Management**

- Diabetes accounts for about 3% of the total health care costs in most countries.
- The 2000-01 cost of diabetes in Australia was estimated at $784 million, 1.7% of health expenditure. Average health expenditure on diabetes was $1469 per known (self reported) case of diabetes, or $42 per Australian.
- UKPDS and DCCT data show that intensive diabetes therapy is more expensive, but has justifiable long-term benefits from an economic perspective.
- Preventive/screening programs targeted at DR are not only highly cost-effective, but also cost saving.

**Cost Implications of Diabetic Retinopathy Screening**

- Despite the high level of efficacy, clinical effectiveness and cost-effectiveness, problems remain with screening and treatment compliance.
- The cost of non-mydriatic retinal photography by non-medically trained staff, with photograph grading by an ophthalmologist in a 2-year mobile community-based DR screening program in rural Victoria, was similar to Medicare rebate costs for eye examinations.
- A cost-minimisation analysis revealed that telemedicine was cheaper than conventional examination (ophthalmoscopy) at high patient numbers, but that this technology was hampered by a relatively high technical failure rate (around 10%) and the difficulties in reliably detecting DME.

# D. Executive Summary

## 1. Diabetes and Diabetic Retinopathy

### 1.1. Diabetes: Definition, Diagnostic Criteria and Types

Diabetes mellitus (diabetes) is characterised by chronic hyperglycaemia secondary to insulin resistance or defects in insulin secretion leading to long-term multi-organ complication. A fasting plasma glucose of ≥7.0 mmol/l is usually the diagnostic laboratory threshold for diabetes.

Two common types of diabetes (types 1 and 2) are recognised, and have some overlap in age at onset. Other types are relatively uncommon and include diabetes secondary to pancreatic diseases, gestational diabetes and diabetes occurring as part of a genetic syndrome. Many studies in this report assumed that persons with diabetes onset before age 30 and treated with insulin from that time have type 1 diabetes (T1DM), while people with diabetes diagnosed from age 30 and treated either with lifestyle change (diet and exercise) alone, or with oral therapy or insulin, have type 2 diabetes (T2DM).

An intermediate form of diabetes (late onset autoimmune diabetes in adults) is like T1DM in that an autoimmune process destroys pancreatic β-islet cells. However, its clinical onset is usually slower and insulin therapy is often not required for some time after diagnosis. Generally these people do not have the common characteristics of T2DM (central obesity or overweight and family history) but develop their diabetes in adulthood, as do most people with T2DM.

### 1.2. Epidemiology and Trends for Diabetes in Australia and Worldwide

The global prevalence of diabetes among adults aged ≥ 20 years in 2000 was around 171 million (2.8% of the world population), and is expected to rise to 366 million (4.4% of the estimated world population) by the year 2030. Asia is expected to be home to 61% of the total global projected number of people with diabetes by 2010, not only because it is the most populous continent, but also because of increased urbanisation and improved life expectancy. India, China and the US are expected to have the highest numbers of people with diabetes in 2030.

In 2002, the AusDiab group reported a diabetes prevalence of 8.0% in adult men and 6.8% in adult women from an Australian nationwide cross-sectional survey. These data reveal that the prevalence of diabetes has more than doubled since 1981. An additional 16% of adults had impaired glucose tolerance or impaired fasting glucose. Blue Mountains Eye Study data indicated that diabetes prevalence increased by 27% (from 7.8% to 9.9%, among persons aged 50 years or older) over the 6-year period from 2003, and reported a 10-year incidence of 9.3%.

Diabetes is around twice as prevalent in Aboriginal as in non-Aboriginal Australians. One report indicated that the prevalence of diabetes in the Aboriginal population increased from 12% to 21% between 1983 and 1997.

### 1.3. Diabetic Retinopathy: Definition and Types

Diabetic retinopathy (DR) may be defined as the presence and characteristic evolution of typical retinal microvascular lesions in an individual with diabetes. For the purposes of this report, retinopathy in association with diabetes is considered DR.

DR is first evident ophthalmoscopically as non-proliferative (previously termed 'background') retinopathy (NPDR), which may evolve to proliferative retinopathy (PDR). Typical early NPDR lesions include microaneurysms (Ma) and dot, blot or flame haemorrhages (H/Ma). More advanced NPDR lesions include hard exudates (Hex), cotton wool spots (CWS) or soft exudates, intraretinal microvascular abnormalities (IRMA) and venous beading (VB). Proliferative diabetic retinopathy (PDR) is characterised by growth of abnormal new vessels and fibrous tissue in response to retinal ischaemia, and the subsequent development of pre-retinal or vitreous haemorrhage, or fibrous proliferation. If new vessels appear on or within one disc diameter of the

disc margin, they are known as new vessels on the disc (NVD). In other locations, they are referred to as new vessels elsewhere (NVE).

High-risk characteristics (HRC) of PDR, signifying a poor visual prognosis, are (1) NVD ≥ ⅓ disc area in extent, or (2) any NVD with vitreous or pre-retinal haemorrhage, or (3) NVE ≥ ½ disc area in extent associated with vitreous or pre-retinal haemorrhage, or (4) vitreous or pre-retinal haemorrhage obscuring ≥ 1 disc area.

Capillary leak in the macular or perimacular region results in retinal thickening or diabetic macular edema (oedema)/(DME), defined as thickening located within two disc diameters of the centre of the macula. When this is present within or close to the central macula, it is termed clinically significant macular oedema (CSME)

### 1.4. Prevalence and incidence of diabetic retinopathy and trends

Between 25 and 44% of people with diabetes have some form of DR at any point in time. A recent large meta-analysis pooling data from 8 population-based studies of older groups reported an overall DR prevalence of 40%. The prevalence of sight-threatening retinopathy (PDR or CSME) varies principally with the known duration of diabetes, with some influences from age and type of diabetes. Projections from these data indicate that around 300,000 Australians have some DR and that 65,000 have sight-threatening retinopathy (PDR or CSME).

From earlier reports from the WESDR study to more recent reports from the UKPDS, Liverpool DR Study, and the BMES, the incidence of DR appears to have decreased. The most recent Australian DR prevalence data derive from the AusDiab Study, which found an overall DR prevalence of 24.5%, with PDR in 2.1%. Few Australian DR incidence data are available, with recent annual incidence lower at 4.5% in the BMES compared to 8.0% in the older Newcastle study. Typical DR lesions are also found in older persons without diabetes (possibly due to hypertension and other conditions), with the prevalence varying from 7.8% (BDES) to 9.8% (BMES)

### 1.5. Pathogenesis of diabetic retinopathy

Many biochemical pathways link the altered glucose metabolism of diabetes directly to development and progression of DR, which has a multifactorial pathogenesis. This involves many pathways linked to glycaemia (aldose reductase, protein glycation, protein kinase C activation, angiotensin enzyme expression, vascular endothelial growth factor expression, and others). New therapies may target these pathways. These biochemical changes are accompanied by increased permeability across the blood retinal barrier, and initially by increases in retinal blood flow. Widened venular calibre is a marker of retinopathy severity.

### 1.6. Risk factors associated with diabetic retinopathy

All people with diabetes are at risk of developing DR. Duration of diabetes is the strongest factor determining DR prevalence. The most important systemic factor associated with increased risk of DR is glycaemic control, followed by control of blood pressure and blood lipids. The DR risk is continuous with no evident glycaemic or blood pressure threshold.

Any lowering of $HbA_{1c}$ will assist in reducing the development and progression of DR. For patients with diabetes, the $HbA_{1c}$ target should be less than 7%. Any lowering of blood pressure will assist in reducing the development and progression of DR. The target for systolic blood pressure should be less than 130 mmHg. Normalising blood lipid levels may also benefit DR, particularly diabetic macular oedema.

Other risk factors for DR include renal impairment, pregnancy and certain identified susceptibility candidate genes.

A multidisciplinary approach should be undertaken in all patients with diabetes to achieve optimal glycaemic control and to adequately manage blood pressure and serum lipid levels.

**Effect of diabetes duration on diabetic retinopathy**

The known duration of diabetes strongly predicts the prevalence and severity of diabetic retinopathy. A longer pre-pubertal diagnosis of diabetes may predict earlier development of diabetic retinopathy.

**Effect of diabetes type on diabetic retinopathy**

Earlier studies suggested a greater long-term DR susceptibility among persons with T1DM than T2DM after comparable duration, although recent research reported a slightly higher risk in T2DM. This changing trend could indicate that recent improvements in metabolic control have been more effective in people with T1DM.

# 2. Assessment of Diabetic Retinopathy

## 2.1 Grading of Diabetic Retinopathy

The modified Airlie House classification (Wisconsin system) has become the basis for detailed grading of DR and was used in all the major studies of risk factors and trials of laser and other treatments. It was based on grading seven 30˚ stereoscopic fields. Newer cameras now mostly utilise wider fields, so that two- to four-field photography is likely to be sufficient to document DR in current clinical practice.

The Early Treatment of Diabetic Retinopathy Study (ETDRS) quantified the risk of DR progression associated with the severity of individual lesions, from masked photographic grading. Specific lesions including intraretinal microvascular abnormalities, severe haemorrhages, microaneurysms or venous beading, indicated a high risk of progression from NPDR to PDR.

The International Clinical Diabetic Retinopathy and Diabetic Macula Edema Disease Severity Scale proposes five levels for grading of DR, based on risk of progression: None, Mild NPDR, Moderate NPDR, Severe NPDR or PDR, in the presence or absence of DME, classified separately.

It is important to detect DME in the assessment of DR as this is the most frequent cause of decreased vision from retinopathy. Both macular oedema (ME) and clinically significant macular oedema (CSME), defined by proximity of these signs to the foveal centre, are best assessed using slit lamp biomicroscopy or by grading stereoscopic macular photographs. Optical coherence tomography (OCT) may be also used to provide valuable confirmation and quantification of the clinical grading for DME, and facilitates monitoring of its response to therapy. The DR severity scales should be applied at every assessment to determine the need for referral, follow-up and laser treatment.

## 2.2 Examinations, Sensitivity and Specificity in Detecting Diabetic Retinopathy

Stereoscopic seven-field fundus photography by a trained grader is the gold standard method of detecting DR. It is mainly a research tool and is rarely performed in routine practice. Clinical examinations to assess the presence and severity of DR may use slit lamp biomicroscopy (routine practice), ophthalmoscopy or retinal photography. Pupils may be dilated or undilated.

The level of sensitivity needed by the examination or screening test cannot be defined unequivocally. Screening examinations or tests should aim for a sensitivity of at least 60%, though higher levels are usually achievable. It is considered that mild DR missed at one visit would likely be detected at the next. Specificity levels of 90-95% and technical failure rates of 5-10% are considered appropriate for both measures.

Dilated direct/ indirect ophthalmoscopy by ophthalmologists, optometrists, or other trained medical examiners, or fundus photography by trained personnel, meet screening sensitivity guidelines.

Clinical assessments to screen for DR should usually include measurement of visual acuity and a dilated fundus examination. Examiners need adequate sensitivity and specificity in

performing assessments. Alternately, retinal photographic screening (which may be non-mydriatic) with adequate sensitivity should be performed. Technical failure, however, should prompt a referral for clinical assessment. Non-mydriatic digital retinal photography is increasingly used in screening DR. Its usefulness may be limited by reduced sensitivity for screening and detecting DR and by technical failure with ungradeable photographs caused by small pupils and media opacities. Adequate training of staff is very important. Stereoscopic macular photographs are difficult to obtain. Without stereoscopic views, CSME may be difficult to detect when few exudates are present. Patients should be referred promptly for dilated fundus examination if non-mydriatic photographs cannot be graded.

People with diabetes present to many examiners, including general practitioners, physicians, endocrinologists, optometrists and ophthalmologists. All can potentially screen for DR. Digital photography has allowed screening services to reach rural and remote areas via tele-ophthalmology.

### 2.3 Safety of Pupil Dilation

Pupil dilation using 0.5 to 1.0% tropicamide and/or 2.5% phenylephrine is safe and markedly increases the sensitivity of DR screening, so should be considered mandatory in performing ophthalmoscopy or slit lamp biomicroscopy.

Two large Australian population studies (MVIP and BMES) showed high levels of patient acceptance for pupil dilation. These and other population studies have also confirmed the safety of pupil dilation. Although practitioners should be aware of the potential to induce acute angle closure glaucoma from use of mydriatic drops, its incidence is rare (1-6:20,000 people).

### 2.4 Referral and Frequency of Examinations

Persons with diabetes should have a dilated fundus examination by a trained examiner, with adequate sensitivity and specificity, at the time diabetes is diagnosed and at least every two years thereafter. Alternately, retinal photographic screening (usually non-mydriatic), with adequate sensitivity, should be performed. Technical failure should prompt referral for a dilated fundus examination. It is important to measure visual acuity of both eyes, at the time of DR screening.

Children with pre-pubertal diabetes onset should be screened at puberty, unless other considerations indicate the need for an earlier examination. Women with diabetes who become pregnant should have a comprehensive eye examination in the first trimester and, if DR is found, they need close follow-up throughout pregnancy. Women with gestational diabetes do not need ophthalmic surveillance during or after pregnancy, unless diabetes persists.

Large, multicentre randomised controlled trials have shown that timely laser treatment will prevent vision loss from PDR and CSME. Early detection of sight-threatening retinopathy by regular eye exams is the key to reducing visual loss and blindness from DR.

If no retinopathy is present when examined at the diagnosis of diabetes, eye examinations are recommended at least every two years thereafter. Indigenous Australians or those of non-English speaking backgrounds, those with longer duration of diabetes, or patients with poor glycaemic, hypertension or blood lipid control, or with renal disease, have higher a risk of DR or visual loss and could be considered for annual examinations.

Once any NPDR is detected, further examinations should be conducted annually or at 3-6 monthly intervals, depending on the level of DR.

Referral to an ophthalmologist should be urgent (eithin 4 weeks), if DME or PDR is suspected or if an unexplained fall in visual acuity is recorded. Any visual symptoms should prompt a referral.

### 2.5 Role of Fluorescein Angiography in Assessing Diabetic Retinopathy

Fluorescein angiography (FA) is inappropriate to screen DR. Use of FA in managing DR has decreased substantially. Routine use of FA should be guided by clinical experience, as there is little evidence to provide firm guidelines. The presence of CSME is the principal justification for FA in DR patients. It may not be needed to guide treatment if DME is occurring from a well-defined ring of hard exudates or from focal maculopathy. Nevertheless, FA should be performed whenever

diffuse macular oedema is present, in order best to identify sources of perimacular leakage and non-perfusion, guiding focal/ grid laser treatment. FA can also detect presence of macular ischaemia.

FA may be warranted in selected cases of severe NPDR to assess severity of retinal ischaemia, or to detect subtle NVE, and may also be helpful in certain cases to determine adequate regression of DR after laser treatment.

FA has a small risk of significant side effects. Frequent adverse reactions include mild transient reactions that require no medical management such as nausea, vomiting, dizziness, and itching. Moderate adverse reactions, include urticaria, syncope, thrombophlebitis or local tissue necrosis from extravasation of injected fluorescein. Severe adverse reactions such as anaphylaxis or cardiac arrest were reported in 1:20,000 FA procedures. Deaths occurred in 1:50,000-200,000 FA procedures. A number of FA-related deaths have been reported in Australia. It is important to have resuscitation equipment and medications readily available wherever FA is performed.

### 2.6 New Modalities to Assess the Severity of Diabetic Retinopathy

Slit lamp biomicroscopy, fundus photography and fluorescein angiography (FA) have traditionally been used to assess the severity of DR. Optical Coherence Tomography (OCT) provides an effective qualitative and quantitative method of examining the eye, in particular screening for early macular thickening, and also following progression or regression of macular oedema over the course of treatment. OCT has good reproducibility and accuracy for the measurement of retinal thickness with an axial resolution in the order of 10μm. OCT also correlates reasonably with both biomicroscopic examination and FA in CSME.

Heidelberg Retinal Tomography (HRT) and the Retinal Thickness Analyzer (RTA) are two other modalities with potential to provide indirect measures of retinal thickness to quantify DME. Both have acceptable reproducibility and axial resolution of around 150μm and 50μm, respectively.

All three new imaging modalities are limited by image degradation from ocular media opacities such as significant cataract (particularly posterior subcapsular or cortical cataract) or vitreous haemorrhage, by small pupils and relatively high cost of the currently available equipment.

The electroretinogram (ERG) may possibly detect abnormalities at the retinal level before overt DR is evident. As with other imaging, severe media opacities can also interfere with some standard ERG measures, although bright-flash ERG techniques can overcome this to some extent.

## 3. Management of Diabetic Retinopathy

### 3.1 Laser Treatment (Photocoagulation) for Diabetic Retinopathy

Multiple randomised controlled trials (Level II evidence), including the DRS and ETDRS, showed that scatter (panretinal) laser photocoagulation (PRP) significantly reduced the risk of severe vision loss (severe blindness) from PDR by at least 50%, and that focal or grid laser photocoagulation reduced the risk of moderate vision loss (doubling of the visual angle) from CSME by at least 50%. Recommendations for the type and pattern of laser treatment for DR have not changed since these studies were first reported.

PRP is performed using 200- to 500-μm burns placed approximately one-half burn width apart, from the posterior fundus to the equator. Focal laser treatment using 100- μm laser burns is applied to areas of focal leakage (i.e. leaking microaneurysms) plus areas of capillary non-perfusion in the para-macular region. Grid laser photocoagulation, using 100- μm burns, is applied in a grid pattern to areas of diffuse leak and non-perfusion around the macula. Mild macular grid laser that does not directly treat focal leaks is not recommended. Although treatment is ideally guided by fluorescein angiography, this may not be needed to treat many cases with focal DME. Treatment is unlikely to be beneficial in the presence of significant macular ischaemia.

ETDRS results were achieved by rigorously applying laser recommendations and through close follow-up, with re-treatment as needed.

For high-risk PDR, PRP should be performed as soon as possible. At earlier stages, PRP should be commenced after maculopathy is stable. Focal or grid macular laser treatment should be considered for all eyes with CSME. Either laser treatment or deferral should be considered for macular oedema not meeting CSME criteria, depending upon progression of signs, the fellow eye, or ability to follow-up closely. Consider laser treatment for DME threatening the macula but warn patients of potential risks, particularly when vision is 6/6 or better. For eyes with both PDR and CSME, but without high-risk PDR, PRP should be delayed until focal or grid macular laser treatment is completed.

Consider PRP for severe NPDR, particularly if there is T2DM, poor follow-up compliance, impending cataract surgery, renal disease, pregnancy, severe disease in the fellow eye or evidence of progression. For less severe retinopathy, benefits of laser should be balanced against the small risk of damage to vision from use of the laser.

Patients need to be closely and regularly reviewed after laser treatment is completed. If high-risk characteristics fail to regress or if they re-develop, supplemental laser treatment is needed. All NPDR cases should be regularly observed for signs of sight-threatening retinopathy.

### 3.2. Role of Vitrectomy in Managing Diabetic Retinopathy

The Diabetic Retinopathy Vitrectomy Study (DRVS) was the landmark randomised controlled trial to evaluate indications and timing of pars plana vitrectomy for the management of advanced diabetic retinopathy (DR). The indications and rationale for vitrectomy established by the DRVS still guide therapy, but the thresholds for performing surgery are now lower, due to improved surgical results. This has resulted from improvements in vitreoretinal instrumentation and technique, and the introduction of ancillary modalities or modified techniques.

Early vitrectomy (within 3 months) for treatment of vitreous haemorrhage secondary to DR was highly cost-effective in a cost-utility analysis using DRVS results. The benefits of early vitrectomy for non-resolving severe vitreous haemorrhage were greater for patients with T1DM and lower for T2DM. Vitrectomy, particularly in eyes with diffuse or chronic DME, or a thickened or taut posterior hyaloid, reduces DME. Combined cataract surgery with vitrectomy results in earlier visual rehabilitation by avoiding the need for later cataract surgery.

Complications from vitrectomy include recurrent vitreous haemorrhage, glaucoma, endophthalmitis, retinal detachment, rubeosis, and premature cataract.

Urgent pars plana vitrectomy (within three months) should be considered for:

1) T1DM diabetes with severe vitreous haemorrhage in eyes considered to have very severe PDR;
2) severe PDR, not responding to aggressive, extensive PRP;
3) to relieve macular or other retinal traction in advanced PDR cases, in an attempt to salvage some vision.
4) in selected cases with diffuse, severe DME not responsive to other therapies, particularly if vitreomacular traction is present.

Complete as much PRP as possible before considering vitrectomy surgery, in order to minimise post-operative complications.

### 3.3. Medical Therapies for Diabetic Retinopathy

Hypertension/ elevated blood pressure is a major modifiable risk factor for DR, although it is unclear from trials of blood pressure lowering therapy whether a threshold exists. Anti-hypertensive agents have shown benefits on DR in people with diabetes and both elevated and normal blood pressure. Consider adjunctive blood-pressure-lowering therapy in patients with DR, to achieve any reduction (Level I evidence). Aim to keep systolic BP <130 mm Hg in patients with DR (Level II evidence).

ACE inhibitors have been evaluated for effects on DR, because of likely involvement of this enzyme in the pathogenesis of DR. Although lisinopril reduced DR progression over 2 years (Level II evidence), other trials did not confirm that this class of medication was superior to other anti-

hypertensives. Thus, blood pressure reduction alone may be the important parameter in determining progression of DR.

Disordered blood lipids may increase DR risk, particularly macular hard exudate deposition and CSME. Fibrates or statins may assist in managing DR. Consider lowering blood lipids to reduce DME progression (Level II evidence), or in patients with extensive hard exudates (Level III-3 evidence).

Aspirin is safe to use in the presence of DR, at any severity level.

A protein kinase C (PKC) inhibitor (ruboxistaurin) had mixed benefit on the progression of DR. As some reduction in risk of moderate visual loss was demonstrated, trials are continuing. There is insufficient evidence to recommend use of this agent.

Benefits from use of intravitreal depot steroid therapy (triamcinolone, IVTA) for DME have been shown in an RCT. Consider IVTA to manage DME that persists despite focal/ grid laser treatment (Level II evidence), for extensive macular hard exudate deposition, or as an adjunct to PRP (Level III-3 evidence). Warn patients about adverse effects (development of elevated intraocular pressure or posterior subcapsular cataract, often needing surgery) and frequent need for repeat injections.

Anti-Vascular Endothelial Growth Factor (VEGF) drugs (pegaptanib, ranibizumab and bevacizumab), administered by repeat intravitreal injection, are promising therapies for both PDR and for DME. These treatments have acceptably low serious adverse ocular effects rates, but there are some concerns about the systemic safety of bevacizumab (the most frequently used agent at present), and repeated intravitreal applications are needed. Although one trial showed benefit of pegaptanib for DME, evidence at the time of these *Guidelines* was insufficient to recommend the routine use of these agents.

### 3.4. Management of Cataract

Diabetes is associated with an increased risk of both cataract (particularly cortical and posterior subcapsular cataract) and cataract surgery. Vitrectomy in diabetic patients is associated with earlier onset of cataract and need for cataract surgery.

Cataract surgery may be needed to adequately assess need for laser and to permit laser treatment to be completed. Cataract surgery may also lead to substantial visual improvements in diabetic patients. The visual outcome after cataract surgery in people with diabetes depends on the severity of pre-operative DR and presence of DME. Asymmetric retinopathy progression can occur in the operated eye, and the risk of rubeosis iridis or neovascular glaucoma increases after cataract surgery. Pre-operative DME and active PDR are strong predictors of a poor visual result.

Although modern cataract surgical techniques show consistently improved visual outcomes in diabetic patients, a systematic review of case series and clinical trials consistently demonstrated worse visual results from cataract surgery in persons with than without DR.

Progression of DR after cataract surgery is correlated with diabetic control at the time of surgery and the presence of T2DM and PDR at baseline.

While no RCT have examined timing of laser treatment in relation to cataract surgery, current opinion recommends that adequate laser treatment of significant DR be completed before cataract surgery. Where possible, adequate laser treatment of significant DR (particularly DME) should be performed before cataract surgery (Level III-3). Cataract surgery should be delayed until DR and DME signs are stabilised (consensus). Once DR is stable, consider cataract surgery to improve vision in diabetic patients. If cataract is moderate to advanced, consider surgery to adequately assess the need for laser or to permit completion of laser (Level IV).

Diabetic patients develop posterior capsule opacification (PCO) earlier and with greater magnitude than do non-diabetic patients; but no correlation has been found between PCO and stage of DR, duration of diabetes, or HbA1c level.

In relation to visual acuity or DR progression, no important differences exist between phacoemulsification and extra-capsular cataract extraction (ECCE).

### 3.5 Consideration of Special Groups in Managing Diabetic Retinopathy

The prevalence of diabetes in Aboriginal and Torres Strait Islander communities is between 2- and 4-fold higher than in non-Aboriginal communities. Australians in rural and remote communities experience considerably higher hospitalisation due to diabetes than in metropolitan areas, which demonstrates the need for improved diabetes care services.

Non-English speaking background (NESB) may be an independent risk factor for DR, given the increased difficulty in achieving blood glucose, blood pressure and blood lipid control, and in communicating with medical personnel.

Annual screening should be conducted for Aboriginal or Torres Strait Islander groups with diabetes (Level IV evidence), because of their higher risk of DR. Also consider annual screening for persons with diabetes from non-English speaking backgrounds, and those living in rural and remote communities (Level IV evidence).

## 4. Costs and Co-ordinated Care for Diabetic Retinopathy

### 4.1 Cost to Australia of diabetic retinopathy and its management

Diabetes is estimated to account for at least 3% of the total health care costs in most countries. In 1996, diabetes cost the Australian community over A$1 billion annually, an average A$1,100 per diabetic person, including those with undiagnosed diabetes70.

UKPDS and DCCT data show that intensive diabetes therapy is more expensive, but has justifiable long-term benefits from an economic perspective.

Preventive/screening programs targeted at diabetic retinopathy are not only highly cost-effective, but are also cost saving70.

### 4.2 Cost implications of diabetic retinopathy screening

Diabetic retinopathy screening and treatment are both cost-effective and cost saving. Despite the high level of efficacy, clinical effectiveness and cost effectiveness, problems remain with screening and treatment compliance. Tele-medicine and non-mydriatic retinal photography may be cheaper than conventional examinations (ophthalmoscopy) at higher patient numbers, but these technologies are hampered by relatively high technical failure rates (around 10% or higher) and difficulties in reliably detecting macular oedema.

# 1. Diabetes and Diabetic Retinopathy

## *1.1 Diabetes: Definition, Diagnostic Criteria and Types*

### *Definition of Diabetes*

Diabetes mellitus (diabetes) is characterised by chronic hyperglycaemia secondary to insulin resistance or defects in insulin secretion leading to long-term multi-organ complications including complications in the eyes, kidneys, nerves, blood vessels and heart.

### *Diagnostic Criteria for Diabetes*

Table 1.1 outlines the diagnostic thresholds for diabetes[71]. Impaired fasting glucose (IFG) is defined as a fasting plasma glucose of 5.6-6.9 mmol/L. Impaired glucose tolerance (IGT) is defined as a 2-hour plasma glucose of 7.8-11.0 mmol/L.

**Table 1.1: Diagnostic thresholds for Diabetes[71]**

| Category | Test | |
|---|---|---|
| | fasting plasma glucose | 2-hour plasma glucose (75gm glucose load) |
| Normal | <5.6 mmol/l | <7.8 mmol/l |
| Diabetes | ≥7.0 mmol/l | ≥11.1 mmol/l |

The use of haemoglobin $A_{1c}$ as a diagnostic test for diabetes is problematic because a lack of standardised laboratory methodology results in variable reference ranges, particularly for earlier studies[72].

### *Types of Diabetes*

The World Health Organization (WHO) defines two main types of diabetes[73]:

**Type 1 diabetes mellitus** (T1DM), previously called 'insulin dependent diabetes' or 'juvenile-onset diabetes', is primarily due to an autoimmune-mediated destruction of the insulin-producing pancreatic β-islet cells. This results in an absolute insulin deficiency, so that all people with type 1 diabetes require exogenous insulin for prevention of ketoacidosis, and survival.

**Type 2 diabetes mellitus** (T2DM), previously called 'non-insulin dependent diabetes' or 'adult-onset diabetes', is characterised by relative insulin deficiency due to insulin resistance and/or impaired insulin secretion. People with T2DM are not dependent on exogenous insulin replacement, but may require insulin if blood glucose is inadequately controlled by diet or oral hypoglycaemic agents.

These two common types of diabetes have some overlap in age at onset. Many of the studies in this report have assumed that persons with diabetes onset before age 30 and treated with insulin from that time have T1DM, while people with diabetes diagnosed from age 30 and treated either with lifestyle change (diet and exercise) alone, or with oral therapy or insulin, have T2DM.

Other types of diabetes are relatively uncommon and include diabetes secondary to pancreatic diseases, gestational diabetes and diabetes occurring as part of a genetic syndrome. An intermediate form of diabetes (late onset autoimmune diabetes in adults) is most like T1DM, in that pancreatic β-islet cells are destroyed by an autoimmune process. However, its clinical onset is usually slower than in T1DM and insulin therapy is often not required for some time after diagnosis (usually within the first year). Generally these people do not have the common characteristics of T2DM

(central obesity, or overweight and family history) but do develop their diabetes in adulthood, as do most people with T2DM.

## 1.2 Epidemiology and Trends for Diabetes in Australia & Worldwide

**Key Points**

- The global prevalence of diabetes among adults aged ≥ 20 years was estimated in 2000 to be around 171 million (2.8% of the world's population), and is expected to rise to 366 million (4.4% of the estimated world population) by the year 2030.
- Asia is expected to be home to 61% of the total global projected number of people with diabetes by 2010, not only because it is the most populous continent on earth, but also because of increased urbanisation and improved life expectancy. India, China and the U.S.A. are expected to have the highest numbers of people with diabetes in 2030.
- In 2002, the AusDiab group reported a diabetes prevalence of 8.0% in adult men and 6.8% in adult women from an Australian nationwide cross-sectional survey. These data reveal that the prevalence of diabetes has more than doubled since 1981. An additional 16% of adults had impaired glucose tolerance or impaired fasting glucose.
- Diabetes is around twice as prevalent in Aboriginal as in non-Aboriginal Australians. One report indicated that the prevalence of diabetes in the Aboriginal population increased from 12% to 21% between 1983 and 1997.

Diabetes was long considered a disease of minor significance to world health, but in the 21st century it is a significant threat to human health. While new cases of cardiovascular disease and cancer are stable or decreasing[74], the incidence of diabetes is increasing worldwide[75-78].

### Global Prevalence of Diabetes

Wild *et al.*[79] updated the estimates for the global prevalence of diabetes, applying age-sex specific population-based prevalence data where possible; prevalence estimates from incidence data; or extrapolation from geographically, ethnically and socioeconomically similar populations, to United Nations population estimates. The estimated prevalence of diabetes for all age groups worldwide is 2.8% in 2000 and 4.4% in 2030[79]. In the year 2000, the estimated global prevalence of diabetes among adults ≥20 years of age was 171 million, about 11% higher than the previous estimate of 154 million reported by King *et al*[77]. The total number of people with diabetes worldwide is projected to double to 366 million by 2030[79]. The well-established association between increasing age and prevalence of diabetes, and the expected global shift to increased life expectancy largely explains this increase in prevalence. Overall, the highest rates are seen in Native Americans and Pacific Islanders, followed by Hispanics, people originating from the Indian subcontinent, South East Asians and African Americans. Caucasians of European origin (Europids) have somewhat lower prevalence rates. The only racial subgroups for whom diabetes remains rare are indigenous peoples living traditional lifestyles[78].

### Proportions of Type 1 and Type 2 Diabetes

Because type 2 diabetes is much more prevalent than T1DM, more data on it have been collected. Estimates of the proportion of diabetes which is T2DM range from 70%[80] to 90%[78]. Although T2DM is more prevalent in the general population, T1DM is among the most common chronic diseases of children. The documented increasing prevalence of T2DM in children may reverse this order within two decades[81;82]. Recent studies suggest that up to 45% of children with newly diagnosed diabetes have diabetes with a type 2 pattern[83]. Among children in Japan, T2DM is already more common than T1DM and accounts for 80% of childhood diabetes[78]. This fall in the age at onset of T2DM will be an important factor influencing the future burden of the disease and its complications.

### *Prevalence and Incidence of Type 1 Diabetes*

The prevalence of T1DM differs greatly among different populations, with considerable geographical and ethnic variations. The greatest documented incidence is in Nordic countries, particularly Finland, where the incidence rate is approx 35 new cases annually per 100,000 children up to age 14[84]. The documented geographical variability does not reflect a simple north-to-south pattern. The incidence of T1DM in Sardinia approaches that of Finland, but is several times greater than in the rest of Italy[84]. Chinese populations have the lowest reported T1DM incidence rates[84].

### *Prevalence and Incidence of Type 2 Diabetes*

Both prevalence and incidence of T2DM vary widely among different populations, with prevalence rates ranging from almost zero in rural Melanesia to 40% in Micronesia (Nauru) and greater than 50% in Pima Indians in the USA[80]. In the UK, the prevalence of T2DM is 1-3%[80]. Asians (including those in countries within the Indian sub-continent) have a 3-4 times higher prevalence of T2DM than Europeans[80]. There are also significant differences in the prevalence of T2DM in different ethnic groups within a country. In the UK, people originating from the Indian sub-continent have a higher prevalence of diabetes compared to the general UK population[80]. In the USA, the prevalence of T2DM is highest among Pima Indians, followed by Hispanics, blacks and then whites[80].

### *Effect of Migration on Prevalence of Type 2 Diabetes*

Several studies have examined the effect of migration on the prevalence of T2DM. Japanese men have a prevalence of 5% compared with 20% among Nisei men living in Seattle, USA[85]. Similar effects were described among migrating African subgroups. Type 2 diabetes prevalence among black Africans aged over 55 years ranged from 2.9% among blacks living in Nigeria, 15.9% for blacks living in Jamaica, 20.5% for blacks in Manchester (UK) and 25.7% for blacks living in Maywood (USA)[86].

### *Emerging Trends Worldwide*

Epidemiological studies provide overwhelming evidence that the prevalence of diabetes is increasing steadily in many nations. The diabetes 'epidemic' relates particularly to T2DM and is taking place in both developed and developing countries[78]. The region most likely to experience the brunt of this increasing prevalence is Asia. Here, T2DM could become 2 to 3 times more frequent in the coming decade than it is at present. By 2010 Asia is expected to hold 61% of the total global projected number of people with diabetes[78], not only because it is the most populous continent on earth, but also because urbanisation will increase and life expectancy will improve. By 2030, India, China and the U.S.A. are expected to have the most numbers of people with diabetes.[79]

Part of the problem derives from public health achievements that have resulted in people living longer. This 'epidemiological transition' has occurred in developed countries in the past 50 years and now affects many developing countries. The transition has catapulted T2DM from a rare disease at the beginning of the 20$^{th}$ century to a major global contributor to morbidity and mortality in the 21$^{st}$ century. Other factors that underlie the increase in diabetes, including T2DM in children, include an increasing prevalence of obesity and a sedentary lifestyle[87] and increases in the proportion of the population aged over 65[79].

Overall data from different countries indicate an expected doubling of the current world diabetic population by 2025[78;88-92]. Further, the majority of this increase is likely to occur in developing countries where health resources are already inadequate. A 42% increase in diabetes prevalence (from 51 to 72 million persons) is estimated for developed countries, compared with an estimated 170% increase (from 84 to 228 million persons) in developing countries[77].

### *Epidemiology of Diabetes in Australia*

Limited data are available for the prevalence and incidence of diabetes in Australia, and even fewer reports of prevalence and incidence among Aboriginal Australians.

#### *Adults*

The Australian Diabetes, Obesity and Lifestyle (AusDiab) study, the Melbourne Visual Impairment Project (MVIP), and the Blue Mountains Eye Study (BMES) were each well-defined cross-sectional population surveys. The AusDiab group surveyed a total of 42 randomly selected urban and non-urban areas across 6 states and the Northern Territory, while the MVIP examined 9 randomly selected pairs of adjacent Census districts in urban Victoria and 4 randomly selected pairs of adjacent Census districts in rural Victoria. The BMES surveyed 2 adjacent postcode areas in the Blue Mountains representative of the population in NSW. Information on the epidemiology of diabetes in the Australian Aboriginal population was obtained from surveys of remote Australian Aboriginal settlements representative of the spectrum of remote settings in which Aboriginal Australians reside.

In 2002, the AusDiab group reported a diabetes prevalence of 8.0% in adult men and 6.8% in adult women from a nationwide cross-sectional survey[93]. The diabetes prevalence among persons aged 25-34 years was 0.3% and increased to 23.0% among those aged 75 years or older. These data reveal that the prevalence of diabetes has more than doubled since 1981[93]. An additional 17.4% of men and 15.4% of women had impaired glucose tolerance or impaired fasting glucose[93]. Given these rates, it could be reasonably expected that the prevalence of diabetes will continue to increase in Australia.

Cross-sectional data from the BMES (New South Wales) found a diabetes prevalence of 7.8% during 1992-94 which increased six years later to 9.9% in persons aged over 49 years[94;95]. The overall 10-year incidence of diabetes and impaired fasting glucose was 9.3% and 15.8%, respectively. Participants with metabolic syndrome at baseline had a higher risk of incident diabetes than those without metabolic syndrome (29.2% versus 8.6%)[96].

The MVIP (Victoria) reported a 5.1% prevalence for self-reported diabetes[97] among persons aged over 40 years, and found no significant urban-rural diabetes prevalence differences.

Daniel *et al.* pooled data from Aboriginal populations screened for diabetes in 15 remote settlements in central, northern and northwest Australia between 1983 and 1997. The diabetes prevalence, adjusted for age and gender, was 15%; the age-gender-adjusted IGT prevalence was also 15%[98]. In an 8-year prospective study of two remote central Australian Aboriginal communities, the incidence of diabetes among persons aged over 15 years was reported to increase from 11 to 47 cases per 1000 person-years, which rates amongst the highest reported incidence rates worldwide[99]. In a further 8-year follow-up study between 1987 and 1995, the prevalence of diabetes had increased from 11.6% to 20.7% in a central Australian Aboriginal community[100]. In 2007, Hoy[101] reported that the rate of diabetes in persons age 25 to 74 years in three remote Aboriginal communities were 5.4-10-fold higher than that in the nationwide AusDiab study.

#### *Children and adolescents*

A few studies used the NSW Diabetes Register to examine the incidence of diabetes. Taplin and others report that the incidence of childhood onset of T1DM increased from a mean age-standardised 17.8 per 100,000 person-years in 1990-1996, to 20.9 per 100,000 person-years in 1997-2002[102]. Overall, the incidence increased by 2.8% per year and with increasing age.

Craig and others documented incident cases of diabetes in young people aged less than 19 years between 2001-2006 from the NSW Diabetes Register[103]. Among 10-18 year olds, they reported

mean annual incidences of T1DM in 21.1 per 100,000 persons and of T2DM in 2.5 per 100,000 persons. Although the incidence of T1DM was similar in the indigenous and non-indigenous groups, the incidence of T2DM was around 6 times higher in the indigenous compared to the non-indigenous group. Of the 128 incident cases with T2DM, the median age was 14.5 years; 90% were obese or overweight.

## 1.3 Diabetic Retinopathy: Definition and Types

Diabetic retinopathy (DR) may be defined as the presence of typical retinal microvascular lesions in an individual with diabetes. Microaneurysms (Ma), haemorrhages, hard exudates (HEx), cotton wool spots (CWS), intraretinal microvascular abnormalities (IRMA), venous beading (VB), new vessels and fibrous tissue comprise the clinical features of DR. However, no individual lesion is specific for diabetes, as each may occur in other disease processes such as hypertension, hyperviscosity, inflammation or radiotherapy. It is the pattern and evolution of the lesions that characterises DR.

### *Non Proliferative Diabetic Retinopathy*

DR is first evident ophthalmoscopically as non-proliferative (previously termed 'background') retinopathy (NPDR), which is characterised by Ma, dot, blot or flame haemorrhages, HEx, CWS (soft exudates), IRMA and VB.

### *Proliferative Diabetic Retinopathy*

The proliferative stage of diabetic retinopathy (PDR) is characterised by the growth of abnormal new vessels and subsequent fibrous proliferation in response to retinal ischaemia, as well as the development of pre-retinal or vitreous haemorrhage. If new vessels appear on or within one disc diameter of the disc margin, they are known as new vessels on the disc (NVD). In any other location, they are referred to as new vessels elsewhere (NVE).

### *High-Risk Proliferative Diabetic Retinopathy*

The Diabetic Retinopathy Study (DRS) identified patients with "high-risk characteristics" (HRC) of PDR with a poor visual prognosis[104]. These HRC are (1) NVD $\geq$ ⅓ disc area in extent, or (2) any NVD with vitreous or pre-retinal haemorrhage, or (3) NVE $\geq$ ½ disc area in extent associated with vitreous or pre-retinal haemorrhage, or (4) vitreous or pre-retinal haemorrhage obscuring $\geq$ 1 disc area.

### *Diabetic Macular Oedema*

Capillary leak in the macular or perimacular region results in retinal thickening or diabetic macular oedema (DME), defined as thickening located within two disc diameters of the centre of the macula. When this is present within or close to the central macula, it is termed clinically significant macular oedema (CSME)[105].

## 1.4 Prevalence and Incidence of Diabetic Retinopathy Worldwide, in Australia, and Trends

**Key Points**

- Overall, between 25 and 44% of people with diabetes have some form of DR at any point in time. A recent large meta-analysis pooling data from 8 population-based studies of older groups reported an overall DR prevalence of 40%. The prevalence of sight-threatening retinopathy (PDR or CSME) varies principally with the known duration of diabetes, with some influences from age and type of diabetes.
- Projections from these data indicate that around 300,000 Australians have some DR and that 65,000 have sight-threatening retinopathy (PDR or CSME).
- From earlier reports from the WESDR study to more recent reports from the UKPDS, Liverpool DR Study, and the BMES, the incidence of DR appears to have decreased.
- The most recent Australian DR prevalence data derive from the AusDiab Study, which found an overall DR prevalence of 25.4%, with PDR in 2.1%.
- Few Australian DR incidence data are available, with recent annual incidence lower at 4.5% in the BMES compared to 8.0% in the older Newcastle study.
- Typical retinopathy lesions are also found in older persons without diabetes (possibly due to hypertension and other conditions), with the prevalence varying from 7.8% (BDES) to 9.8% (BMES)

### Prevalence of Diabetic Retinopathy Worldwide

In 2002, WHO reported that DR caused 4.8% of blindness globally[106]. A number of population-based studies have assessed the prevalence of diabetes and DR. Other surveys targeted persons with type 1 or type 2 diabetes using a diabetes register or similar means of patient identification. While there appears to be considerable variability in the prevalence of DR from these reports, an emerging trend is that the DR prevalence after long duration may be higher in persons with T1DM than in T2DM. Differences in the methods of ascertainment, however, make direct comparisons difficult.

### Population Studies

Diabetic retinopathy (DR) is the leading cause of blindness among persons aged 20-64 years in the United States (US)[107] and is the most common complication of diabetes[108], with some form of DR present in around 25%-33% of persons with diabetes at any time. After a duration of 10 years, around 7% of persons with diabetes have retinopathy, rising to 90% after 25 years[107]. In persons diagnosed with diabetes before age 30 years, the prevalence of proliferative retinopathy (PDR) is around 25% after 15 years and 55% after 20 years. In persons diagnosed after age 30 years, the PDR prevalence is 20% after 20 years[107].

#### *Type 1 diabetes*

Pooled data from two US studies of T1DM (Wisconsin Epidemiologic Study of Diabetic Retinopathy, WESDR, and the New Jersey 725 study) found prevalences for any DR and sight-threatening retinopathy of 82% and 32%, respectively[109].

#### *Type 2 diabetes*

The Aravind Medical Research Foundation Eye Disease Survey in the Palakkad district of the state of Kerala in southern India followed a population aged 50 years or older with self-reported diabetes and reported a DR prevalence of 27%[110], similar to the 22% DR prevalence reported from an urban population in Hyderabad in the Indian state of Andhra Pradesh[111].

The US National Eye Institute pooled data from 8 well-conducted population-based studies[112] of persons aged 40 years or older with consistent retinopathy grading from retinal photographs. Data included that from five US studies, one West Indian study and two Australian studies (Blue Mountains Eye Study, BMES, and Melbourne Visual Impairment Project, MVIP). The overall crude DR prevalence was 40%[112]. The prevalence of sight-threatening retinopathy (CSME or PDR) was 8.2%. The general US population prevalences of DR and sight-threatening retinopathy were 3.4% (4.1 million persons) and 0.8% (900,000 persons), respectively. Projected to the current Australian population, these rates suggest prevalences of 300,000 and 65,000 for any DR and sight-threatening retinopathy, respectively, in persons aged over 40 years.

### *Targeted Diabetes Patient Studies*

Numerous case series report the prevalence of DR identifying patients from diabetes registers or diabetes clinics. The studies listed below are not comprehensive. All report an increasing rate and severity of DR with increasing duration since diagnosis.

#### *Type 1 diabetes*

The Diabetes Control and Complications Trial (DCCT), a multi-centre clinical trial of 1613 volunteer type 1 diabetic subjects, reported that 44% of subjects with duration of T1DM less than 5 years had DR[113]; an additional 7% had very mild retinopathy present only on fluorescein angiography (FA). DR was observed in 19% of subjects with duration of diabetes less than 1 year; the prevalence progressively increased to 48% of subjects who had had diagnosed diabetes for 5 years.

A cross-sectional population survey using a Swedish childhood diabetes register of relatively young T1DM patients aged over 9 years but diagnosed before age 15 years reported a DR prevalence of 15%[114]. The prevalence increased from 4% in patients who had had diabetes less than 2 years to 32% among those who had had diabetes between 10 and 12 years[114]. A second Swedish study, also a cross-sectional population survey using a diabetic incidence register of all newly diagnosed diabetics aged 15-34 years, observed a 39% prevalence of DR 10 years after diagnosis in a nationwide population-based cohort of T1DM aged 15-34 years[115].

A French study of 504 children and adolescents aged 10-18 years (mean 13 years) attending summer camps with a mean T1DM duration of about 5 years, found mild NPDR in 4.6%[116]. Those with DR had a longer duration of diabetes.

#### *Type 2 diabetes*

The Atherosclerosis Risk in Communities Study examined persons with diabetes (mean duration 7 years) aged 51-72 years. Retinopathy was detected in 328/1600 (20.5%) of those with diabetes, 28/1600 (1.8%) had proliferative diabetic retinopathy, and 27/1662 (1.6%) had macular oedema[117]. An Irish hospital survey of patients diagnosed with diabetes after age 70 years reported an overall DR prevalence of only 14%[118]. Patients with DR had a significantly higher median duration of diabetes (5.0 years) compared with those patients without DR (3.5 years).

One south Indian series of 448 consecutive newly diagnosed type 2 diabetic patients attending a diabetes centre found 7.3% had retinopathy[119]. In a rural Thai series of 3049 patients, mostly aged 21 years and older, attending 13 community diabetes clinics, 78.1% had no DR, 18.9% NPDR and 2.9% PDR[120]. Rates of DR almost tripled in those with diabetes diagnosed 10-15 years (43.5%), compared with those with diagnoses less than 5 years (15.3%).

### *Impaired glucose tolerance*

The Diabetes Prevention Program Research Group followed persons with elevated fasting glucose and impaired glucose tolerance, but no history of diabetes over a mean of 3.1 years. DR was found in 12.6% of persons who developed diabetes, compared to 7.9% in those without diabetes[121].

## *Incidence of Diabetic Retinopathy Worldwide*

### *Type 1 diabetes*

The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), a prospective cohort study, reported DR incidence in a 14-year follow-up of a defined diabetic population in southern Wisconsin and provided DR incidence data for T1DM (diabetes onset before age 30 years). The incidence of any retinopathy after 14 years was 96% among those with no retinopathy at baseline. Over the period, 37% developed PDR and 28% developed DME[122].

### *Type 2 diabetes*

The United Kingdom Prospective Diabetes Study (UKPDS) followed 1919 patients with newly diagnosed T2DM. Of these, 1216 had no retinopathy at baseline. The 2001 report described the 6-year incidence of DR. Over this period, 41% of patients without retinopathy at baseline had developed retinopathy lesions[15]. Of those with DR at baseline, 29% progressed by two or more steps on the ETDRS scale over the 6 years[15].

The Liverpool study[123;124] was a prospective study of patients with T2DM registered with enrolled general practices who had retinopathy data available at baseline and at least one further screening event. The annual incidence of sight-threatening DR in patients without retinopathy at baseline was 0.3% in the first year, rising to 1.8% in the fifth year[123]. The cumulative 5-year incidence of any retinopathy, sight-threatening maculopathy, or sight-threatening DR was 31%, 3.2% or 3.9%, respectively[123]. The incidence of sight-threatening DR in patients increased over time and with the presence and severity of retinopathy lesions at baseline. These results were similar to those found in the BMES (see below).

Data from the BMES[95], Liverpool Diabetic Retinopathy Study[123] and the UKPDS[15] indicate that incidence rates for any new retinopathy and for the incidence of vision-threatening stages (PDR or DME) are around half those recorded previously by the WESDR[122;125] and the Newcastle Diabetic Retinopathy Study[126;127], both conducted 15-20 years earlier. This difference in reported DR incidence may relate in part to the different duration of diabetes in participants of the three studies together with changes in glycaemic control. The WESDR reported that its participants had a mean duration of diabetes of 12 years, compared to newly diagnosed diabetes in the UKPDS and 3-7 year diabetes duration in the Liverpool study.

The Mauritius Diabetes Complication Study reported a six-year incidence of DR and sight-threatening retinopathy of 23.8% and 0.4%, respectively.[128]. Janghorbani *et al.*[129] provided DR incidence rates in patients attending an endocrinology clinic in Iran without DR at baseline. Of 436 patients with T2DM, DR incidence was 45% over an average follow-up period of 5.4 years. The 113 insulin-treated patients with T2DM had a slightly higher DR incidence (108.4 per 1000 person years) than patients treated without insulin (83.4 per 1000 person years)[129].

Overall, studies suggest that the incidence of diabetes is increasing, whilst the incidence of DR is decreasing.

## *Epidemiology of Diabetic Retinopathy in Australia*

### *Prevalence of Diabetic Retinopathy in Australia*

Few Australian data were available since 1996, with only three studies identified. Two were studies of defined general older community-based samples (BMES and MVIP) and the third was an Australia-wide sample of adults aged 25 years or older (AusDiab).

The AusDiab study was an Australia-wide study of 11,247 adults aged 25 years or older from 42 randomly selected urban and rural communities[130]. Overall, 25% of participants with known diabetes had DR, including 2.1% with PDR, with the prevalence strongly related to the known duration of diabetes. DR prevalence was 9.2% among those with duration less than 5 years, 23% for durations between 5 and 9 years, 33% for durations 10-19 years, and 57% for those with duration of 20 or more years. Among persons found to have newly diagnosed diabetes (i.e. undetected diabetes), the DR prevalence was 6.2%[130]. After accounting for duration of diabetes, the prevalence findings from these three Australian studies are relatively similar.

The Melbourne Visual Impairment Project (MVIP) reported a DR prevalence of 29% among persons aged 40 years or older with self-reported diabetes[108]. The prevalence of untreated, vision-threatening retinopathy in this population was 2.8%[108]. The Blue Mountains Eye Study (BMES) reported a DR prevalence of 32% among persons in people with known or newly diagnosed diabetes[131], and that 1.6% had signs of PDR and 5.5% had DME. Among people found to have undiagnosed diabetes, 16% had DR16%[131]. Neither study found gender differences in DR prevalence.

The Newcastle Diabetic Retinopathy Study (an 11-year longitudinal study of people with diabetes from all age groups attending regional diabetes services) is the largest reported Australian study of DR, and reported an overall DR prevalence of 35%[126;132-134].

It is important to recognise that typical retinopathy lesions (retinal microaneurysms and haemorrhages) are also found in persons without diabetes, and are presumably caused by factors such as hypertension, atherosclerosis, carotid disease, blood dyscrasias, inflammatory and other retinal diseases. The prevalence of retinopathy in non-diabetic subjects was previously thought to be rare, from data using clinical examinations[135;136]. However, two studies that have graded stereo retinal photographs have demonstrated retinopathy prevalence rates of 7.8% (BDES)[137;138] and 9.8% (BMES)[139].

### *Incidence of Diabetic Retinopathy in Australia*

Donaghue et al.[140] followed an incident cohort of children aged less than 15 years identified from the New South Wales Type 1 Diabetes register and National Diabetes Supply scheme, and examined them 6 years after diagnosis. Retinopathy was present in 24%, but the authors felt this figure to be an underestimate because non-responders were likely to be older.

The Newcastle Diabetic Retinopathy Study[126;133] followed 1210 diabetic clinic patients seen during 1977-78 and for a 10-year period. Overall, among diabetic patients without DR, around 8% per year developed DR. For those with NPDR, 7% per year progressed to vision-threatening retinopathy, either PDR or DME. For the group with diabetes onset before age 30 years, the incidence was 6%, 14%, 11% and 8% for diabetes duration of less than 5 years, 5-9 years, 10-14 years and 15-19 years, respectively. For the group with diabetes onset at age 30 years or older, corresponding DR incidence was 7%, 10%, 14% and 13% for the same duration intervals. Lower incidence rates were reported for persons with diabetes duration 20 years or longer.

The MVIP examined 121 out of 169 self-reported persons aged 40 years or older with diabetes at baseline in 1992-1994 and 5 years later. This study reported an 11%, 2.9% and 8% 5-year incidence of any DR, PDR and DME, respectively[141].

The cumulative 5-year incidence of DR in the BMES (2335 persons aged 50 years or older examined on two occasions 5 years apart, 1992-4 and 1997-9) was 22.2%[142]. Retinopathy progression of 1 or more steps on the ETDRS scale was documented in 25.9%. Only 1.5% of persons with diabetes developed PDR over 5 years, including only 4.2% of those with any retinopathy. The 5-year incidence of new DME was also only 4%. The equivalent 5-year incidence rates from the 20-year old WESDR data (projected from the 10-year data)[125;143] included DR and DME incidence rates of 40% and 13%, respectively, for patients with T2DM treated with insulin. Corresponding rates were 33% and 7% for type 2 patients not treated with insulin. Projected 5-year incidence from the Newcastle Study for all T2DM cases was around 60% for any retinopathy and around 25% for any vision-threatening DR (PDR and DME).

While body-mass-index-specific diabetes incidence rates in Australian Aboriginal people are reported as among the highest in the world[98], only one study has provided DR prevalence and incidence data. The Katherine Region Diabetic Retinopathy Study performed two cross-sectional surveys in 1993 and 1996[144]. It found a lower 5-year annual incidence (5.6%) compared to the overall Australian diabetic population (8%). However the rate of progression from no retinopathy to vision-threatening retinopathy was 1.2% per year.

### *Trends in Diabetic Retinopathy*

#### *Type 1 diabetes*

Several studies report declining severity and incidence of retinopathy. The Linköping Diabetes Complications Study, Sweden, followed 269 persons with T1DM diagnosed between 1961-1985[145]. The cumulative proportion of severe retinopathy (defined as laser-treated retinopathy) increased after 10 years of diabetes. However, after 25 and 30 years duration, the cumulative proportion of severe retinopathy had declined. After 25 years duration it was 47%, 28% and 24% in the 1961-1965, 1966-1970 and 1971-1975 cohorts, respectively.

The Wisconsin Diabetes Registry Study[146] followed 474 persons with incident T1DM for 4-14 years during 1990-2002. The prevalence of retinopathy increased with duration of diabetes, from 6% at four years to 73% at 14 years, and was highest among adults (20 years and older). Risk of developing retinopathy increased with increasing duration and worse glycaemic control. These prevalence rates were lower than expected compared to the population-based WESDR, conducted 1979-1980, which reported a prevalence of 74% at 9-10 years duration and 95% at 13-14 years duration[122].

#### *Type 2 diabetes*

The BMES reported a DR prevalence among participants with diabetes of 29.4% in 1992-1994 and 33.4% in 1997-2000[95], similar to the small increase reported by the MVIP of 29% in 1992-1996 and 35.7% in 1997 [108;141]. Over the six years, the BMES observed a higher prevalence of mild NPDR (increasing from 19.6 to 27.7%), but lower prevalence of moderate to severe NPDR (decreasing from 8.3 to 4.5%) and PDR (from 1.4 to 1.2%)[95].

These trends suggest that improvements in caring for diabetes and associated risk factors such as hypertension may have contributed to the lower DR prevalence and reduced severity observed.

**Table 1.4.1: Characteristics of Australian diabetic retinopathy (DR) studies**

| Study & year | Study population | Sample size (participation rate %) | Diagnostic methods | Diagnostic criteria | Potential bias or pitfalls |
|---|---|---|---|---|---|
| Newcastle NSW 1977-78[132;133] (a, b)<br>1977-88[126] (c) | a) diabetic clinic<br>b) known diabetes in Singleton, NSW<br>c) diabetic clinics and education programs | a) 1210 (98%)<br>b) 99 (94%)<br>c) 5519 (unknown) | fundus photography | US Diabetic Retinopathy Study protocol, 1973[147] | Selection bias could have overestimated DR prevalence |
| Melbourne Visual Impairment Project 1993-4[97] | Cluster sampling method, random pairs of Census districts, Victoria<br>Selected city and rural households<br>Age >40 years old | 5520 (86%) | ophthalmoscopy<br>fundus photography | ETDRS, 1991 | N/A - Good participation rate of population including rural & urban Victoria |
| AusDiab study 2003[130] | Australia-wide sample<br>Age ≥25 years old | 11,247 (55.3%) | Non-mydriatic fundus photography | Simplified version of the Wisconsin Grading System | Selection bias from low participation rate |
| Blue Mountains Eye Study 1992-3[131] | Population based survey, door-to-door census in 2 postcode areas, west of Sydney, NSW<br>Age ≥49 years | 4433 (82.4%) | fundus photography | Modified Airlie House classification used in ETDRS | N/A – Good participation rate, population representative of Australian population (Australian Bureau of Statistics) |

**Table 1.4.2: Prevalence of diabetic retinopathy (DR) in Australia**

| Study | Number of people examined | DR prevalence (%) in persons with diabetes | | | |
|---|---|---|---|---|---|
| | | any retinopathy | vision-threatening retinopathy | | |
| | | | proliferative | macular oedema | combined |
| Newcastle NSW 1977-78[132;133] (a,b) 1977-88[126] (c) | a) 1210<br>b) 99<br>c) 5519 | a) 49<br>b) 36<br>c) 35 | a) 7<br>b) 3<br>c) 5 | 10<br>6<br>10 | 15<br>11<br>11 |
| Melbourne Visual Impairment Project; 1993-4[108] | 4744/ 5520 | 29 | 4 | 6 | NS |
| AusDiab study 2003[130] | 6220/ 11247 | 15 | 2* | NS | NS |
| BMES 1992-3[131] | 3654/ 4433 | 32 | 2 | 6 | 7 |

NS=not stated

*among persons with known diabetes

**Table 1.4.3: Annual incidence (rate % per year) for development of any retinopathy lesions in 1210 diabetic subjects first examined in Newcastle 1977-78, Australia**

| | Duration of diabetes (years) | | | | | |
|---|---|---|---|---|---|---|
| Age at onset | <5 | 5-9 | 10-14 | 15-19 | 20-29 | 30+ |
| <30 years | 6 | 14 | 11 | 8 | 0 | 0 |
| 30+ years | 7 | 10 | 14 | 13 | 9 | 0 |

## 1.5 Pathogenesis of Diabetic Retinopathy

**Key Points**

- Many biochemical pathways link the altered glucose metabolism seen in diabetes directly to development and progression of diabetic retinopathy.
- DR has a multifactorial pathogenesis, involving many pathways linked to glycaemia (aldose reductase, protein glycation, protein kinase C activation, angiotensin enzyme expression, vascular endothelial growth factor expression, and others). New therapies may target these pathways.
- These biochemical changes are accompanied by increased blood retinal barrier permeability and initially by increases in retinal blood flow.
- Widened venular calibre is a marker of retinopathy severity.

Animal studies of DR[148-150], large randomised control trials (RCT) such as the DCCT[151-153] and epidemiological data[154;155], emphasise the critical relationship between glycaemic control to the development and progression of DR. Chronic hyperglycaemia is now accepted as the common pathway leading to DR[156-159]. Many different pathways link glucose metabolism to the development of DR, including the sorbitol or aldose reductase pathway, increased protein kinase C activity with increased vasodilatory prostaglandins, increased non-enzymatic glycation of proteins and development of advanced glycation end products, increased production of vascular endothelial and other growth factors in the retina, glucose-induced auto-oxidative damage, as well as retinal capillary blood flow changes and increased capillary bed permeability.

### *Aldose Reductase (Sorbitol) Pathway*

Aldose reductase is an integral enzyme in the polyol pathway and catalyses the reduction of glucose to sorbitol. Sorbitol accumulates during hyperglycaemia[158;160]. This causes osmotic damage to vascular cells[161], damages retinal pericytes, via apoptosis, and thickens retinal vascular endothelial cell basement membranes leading to closure of retinal capillaries[156]. These changes have long been identified as the key early lesions of DR[162;163]. The loss of pericytes is thought to play a crucial role in the development of DR. Studies show that pericytes synthesise transforming growth factor ß and inhibit proliferation and migration of vascular endothelial cells. Loss of pericytes contribute not only to vasodynamic changes in the early stage of diabetic retinopathy, but also to neovascularisation in PDR[164]. Inhibition of aldose reductase arrests the impairment of pericytes[164;165]. Aldose reductase inhibitors (ARIs) also have the potential to influence the sorbitol pathway[166;167] and have been the subject of RCT.

### *Nonenzymatic Glycation and Advanced Glycation End Products (AGE)*

Nonenzymatic glycation (glycosylation) of many proteins accompanies diabetes and may play a significant role in the pathogenesis of DR[168;169]. During the normal course of ageing, proteins become irreversibly modified by blood sugars. High levels of serum glucose accelerate this protein modification. Glucose binding to protein side chains results in the formation of non-functional products termed *advanced glycation end products* (AGEs). Formation of AGEs damages cells by impairing the function of proteins, including extracellular structural proteins and matrix components, such as collagen[170]. AGEs can also alter cellular adhesion and cause functional changes associated with DR. By binding to receptors they produce a cascade of cellular signaling events leading to the activation of protein kinase C[170]. Persons with PDR and DME have markedly higher serum[171;172] and vitreous[173;174] AGE levels than those without diabetes. Inhibitors of AGE formation are being investigated.

### *Protein Kinase C Activation*

A large body of evidence indicates that protein kinase C (PKC) plays a major role in hyperglycaemia-induced microvascular dysfunction in diabetes. Increased flux through the polyol pathway[158] and the generation of AGE and oxidative species result in enhanced generation of diacylglycerol, a physiologic activator of the PKC pathway[175]. PKC is a family of related enzymes which function as signaling components for a variety of growth factors, hormones, neurotransmitters and cytokines[176]. PKC activation results in numerous cellular changes, which lead to basement membrane thickening and increased production of vasodilatory prostaglandins, which in turn affect vessel permeability and/or blood flow. Although the activity of many PKC isoforms is increased in vascular tissues in diabetes, many studies suggest that the PKC-beta isoform is preferentially activated[176-178]. PKC-beta was found to be an integral component of cellular signaling by vascular endothelial growth factor (VEGF), one of the most important mediators of ocular neovascularisation. In addition, PKC-beta is considered to influence smooth muscle contractility, and to increase basement membrane protein synthesis and endothelial permeability[175]. A wide array of PKC inhibitory compounds with varying degrees of isoform selectivity is currently being assessed for their potential to arrest DR progression[179].

### *Angiotensin Expression*

The renin-angiotensin system is widely expressed in the eye[180-182]. Gene expression of renin, angiotensinogen and angiotensin-converting enzyme (ACE) have been demonstrated[182] with production by vascular endothelial and retinal pigment epithelial cells[183]. Raised concentrations of intraocular and serum ACE, prorenin and angiotensin II are correlated with the severity of DR[180;181;184]. Non-haemodynamic effects of angiotensin II include regulation of cell growth via expression of growth factors, including VEGF. Angiotensin II influences blood pressure, increases vascular permeability (possibly via VEGF expression) and may act as an angiogenic factor[180;184]. Other studies have shown that development of new retinal vessels in animal models of retinopathy of prematurity can be inhibited by treatment with ACE inhibitors or angiotensin II type 1 ($AT_1$) receptor blockers[183]. A number of agents that influence the renin-angiotensin system are being explored as potential therapies for DR.

### *The Coagulation Pathway*

There is increased activation of the coagulation pathway in DR. The occurrence of DR is connected with higher levels of plasma prekallikrein[185]. The kallikrein-kinin system is linked by a number of molecules that also participate in the renin-angiotensin system[186]. The pathogenic actions of the renin-angiotensin and kallikrein-kinin systems in many tissues, including the retina in diabetes, are mediated by VEGF and connective tissue growth factor[186]. Elevated vitreous levels of extracellular carbonic anhydrase-I detected in persons with DR, may induce increased kallikrein activity with generation of factor XIIa[187].

### *Angiogenesis and Production of Vascular Endothelial Growth Factor (VEGF)*

Considerable research has investigated factors that could stimulate or inhibit retinal blood vessel proliferation and identified many 'growth factors' [157;188-190], including basic fibroblast growth factor (bFGF), insulin-like growth factor (IGF), VEGF, platelet-derived growth factor (PDGF), and pigment epithelial-derived factor (PEDF) . Tissue immunocytochemical studies have localised FGF in patients with diabetic neovascularisation[157;191]. Elevated serum IGF-1 levels have been measured in patients with PDR, both in early-onset[192] and late-onset diabetes[193]. VEGF, a multifunctional cytokine expressed and secreted by many cells, induces angiogenesis and strongly increases vascular permeability[194]. It alters the blood-retinal barrier [195] and is increased in the vitreous of eyes with PDR[196-198]. A role for PDGF ligands and receptors has been postulated in the pathogenesis of different proliferative diseases, including PDR[199]. Release of these factors in response to ischaemia is hypothesised in the pathogenesis of DR[200]. PEDF however inhibits AGE-induced T-cell adhesion

to microvascular endothelial cells by suppressing ICAM-1 expression, and could play a protective role against early DR[189].

Patients with PDR have increased retinal VEGF production as well as an altered expression patterns of VEGF receptors[201]. VEGF is present in both angiogenic and anti-angiogenic isoforms. In the eyes of patients with diabetes, VEGF splicing is switched from anti- to pro-angiogenic isoforms[202]. In-vitro studies indicate that angiotensin II stimulates the secretion of VEGF by vascular smooth muscle cells, mesangial cells and pericytes. These cells have receptors for angiotensin II which stimulate cell growth and up regulate VEGF mRNA expression[184]. Induction of VEGF requires hyperglycaemic or oxidative conditions[203]. VEGF has been implicated in the pathogenesis of PDR[176;184;204;205] and DME[206;207]. VEGF inhibitors (pegaptanib, bevacizumab and ranibizumab) are currently being evaluated for treatment of both PDR and DME.

Levels of other angiogenic factors such as erythropoietin[208] and angiopoietin-2[209;210] have also been found to be higher in the vitreous fluid of patients with PDR compared to non-diabetic patients. Erythropoietin appears to act independently of VEGF[208], whereas angiopoietin-2 appears to act synergistically with VEGF[209]. Reduced somatostatin expression may also be an early event in DR[211].

### *Inflammation*

Chronic or low-grade inflammation and endothelial cell dysfunction are hypothesised to play a role in the pathogenesis of DR. Numerous studies have measured the concentrations of many different inflammatory chemokines in the serum, vitreous or aqueous of patients with DR[190;212-217]. Inflammatory mediators studied include: prostaglandins (PgE1, PgE2), C-reactive protein (CRP), soluble intercellular adhesion molecule-1 (sICAM-1) and stromal cell-derived factor (SDF-1α). Their complex interactions are not well understood. One animal study has shown that hypertension increases retinal inflammation (as measured by VEGF, ICAM-1 levels) and suggested that this could be a mechanism for aggravating DR[218]. The mechanism by which VEGF interacts with inflammatory mediators remains uncertain.

### *Retinal Blood Flow Changes in Diabetic Retinopathy*

Laser Doppler studies have shown that DR increases retinal blood flow in comparison with non-diabetic controls and in diabetic subjects without DR[219]. However, in the presence of severe capillary non-perfusion and PDR, blood flow rates are reduced[220]. Dilation of larger retinal arterioles[221;222] appears to counteract increasing resistance in smaller vessels[221], leading to vascular leakage[222]. Retinal capillary pericyte contractility is inhibited by high glucose concentrations, consistent with the hypothesis that increased retinal blood flow is involved in the early pathogenesis of DR[223].

Nitric oxide (NO) is an inorganic, labile gaseous molecule released from endothelial cells and perivascular nitrergic neurons, and plays an important role in the homeostasis of vasodilation and blood flow[224;225]. Endothelial NO has antiplatelet, antithrombotic, antiproliferative and anti-atherosclerotic actions[225]. However, massive NO production expressed under the influence of inflammatory mediators induces neuro-degeneration and cell apoptosis. Plasma and vitreous nitrite/nitrate levels may be higher in persons with than without diabetes[225;226].

The control of hypertension and hyperglycaemia can alter blood flow changes and reduce DR. Biochemical, haemodynamic and hormonal mechanisms may interact together to produce the typical lesions of vascular occlusion, microaneurysms, haemorrhages, hard exudates and new vessels[227]. Increased retinal blood flow is thus initiated by high blood glucose levels and exacerbated by high blood pressure (BP)[228] and impaired autoregulation. High glucose levels have a direct damaging effect on both pericytes and endothelial cells, with further vessel wall damage,

occlusion of vessels and ischaemia, resulting in PDR[227]. These studies support the early and effective treatment of elevated BP levels in diabetes[229].

### *Blood-retinal Barrier Changes*

Breakdown of the blood-retinal barrier occurs as part of the process leading to DR. Pericyte survival relies on signals derived from extracellular matrix proteins. Proteolytic enzymes, such as matrix metalloproteinases, degrade the supporting extracellular matrix. Elevated expression of matrix metalloproteinases may contribute to the increased vascular permeability in DR[230]. Vitreous fluorophotometry studies[231;232] demonstrate that in patients with DR, the blood-retinal barrier is stable until puberty, then progressively declines[233]. This early sign may also predict an unfavourable course over the long-term[234].

### *Retinal Vascular Changes*

Many studies show that retinal vascular changes occur early in the course of diabetes, and variations in calibre may reflect structural and/or functional alterations in blood flow[235]. In the WESDR, both wider arteriolar and venular diameters were associated with progression of DR, with venular calibre particularly associated with PDR and risk of nephropathy[236;237]. Data indicate that increases in venular calibre predict worsening DR[238] and other complications[239].

### *Pregnancy*

Glycodelin is a glycoprotein released by secretory endometrial glands with immunomodulatory properties. It inhibits several inflammatory mediators including E-selectin, a key protein in leucocyte-endothelium adhesion. Low glycodelin concentration is associated with DR progression in pregnant women with T1DM[240]. It is postulated that low levels of glycodelin increase E-selectin-mediated leucocyte adhesion. Resulting endothelial damage, combined with the hyperdynamic circulation and proangiogenic parameters in early pregnancy, may lead to a progression of existing DR.

### *Other Factors*

**Homocysteine** is an amino acid important in vascular injury in peripheral and coronary artery disease. Hyperhomocystinaemia is a well-established independent risk factor for the development of vasculo-occlusive disease[207]. Patients with diabetes have two to three times the incidence of atherosclerosis compared to the general population[241]. Plasma homocysteine levels were significantly increased in diabetic patients with retinopathy compared with diabetic patients without retinopathy [242;243].

**Adiponectin**, a hormone secreted by adipocytes to regulate glucose and lipid metabolism, reverses insulin resistance in animal models. Plasma adiponectin concentrations are independently and significantly higher in persons with T1DM[244], but lower in persons with T2DM[245;246], compared with controls. Differences in the regulation of adiponectin in T1DM and T2DM and the relationship to microvascular and macrovascular disease are yet to be fully established.

## 1.6 Risk Factors Associated with Diabetic Retinopathy

**Guidelines**

1. Undertake a multidisciplinary approach in all patients with diabetes to achieve optimal glycaemic control (target $HbA_{1c}$ levels 7.0% or below) and to adequately manage blood pressure (target systolic blood pressure less than 130 mmHg) and serum lipids (target LDL cholesterol less than 2.5 mmol/L and target triglycerides <2.0 mmol/L); level I evidence (glycaemic control)[13;14]; level II evidence (blood pressure control)[14-16]; level II evidence (blood lipid control)[17-19].

**Key Points**

- All people with diabetes are at risk of developing retinopathy.
- Duration of diabetes is the strongest factor determining DR prevalence.
- The most important systemic factors associated with increased risk of DR are:
  - Glycaemic control – evidence from RCT (DCCT, UKPDS) and large cohort studies (WESDR); any lowering of HbA1c will assist in reducing the development and progression of DR. For patients with DR, the target for HbA1c levels should be around 7%.
  - Blood pressure control – evidence from RCT (UKPDS) and cohort studies (WESDR); any lowering of blood pressure will assist in reducing the development and progression of DR. For patients with DR, the target for systolic blood pressure should be less than 130 mmHg.
  - Blood lipids – evidence from RCT (ETDRS) and cohort studies (WESDR); Normalising blood lipid levels may also benefit DR, particularly DME.
- A multidisciplinary approach to managing these three risk factors is needed.
- The DR risk associated with hyperglycaemia and hypertension is continuous, with no evident glycaemic or blood pressure threshold.
- Other documented risk factors include:
  - Renal impairment
  - Pregnancy
  - Candidate genes (ALR2, RAGE, TGF-beta1, VEGF, eNOS, MTHFR, IGF-1 and vitamin D receptor genes) – evidence from case-control studies.

### *Type of Diabetes*

Earlier studies suggested a greater long-term DR susceptibility among persons with T1DM than T2DM after comparable duration, although recent research reported a slightly higher risk in type 2 patients. This changing trend could indicate that recent improvements in metabolic control have been more effective in people with T1DM (evidence from cohort studies).

The Diabetes Incidence Study (cohort study) in Sweden registered patients aged 15-34 years with newly diagnosed diabetes and followed this cohort for 10 years[115]. The group included T1DM (79%), T2DM (12%), and a further 9% whose diabetes type could not be classified definitively. After 5 years duration, there was no significant difference in DR risk between type 1 and type 2 participants[115], while after 10 years, 37% of type 1 and 41% of type 2 cases had developed retinopathy. This contrasts with earlier studies that suggested a greater long-term risk among patients with T1DM. This trend could indicate that recent improvements in metabolic control have brought the DR risks in people with T1DM and T2DM closer together.

In a large Danish cohort study of 339 T1DM patients[247], the pre-pubertal duration of diabetes was estimated to have contributed twice as much to the development of DR than the post-pubertal

duration. These data emphasise the importance of tight diabetic control early in the course of diabetes.

### *Effect of Diabetes Duration on Diabetic Retinopathy*

- Duration of diabetes predicts the prevalence and severity of diabetic retinopathy (evidence from cohort studies).
- An earlier pre-pubertal diagnosis of diabetes may predict earlier development of diabetic retinopathy (evidence from cohort studies).

The duration of diabetes is strongly associated with the development and severity of DR[127;133;134;248-253]. Data from 5,500 patients seen in Newcastle, Australia[127;132-134] strongly demonstrate the relationship of diabetes duration to the prevalence of retinopathy in both T1DM and T2DM subjects.

#### *Type 1 diabetes*

In a longitudinal study, retinopathy did not develop before 2 years duration or before puberty[254]. The Pittsburgh Epidemiology of Diabetes Complications Study reported that NPDR was virtually universal after 20 years of T1DM and that PDR affected 70% of type 1 subjects after 30 years[252].

In type 1 subjects, the pre-pubertal or post-pubertal duration of diabetes may contribute differently to the development and progression of retinopathy[255;256]. In the WESDR, years of diabetes after menarche in girls with T1DM had a stronger association with prevalence and severity of retinopathy than years before menarche[256]. Data suggest that post-pubertal duration may be a more accurate determinant of development and progression of microvascular complications[254;255].

A small Swedish prospective cohort study of 29 patients with T1DM assessed the 10- and 15-year incidence and course of DR[257]. At entry to the study in 1982, the mean diabetes duration was 3.1 ± 1.9 years with no subjects having signs of DR. After 10 years, 39% of subjects had developed DR; the proportion increased to 80% after 15 years, including 20% of patients who developed vision-threatening retinopathy[257]. This incidence-duration relationship is similar to data reported by D'Annunzio *et al.*[258]. In a second study of 360 patients with T1DM aged less than 36 years recruited from a cohort study conducted in South East Sweden, 29% of subjects were reported to have DR after a mean diabetes duration of 9.5 years[259].

While there are consistent findings that the incidence of DR is strongly associated with the known duration of diabetes, data are conflicting on the influence of another risk factor, namely the pre-pubertal and pubertal onset of diabetes and its temporal relation to the development of DR.

A prospective German cohort study[260] of 441 children and adolescents with T1DM attending a paediatric hospital clinic between 1991 and 1996 assessed the age at which retinopathy was first diagnosed. All participants attended yearly fundus examinations. The median diabetes duration until first occurrence of DR was 16.6 years. This duration is longer than reported in the previous literature review and could have resulted from improved levels of metabolic control in recent years. The study reported that in children with a pre-pubertal onset of diabetes, retinopathy occurred after 10.9 years, compared with 15.1 years among children whose diabetes onset occurred during puberty[260]. This finding is supported by another prospective population-based cohort study[247] on 193 Danish children and adolescents, showing that in addition to diabetes duration and glycaemic control, the mean post-pubertal duration to retinopathy was significantly shorter (9.4 years) in pre-pubertal than post-pubertal onset diabetes (11.8 years). Furthermore, the EURODIAB Prospective Complications Study[261], a multi-centre cohort study recruiting patients aged less than 36 years of age with T1DM found that after a mean follow-up period of 7.3 years, 12.6% of 1,249 patients progressed to PDR. Multivariable logistic regression modeling indicated that metabolic control,

duration of diabetes and age at diabetes onset before age 12 years were significant predictors of progression to PDR, even when adjusted for presence of baseline retinopathy.

***Type 2 diabetes***

The Melbourne Visual Impairment Project, a population-based cluster sample of 4744 participants, reported a mean diabetes duration of 14.6 years among persons with DR, and a significantly shorter mean of 6.8 years duration of diabetes in those without DR[108].

A prospective Israeli cohort study of 833 patients with T2DM from a diabetic outpatient clinic reported that patients who developed retinopathy were younger at their mean onset of diabetes (age 48.7 years) and had longer mean diabetes duration (13.2 years) than patients who did not develop retinopathy (mean age 53.4 years; mean duration 6.1)[262]. The authors concluded that diabetes duration was a significant, independent variable for development of retinopathy[262]. A study of 926 patients with type 1 and type 2 diabetes recruited from 7 hospital clinics in different geographic regions of Malaysia reported a similar finding. For both forms, diabetes duration was strongly related to the risk of retinopathy[263].

A prospective population-based study followed 411 Pima Indian subjects in Arizona with T2DM from the time of diagnosis. NPDR was increasingly prevalent after 10 years, with moderately severe NPDR more frequent among those with diabetes duration between 10-25 years[264]. Further, a retrospective Irish cohort study of 150/230 patients with T2DM diagnosed after age 70 years reported a median diabetes duration of 5.0 years in those with DR and 3.5 years among those without DR[118].

While the reported studies demonstrate different risks of retinopathy for particular diabetes duration periods, a consistent trend of increased incidence with longer diabetes duration is evident. Variability among the different studies in diabetes duration after which retinopathy develops may have resulted from the influence of other risk factors, particularly the level of diabetes control achieved.

In contrast, a prospective New Zealand population-based study conducted between 1984 and 1997 of 286 T1DM patients under 20 years at diagnosis on the Canterbury diabetes register assessed the effect of diabetes duration on development of DR[265]. At baseline, 107 patients already had DR and had annual eye reviews. This study reported that 35.2% of 179 incident cases had diabetes for a mean 8.4-year duration, while the remaining 64.8% had diabetes for a mean of 3.6 years. The major predictors of retinopathy were duration of diabetes and glycaemic control. For each additional year that an individual had diabetes, expected mean time to development of DR decreased by 14%, controlling for other factors. This study did not find that peri-pubertal age at diabetes onset affected the time to DR[265].

### *Systemic Risk Factors*

The most important systemic factors associated with increased risk of DR are glycaemic control, blood pressure control and blood lipid control. A multidisciplinary approach to managing these factors is needed[266]. The Steno II trial showed that in T2DM patients, the implementation of behaviour modification techniques combined with pharmacological therapy targeting hyperglycaemia, hypertension, hyperlipidaemia and microalbuminuria, resulted in decreased progression of retinopathy, nephropathy and neuropathy[266].

### *Glycaemic Control*

RCT conducted to evaluate the effects of glycaemic control on DR are listed in Table 1.6.1 (adapted from Mohamed et al.). Optimal glycaemic control can be defined as $HbA_{1c}$ levels of 7.0% or below)[14].

Population-based studies have shown a consistent relationship between glycosylated (glycated) haemoglobin ($HbA_{1c}$) levels and the incidence and progression of DR[267]. Subjects in the WESDR with mean $HbA_{1c}$ levels over 12% were 3.2 times more likely (95% CI; 1.1-9.9) to have retinopathy after 4 years than subjects with $HbA_{1c}$ levels under 12%.

Two landmark RCT, the Diabetes Control and Complications Trial (DCCT) and the UK Prospective Diabetes Study (UKPDS), provided strong evidence that intensive glycaemic control slowed the onset and progression of DR in patients with type 1 and type 2 diabetes, respectively. Many other studies, including systematic reviews and meta-analyses of published trials[13;268], confirmed these findings [13;268](Level I evidence).

The DCCT was a US multi-centre RCT conducted between 1982 and 1993 to examine whether intensive glycaemic control of T1DM could decrease the frequency and severity of long-term diabetic microvascular complications[269-271]. This trial randomised 1,441 patients with T1DM to receive intensive glycaemic or conventional therapy. The DCCT found that, after 6.5 years of follow-up, intensive treatment (median $HbA_{1c}$ 7.3%) was associated with a reduction in progression (defined as a 3-step increase on the ETDRS retinopathy scale) of 76% in the group with no DR at baseline; and a reduction in progression of 54% in the group with mild to moderate retinopathy at baseline, when each group was compared to conventional treatment (median $HbA_{1c}$, 9.1%)[272]. The DCCT found an exponential relationship between risk of retinopathy and mean $HbA_{1c}$ level, so that for each 10% decrease in $HbA_{1c}$, there was a 39% decreased risk of retinopathy progression[273]. There was no glycaemic threshold at which the risk of retinopathy was eliminated[274], and the risk of retinopathy at any $HbA_{1c}$ increased with duration of disease[273].

The DCCT was stopped prematurely when the benefits of intensive treatment were shown convincingly. Most DCCT participants were subsequently enrolled in the Epidemiology of Diabetes Interventions and Complications (EDIC) study, a long-term observational study in which all recruited DCCT participants were advised to change to intensive treatment[273]. In the EDIC cohort study, the risk of DR progression remained low in the former intensive-therapy group, despite an increase in the median $HbA_{1c}$ values from 7.2% to 7.9%; while the higher risk of DR progression persisted in the conventional therapy group despite a decrease in the median $HbA_{1c}$ from 9.1% to 8.2%[275]. After four years of follow-up, the rate of DR progression in the former intensively treated group was 66-77% less than in the former conventionally treated group, despite the gradual equalisation of $HbA_{1c}$ values. Even after 7 years, the incidence of 3-step progression on the ETDRS retinopathy scale was significantly less in the former intensive-treatment group[273] (See Figure 1.7.2). This finding emphasised the importance of instituting tight glycaemic control early in the course of diabetes[276].

These findings strongly suggest that intensive therapy that maintains near-normal glycosylated haemoglobin levels has a long-term beneficial effect on the development of diabetic eye complications which persists long after the duration of such therapy. Risk of DR is not affected greatly in the short term by hyperglycaemia. There appears to be a long lag from periods of poor or tight metabolic control to changes in the course of retinopathy. Higher DR risk is associated with chronic hyperglycaemia and may decrease only slowly with improved levels of hyperglycaemia.

Several other studies reinforce the DCCT findings. These include a 6-year nationwide cohort study of glycaemic control in 339 patients with T1DM in Denmark, in whom 57% had DR. The only significant risk factors identified in multiple regression analysis were elevated $HbA_{1c}$ ($p<0.0001$) and longer diabetes duration ($p<0.0001$)[277]. In patients with high $HbA_{1c}$ (≥10%), the retinopathy risk increased rapidly within a few years of developing diabetes, while patients with low $HbA_{1c}$ (≤6%) had a low retinopathy risk during the first 8 years of diabetes. It was estimated that after 20

years of diabetes, however, 70-90% of these patients would develop some retinopathy, although this was often mild, irrespective of the $HbA_{1c}$ level[277].

The EURODIAB prospective complications study provided similar findings, including 764 patients with T1DM followed an average 7.3 years, in whom DR developed in 56%. Key risk factors identified by logistic regression were glycaemic control and diabetes duration[278]. This study also could not identify a glycaemic threshold for the development of incident DR[278].

Early reports from the Oslo study[279;280] indicated a transient worsening in DR shortly after the onset of intensified insulin treatment in subjects with previous very poor control. Longer follow-up of these patients, however, revealed no prolonged deleterious effects. A similar transient worsening was also observed early in the course of the DCCT[269], and has been reported following combined kidney-pancreas transplantation[281]. This suggests that patients with advanced DR may need monitoring when converted from very poor to tight glycaemic control.

The United Kingdom Prospective Diabetes Study (UKPDS) assessed the effect of glycaemic control in patients with T2DM. This trial randomised 3,867 newly diagnosed persons with T2DM to intensive or conventional therapy over 10 years. The UKPDS reported an 11% reduction in $HbA_{1c}$ level associated with a 25% risk reduction (95% CI, 7%-40%) in microvascular endpoints, including a 29% reduction in the need for diabetic laser treatment. This treatment, however, did not influence macrovascular complications[282]. In the 6-year study, using detailed grading of retinal photographs, the development of DR was strongly influenced by baseline glycaemia and glycaemic exposure over the follow-up period[15].

Tight glycaemic control has important adverse effects, early worsening of DR, and hypoglycaemia or ketoacidosis[283]. In the DCCT, this occurred in 13.1% of the intensive compared with 7.6% of the conventional treatment group[284]. It was reversed by 18 months and did not result in serious visual loss. Participants at risk of this early worsening had higher $HbA_{1c}$ levels at baseline and a more rapid reduction of $HbA_{1c}$ levels in the first 6 months, suggesting that physicians should avoid rapid normalisation of glycaemic control, where possible. A meta-analysis of RCT[268], as well as the DCCT[285], found that intensive treatment increased the risk of hypoglycaemia three-fold and the risk of ketoacidosis by 70% compared with conventional treatment (level I evidence).

In summary, Level I evidence establishes a strong causal relationship between glycaemic control and duration of diabetes for both the development and progression of DR. There may also be a relationship between glycaemic control and DME (Level IV evidence). Persons with T2DM and persistent DME have a higher $HbA_{1c}$ at the time of their disease than patients with resolved DME, and patients with bilateral disease have a more elevated HbA1c than those with unilateral disease[286].

### *Blood Pressure Control (and Management of Hypertension)*

Cross-sectional data suggest that hypertension is associated with DR, but longitudinal (or cohort) data have been less consistent[287;288]. Cohort studies provide a higher level of evidence for the association between exposure to a risk factor and an outcome than do case-control studies, which may overestimate associations. The available longitudinal data indicate that control of hypertension is important in preventing the development and progression of DR[15;50].

#### *Type 1 diabetes*

The WESDR reported that diastolic blood pressure (BP) was a significant predictor of DR progression to PDR after 14 years follow up in patients with T1DM, independent of $HbA_{1c}$ and presence of gross proteinuria[122]. Additionally, the WESDR previously reported that a 10mmHg increase in mean systolic BP over the last two visits increased the incidence of retinopathy, after controlling for other risk variables, in younger-onset but not in older-onset diabetes[289].

Two cross-sectional and one small prospective study examined the relationship between ambulatory BP monitoring and DR progression in normotensive, normo-albuminuric T1DM patients. High normal baseline ambulatory BP predicted the development or progression of DR[290]. Nocturnal ambulatory BP may provide a better measure for the relationship between BP and severity of DR[291].

***Type 2 diabetes***

Data from the UKPDS showed a strong association between systolic BP and incident DR, graded from retinal photographs at diagnosis and after 6 years, in the 1,919 subjects who completed this follow up. Subjects with BP in the highest tertile range at baseline (systolic BP $\geq$140 mmHg) had a 3-fold higher risk of developing DR (RR 2.8, 95% CI 2.2-3.5) than those with BP in the lowest tertile range (systolic BP <125 mmHg)[15;292]. Each 10 mmHg reduction in systolic BP was associated with an approximate 10% decrease in the risk of microvascular disease, principally DR[15]. The Hypertension in Diabetes Study, a UKPDS substudy, randomised 1,148 persons with T2DM (mean duration 2.6 years) and hypertension (mean BP 160/94) to tight BP control (BP<150/85) using either an angiotensin-converting enzyme inhibitor or beta-blocker, or less tight control (BP<180/105)[50]. After 4.5 years, significantly fewer persons in the tight BP control group progressed two steps or more on the EDTRS retinopathy scale, and had a lower risk of a deterioration in visual acuity by three lines on the EDTRS chart. Patients allocated to the tight BP control group were less likely to develop DME requiring laser.

In contrast, the Appropriate Blood Pressure Control in Diabetes (ABCD) Trial, a prospective blinded RCT comparing the effects of intense (diastolic BP<10mmHg baseline) and moderate BP (diastolic BP 80-89mmHg) control on DR progression in persons with T2DM who were hypertensive[51] (n=470) or normotensive[16] (n=480), found that after 5 years follow-up, only the intensely treated normotensive group had a decreased progression of DR.

The Hoorn study of an older cohort aged 50-74 years reported that glycaemia, hypertension and abdominal obesity were determinants of incident DR[293]. No relationship between BP and incident DR, however, was demonstrated in a prospective study of T1DM[278]. In the EURODIAB/EUCLID Study, a 50% reduction (95% CI, 0.28-0.89) in the progression of DR over 2 years was observed in normotensive persons taking lisinopril, an angiotensin-converting enzyme (ACE) inhibitor frequently used to control BP[294]. No association between BP and DR was found in the Atherosclerosis Risk in Communities Study[117] (Level III-2 evidence).

### *Blood Lipid Control (and Management of Hyperlipidaemia)*

Hyperlipidaemia is well established as a risk factor for DR in several cross-sectional and prospective studies[17;117;295-301], particularly for macular hard exudate deposition and CSME[17;298;302;303]. It is also associated with PDR[304;305]. Randomised controlled trials [18;19] suggests that lipid-lowering therapy with statins or fibrates[54] could be useful in managing DR, and as an adjunct to laser treatment for maculopathy. A recent case-control study, however, did not support an association between statins and DR[306].

Serum lipid levels for persons with diabetes, as recommended by the National Evidence Based Guidelines for the Management of Type 2 diabetes Mellitus: Part 7 – Lipid control in type 2 diabetes, NHMRC 2004) include a target LDL cholesterol of less than 2.5 mmol/L and a target triglycerides of less than 2.0 mmol/L.
http://www.nhmrc.gov.au/publications/synopses/_files/di13.pdf

## *Other Factors*

### *Smoking*

The UKPDS surprisingly reported that smoking was associated with a reduced 6-year incidence of DR. Compared with never smokers, current smokers had around one third lower incidence (RR 0.63)[15]. DR progression was also lower in current than in never smokers (RR 0.50)[15]. This is the first major study to demonstrate any relationship between smoking and DR. Earlier WESDR data did not confirm this relationship.

### *Pregnancy*

Pregnancy was associated with a doubling of DR progression in the WESDR[307] (Level II evidence), although the Pittsburgh EDCS found no short-term differences in PDR in a pair-matched case-control study[308]. One case series assessed effects of pregnancy on retinopathy over 10 years[309]. Among women with no or minimal NPDR before pregnancy, 12% developed at least some additional NPDR during pregnancy, but the majority suffered no visual impairment, with most changes regressing postpartum. Among women with NPDR at the onset of pregnancy, 47% developed increased NPDR and 5% developed PDR during pregnancy, of whom 29% regressed postpartum and 50% required laser treatment. Among women with PDR prior to pregnancy (n=122), 46% progressed during pregnancy. Therefore, early aggressive scatter laser treatment of active neovascularisation is warranted when high-risk characteristics[309-311] are present during pregnancy. Trends toward substantially improved diabetes control during pregnancy are likely to result in lower blood sugar levels and therefore less concern regarding DR risk. Duration of diabetes greater than 15 years, poor glycaemic control and hypertension were identified as high-risk factors in the progression of DR in pregnancy[312].

### *Renal Disease (Nephropathy)*

DR is a well established risk factor for the development of diabetic nephropathy (DN), with a 50% probability that DN will develop within 5 years and a 75% probability that DN will develop within 12 years in patients with existing DR[313]. Few reports, however, show that DN predicts the development or progression of DR. In the WESDR, a population-based cohort study, either gross proteinuria or microalbuminuria was a marker for PDR, though not all studies have confirmed this association with microalbuminuria[314]. Other reports indicate a DN link with DME[315].

### *Genetic Risk Factors*

There has been significant interest in identifying candidate genes that could explain familial clustering of DR[316] and a differential progression of retinal vascular changes in subjects with DR[317-319]. Genetic factors could regulate the severity and rapidity of the onset of DR onset[320]. A number of studies have performed genome-wide linkage analysis in sibships, with inconsistent findings[321;322]. One study found evidence of linkage on chromosome 1p[321], and another (in Pima Indians) found linkage on chromosomes 3 and 9[323]. To date, the majority of candidate genes studied have exhibited only a weak or no association with DR. In studies that detected associations, these findings have not been consistent across different populations.

Many genetic factors could influence the onset of complications in diabetes. One potential candidate gene is the aldose reductase gene (ALR2), a rate-limiting enzyme in the polyol pathway that has been implicated in diabetic complications for over a quarter century. Different ALR2 polymorphisms have been associated with a higher likelihood of DR in Asian Indians with T2DM[320] or with DR progression in a study of adults in Chile[324].

Other gene polymorphisms in the RAGE gene[325], the TGF-beta1 gene[326], the VEGF gene[327-330], the eNOS (endothelial nitric oxide synthase) gene[330] and vitamin D receptor[331] have also been associated with the presence or severity of DR from case-control studies. A meta-analysis that examined the association between DR in T2DM and polymorphisms in the gene for hyper-

homocystinaemia (methylenetetrahydrofolate reductase, MTHFR) found only a marginal association with large heterogeneity between different studies[332]. The Rotterdam study, a population study of persons aged 55 years and older, reported that an IGF-I gene polymorphism predicted an increased DR risk[333].

**Table 1.6.1: Randomised controlled trials that have evaluated the role of glycaemic control in diabetic retinopathy (modified from Mohamed et al.)[14]**

| Study | N | Diabetes Type | Intervention | Outcome | Comments | Follow up |
|---|---|---|---|---|---|---|
| Diabetes Control and Complications Trial (DCCT) [271;273;276;334] | 1441 | Type 1 DM<br><br>(726 No DR and 715 Mild-mod NPDR) | Intensive vs. conventional treatment | Median $HbA_{1c}$ 7.2% IT vs. 9.1% CT (p<0.001)<br>IT ↓ risk of developing DR by 76%.<br>IT ↓ risk of progression DR by 54%<br>IT ↓ risk of maculopathy by 23%*<br>IT ↓ risk of severe NPDR/PDR by 47%<br>IT ↓ risk of laser photocoagulation for macular oedema or PDR by 51% | 43 extra episodes of hypoglycaemia requiring assistance per 100 patient yrs with IT<br>3.4 extra cases of being 'overweight' per 100 patient yrs with IT | 6.5 yrs |
| United Kingdom Prospective Diabetes Study (UKPDS) [282;335] | 3867 | Newly diagnosed type 2 DM | Intensive (sulphonylurea or insulin, aiming for fasting plasma glucose <6 mmol/l) vs. conventional (fasting plasma glucose <15 mmol/l) treatment | Mean $HbA_{1c}$ 7% IT vs. 7.9% CT.<br>IT ↓ risk in microvascular endpoints by 25%<br>IT↓ risk retinal photocoagulation by 29%<br>IT ↓ risk progression DR by 17%<br>IT ↓ risk VH by 23%*<br>IT ↓ risk legal blindness by 16%* | | 10 yrs |
| Kumamoto Study [336] (Japan) | 110 | Japanese patients with type 2 DM<br><br>(55 No DR, 55 with NPDR) | Intensive vs. conventional treatment | Mean $HbA_{1c}$ 7.2% IT vs. 9.4% CT.<br>IT ↓ risk of developing DR by 32%<br>IT ↓ risk of progression DR by 32%<br>IT ↓ progression to pre-proliferative and PDR compared to CT (1.5 vs. 3.0 events/100 patient-yrs) | No patient in the primary cohort developed pre-proliferative or PDR | 8 yrs |
| Wang et al [13;268]<br>Meta analysis | 529 | Type 1 DM | Intensive vs. conventional treatment. | Mean $HbA_{1c}$ for IT groups 7-10.5% across included RCT<br>IT ↓ risk of progression DR by 51%<br>IT ↓ risk of progression to PDR or changes requiring laser reduced by 56%<br>Trend towards progression of DR after 6-12 months of IT which was reversed by 2-5 yrs of IT | Hypoglycaemia episodes requiring assistance 9.1 extra cases per 100 patient years with IT. | 2–5 yrs |
| Kroc collaborative study group[337;338] § | 70 | Type 1 DM with low C-peptide level with NPDR | CSII vs. conventional injection treatment | Mean $HbA_{1c}$ 8.1% CSII vs. 10.0% CT.<br>Retinopathy ↑ in both groups.<br>Trend towards progression DR with CSII (↑ soft exudates and IRMA) in first 8 months*, which was reversed by 2 yrs. | The study continued after the initial 8 months with 23/34 CSII group and 24/34 CT group followed for a further 16 months. | 8 months – 2 yrs |
| The Stockholm Diabetes Intervention Study[339] | 96 | Type 1 DM with NPDR | Intensive vs. conventional treatment | Median $HbA_{1c}$ 7.2% IT vs. 8.7% CT<br>Retinopathy ↑ in both groups (P < 0.001)<br>OR for serious retinopathy was 0.4 in the IT group as compared with CT (P=0.04) | 242 vs. 98 episodes hypoglycaemia in IT and CT groups (p<0.05)<br>IT ↑ BMI by 5.8% | 5 yrs |

| | | | | | | |
|---|---|---|---|---|---|---|
| Oslo Study[279;340;341] | 45 | Type 1 DM | CSII vs. multiple insulin injections (5-6/day) vs. conventional treatment (twice daily injections) | ↓ retinal MA and hemorrhage in CSII and multiple insulin group compared with CT ($p<0.01$). | A transient ↑ in MA and hemorrhages was seen at 3 months in CSII group | 2 yrs |

Studies with less than 40 patients excluded. *Effect was not statistically significant, § included in Meta-analysis by Wang et al[13;268]
DM=diabetes mellitus; NPDR= non proliferative diabetic retinopathy; vs.=versus, $HbA_{1c}$=glycosylated haemoglobin; IT=intensive treatment; CT=conventional treatment, DR=diabetic retinopathy; PDR= proliferative diabetic retinopathy; NPDR= non-proliferative diabetic retinopathy; RCT=randomised control trials; CSII=continuous subcutaneous insulin infusion, IRMA=intraretinal microvascular abnormalities; MA=microaneurysm; HEx=hard exudates; OR= odds ratio

# 2. Assessment of Diabetic Retinopathy

## *2.1 Grading of Diabetic Retinopathy*

**Key Points**

- The modified Airlie House classification (Wisconsin system) has become the basis for detailed grading of DR and was used in all the major studies of risk factors and trials of laser and other treatments, including the DCCT, UKPDS, DRS and ETDRS studies. It was based on grading seven 30˚ stereoscopic fields. Newer cameras now mostly utilise wider fields, so that two- to four-field photography is likely to be sufficient to document DR in current clinical practice.
- The ETDRS study quantified the risk of retinopathy progression associated with the severity of individual lesions from masked photographic grading.
- The presence of IRMA, H/Ma and VB were strong predictors of progression from NPDR to PDR.
- The ETDRS classified DR into the following categories: None, Minimal NPDR, Mild NPDR, Moderate NPDR, Severe NPDR, PDR, High-Risk PDR.
- The International Clinical Diabetic Retinopathy and Diabetic Macula Edema Disease Severity Scale proposes five levels for grading of DR, based on risk of progression: None, Mild NPDR, Moderate NPDR, Severe NPDR or PDR.Presence and severity of DME is classified separately. The World Health Organisation grading system stresses referral urgency: STR requiring immediate referral, lesions needing referral as soon as possible, and lesions that could be reviewed in a few months.
- It is important to detect DME in the assessment of DR as this is the most frequent cause of decreased vision from retinopathy. Both macular oedema (ME) and clinically significant macular oedema (CSME), defined by proximity of these signs to the foveal centre, are best assessed using slit lamp biomicroscopy or by grading stereoscopic macular photographs.
- Optical coherence tomography may be also used to provide valuable confirmation and quantification of the clinical grading for DME.

The 1968 Airlie House Symposium[342] provided the basis for the most commonly used DR grading system in the Diabetic Retinopathy Study (DRS), Early Treatment Diabetic Retinopathy Study (ETDRS), Diabetes Control and Complications Trial (DCCT), United Kingdom Prospective Diabetic Study (UKPDS) and Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR)[32;151;343-346]. This system assessed seven standard 30˚ stereoscopic fields[347] (field 1- optic disc; field 2- macula; field 3- lateral macula; fields 4,5- upper and lower temporal arcades; fields 6,7- upper and lower nasal arcades) photographed with the 30˚ Zeiss fundus camera.

Standard stereoscopic slides using the Wisconsin grading system[348] establish the severity of DR lesions, such as haemorrhages/microaneurysms (H/Ma), hard exudates (HEx), venous beading (VB), intraretinal microvascular abnormalities (IRMA), soft exudates or cotton-wool spots (CWS), neovascularisation involving the optic disc (NVD) or elsewhere in the retina (NVE), as well as preretinal or vitreous haemorrhage. Used in masked grading by physicians or lay readers, the system has good intra- and inter-observer reproducibility[349;350] and discriminates relatively small changes in retinopathy. The classification provides a severity scale with 6 levels of retinopathy for one eye or 11 levels for both eyes[350]. A shortened Wisconsin classification with 8 levels is also used. Compared to seven fields, the agreement rate for two and four fields is 80% and 91% respectively. The sensitivity of two to four fields compared to seven fields for detecting any retinopathy varies from 87 to 95%. This suggests that two to four photographic fields may be sufficient to document DR in clinical practice[351].

The ETDRS provided fundus photography risk factors for DR[352]. In the ETDRS Report 18[353], presence of IRMA, Hex, Ma and VB were strong predictors of progression from NPDR to PDR. The development of high-risk PDR was the predominant risk factor for severe visual loss or vitrectomy over 5 years (odds ratio 13.7, 95% confidence interval 9.4-19.9)[353]. A simplified ETDRS (Wisconsin) classification is shown in Table 2.1.1.

**Table 2.1.1: Classification of diabetic retinopathy into retinopathy stages (Wisconsin level) and predictive value of retinal lesions** (adapted from Focal Points[29;344]).

| **Retinopathy stage** | **Definition** | **Rate of progression (%)** | | | |
|---|---|---|---|---|---|
| | | **to PDR** | | **to high-risk stage** | |
| | | **1 yr** | **3 yrs** | **1 yr** | **5 yrs** |
| Minimal NPDR (level 20) | Ma only | not documented | | | |
| Mild NPDR (level 35) | Ma and one or more of: retinal haem, HEx, CWS, but not meeting Moderate NPDR definition | 5 | 14 | 1 | 15 |
| Moderate NPDR (levels 43, 47) | H/Ma ≥ std photo 2A in at least one quadrant and one or more of: CWS, VB, IRMA, but not meeting Severe NPDR definition | 12-26 | 30-48 | 8-18 | 25-39 |
| Severe NPDR *preproliferative* (level 50+) | Any of : H/Ma >std photo 2A in all four quadrants, IRMA >std photo 8A in one or more quadrants, VB in two or more quadrants | 52 | 71 | 15 | 56 |
| PDR (level 60+) | Any of: NVE or NVD <std photo 10A, vitreous/ preretinal haem and NVE <½ disc area (DA) without NVD | | | 46 | 75 |
| High-risk PDR (level 70+) | Any of: NVD>¼ to ⅓ disc area, or with vitreous/ preretinal haem, or NVE>½ DA with vitreous/ preretinal haem | Severe visual loss (VA≤5/200) develops in 25-40% within 2 years. | | | |
| Advanced PDR | High-risk PDR with tractional detachment involving macula or vitreous haem obscuring ability to grade NVD and NVE | | | | |
| Macular Oedema | Retinal thickening within 2 disc diameters of macular centre | Can occur at any stage of DR | | | |
| Clinically Significant Macular Oedema (CSME) | Retinal thickening within 500µm of macular centre or hard exudates within 500µm of macular centre with adjacent thickening | Can occur at any stage of DR | | | |

The Early Treatment Diabetic Retinopathy Study (ETDRS) staging system is still regarded as the gold standard for grading in clinical trials and epidemiologic studies; however its usefulness in daily clinical practice is limited by relatively complicated rules, multiple severity levels, and the need to correlate with standard photographs. Several groups have independently developed simplified severity scales based on the ETDRS system[346;353-357], some of them for advanced NPDR[358]. Each scale, however, is limited by a lack of standardisation and reported experience in applying the scales.

In 2001, the American Academy of Ophthalmology (AAO) launched the Global Diabetic Retinopathy Project to promote the development of a common clinical severity scale for DR and DME, to facilitate improved communication between retinal sub-specialists, ophthalmologists, endocrinologists/diabetologists and primary care physicians. The International Clinical Diabetic Retinopathy and Diabetic Macula Edema Disease Severity Scale proposed five levels of DR severity – none, mild, moderate, severe and proliferative; in the presence or absence of DME[359;360],

which is graded separately. The separate classification for DR and DME allowed clinically important grades of retinopathy to be recognised and graded even by a relatively inexperienced screener using direct ophthalmoscopy, while still allowing ophthalmologists to grade the extent and severity of retinal oedema using stereoscopic biomicroscopy and/or fundus photography. Several ETDRS disease severity levels are combined because they have a similar clinical course and treatment recommendations using the ETDRS guidelines[32].

Importantly, this new classification system identified patients at high risk of vision loss. ETDRS data identified extensive intraretinal haemorrhage, IRMA, and VB as the most important signs predicting the progression from NPDR to PDR[352]. Patients in the severe NPDR category were identified at greatest risk of disease progression.

This new international clinical system will not replace the ETDRS scale in clinical research or clinical trials, but provides a standardised DR grading system of severity and risk of progression arising from the ETDRS data. The approach to treatment of DR should still be guided using the ETDRS protocol. Table 2.1.2 illustrates the ETDRS lesion grades included under the 5 severity levels. In this proposed new scale, the examiner might evaluate the individual lesions, but will record only the overall severity level.

A further approach has been to develop a grading system that identifies patients with severe DR needing referral for consideration of therapy (i.e., moderate to severe NPDR, PDR or CSME)[355]. This group used multiple regression techniques to identify which retinopathy lesions recorded in ETDRS fundus photographs were predictive of PDR or CSME. This approach determined that H/Ma in the temporal macula (field 3) as severe or more severe than ETDRS standard photograph 1 identified around 88% of eyes with PDR and 92% of eyes with moderately severe to severe NPDR. Extrapolating data from epidemiologic studies of older diabetic populations, the calculated sensitivity for detecting PDR on a single examination was 87% and specificity 80%. Any hard exudate within one disc diameter of the macular centre predicted CSME with a sensitivity of 94% and specificity 54%, while hard exudates of moderate or worse severity anywhere in the macular region predicted CSME with a sensitivity of 89% and a specificity of 58%.

A simpler grading system previously developed for the World Health Organisation divided important DR lesions and their referral urgency, into three groups: (1) sight-threatening retinopathy requiring immediate referral, (2) lesions needing a referral as soon as possible, and (3) lesions that could be reviewed in a screening clinic in a few months[361].

**Table 2.1.2: International Clinical Diabetic Retinopathy and Diabetic Macular Edema Disease Severity scales, and recommended referral patterns[359]**

| Retinopathy stage | Findings on ophthalmoscopy | ETDRS Level | Rate (%) of Progression to PDR | | | | Management |
|---|---|---|---|---|---|---|---|
| | | | Early | | High Risk | | |
| | | | 1 yr | 3 yrs | 1 yr | 3 yrs | |
| No apparent retinopathy | No abnormalities | 10 | | | | | |
| Minimal NPDR | Microaneurysms only | 20 | | | | | |
| Mild to moderate NPDR | More than just microaneurysms but less than severe NPDR | 35, 43, 47 | 5-26 | 14-48 | 1-8 | 7-24 | Ophthalmology referral |
| Severe NPDR | Any of the following:<br>More than 20 intraretinal haemorrhages in each of 4 quadrants<br>Definite venous beading in 2+ quadrants<br>Prominent intraretinal microvascular abnormalities in 1+ quadrant AND no signs of proliferative retinopathy | 53 A-E | 52 | 71 | 17 | 44 | Ophthalmology referral |
| Proliferative DR | One of the following:<br>Neovascularisation<br>Vitreous / preretinal haemorrhage | 61, 65, 71, 75, 81, 85 | | | 46 | 67 | Ophthalmology referral; laser treatment |
| **Macula oedema** | | | | | | | |
| Absent | No retinal thickening or hard exudates in posterior pole | | | | | | |
| Present | Mild – some retinal thickening or hard exudates in posterior pole but distant from the macula<br>Moderate – retinal thickening or hard exudates approaching the centre of the macula but not involving the centre<br>Severe – retinal thickening or hard exudates involving the centre of the macula | | | | | | Ophthalmology referral; consider laser<br>Consider laser<br>Laser treatment |

## 2.2 Examinations, Sensitivity and Specificity in Detecting Diabetic Retinopathy

**Guidelines**

2. Ophthalmologists, optometrists and other trained medical examiners should use dilated ophthalmoscopy or slit lamp biomicroscopy with a suitable lens (e.g. 78 D), to detect presence and severity of DR and DME, with adequate sensitivity and specificity (Systematic review of diagnostic accuracy studies[20] (dilated ophthalmoscopy) and individual diagnostic accuracy study (slit lamp biomicroscopy)[21]).
3. In the absence of a dilated fundus examination by a trained examiner, use non-mydriatic (or mydriatic) photography with adequate sensitivity, specificity and low technical failure rate to detect presence of DR (Systematic review of diagnostic accuracy studies[20] and individual diagnostic accuracy studies[22-26]).

**Consensus Practice Points**

1. Always assess visual acuity at the time of DR screening.
2. Apply DR severity scales to determine need for referral, follow-up and treatment.

**Key Points**

- Stereoscopic seven-field fundus photography by a trained grader is the gold standard method of detecting DR. It is mainly a research tool and is rarely performed in routine practice.
- Clinical examinations to detect DR may use slit lamp biomicroscopy, ophthalmoscopy or retinal photography. Pupils should normally be dilated. An exception is non-mydriatic photography with adequate photographic quality and sensitivity.
- Dilated slit lamp biomicroscopy is used in routine clinical practice to assess the presence and severity of DR.
- The level of sensitivity needed by the examination or screening test cannot be defined unequivocally. Screening examinations or tests should aim for a sensitivity of at least 60% (as defined in earlier studies), though higher levels are usually achievable. It is considered that mild DR missed at one visit would likely be detected at the next. Specificity levels of 90-95% and technical failure rates of 5-10% are considered appropriate for both measures.
- Dilated direct or indirect ophthalmoscopy by ophthalmologists, optometrists, or other trained medical examiners, or fundus photography by trained personnel, generally meet screening sensitivity guidelines.
- Clinical assessments to screen for DR should usually include measurement of visual acuity and a dilated fundus examination. Examiners need adequate sensitivity and specificity in performing assessments. Alternately, retinal photographic screening (which may be non-mydriatic) with adequate sensitivity should be performed. Technical failure, however, should prompt a referral for clinical assessment.
- Non-mydriatic digital retinal photography is increasingly used in screening DR. Its usefulness may be limited by reduced sensitivity for screening and detecting DR and by technical failure with ungradeable photographs caused by small pupils and media opacities. Adequate training of staff is very important. DME may be difficult to detect using this method when few exudates are present.
- Patients should be referred promptly for dilated fundus examination if non-mydriatic photographs cannot be graded.
- Digital photography has allowed screening services to reach rural and remote areas via tele-ophthalmology.
- People with diabetes present to a variety of examiners, including general practitioners, general physicians, endocrinologists, optometrists and ophthalmologists. All are potentially able to screen for DR.

Assessment of stereoscopic seven-field fundal photographs by a trained grader is the gold standard method of detecting DR[344]. Its use in large-scale screening program is limited because of its cost and the need for special equipment and trained personnel[362]. It is mainly a research tool and is rarely performed in routine practice. Clinical examinations to detect DR typically use slit lamp biomicroscopy or ophthalmoscopy with pupils dilated or undilated. Retinal photographs, traditionally taken with 35mm film, may also be taken but they have been greatly replaced by digital imaging.

### *Minimum Sensitivity of an Examination*

The minimum sensitivity required for DR screening methods has frequently been set at either 80%[363] or 60%[364]. The National Institute for Clinical Excellence guidelines recommend that DR screening tests have a sensitivity of at least 80%, specificity of at least 95%, and a technical failure rate of no greater than 5%[28]. Earlier work by Javitt *et al.*[364] indicated that a sensitivity of 60% could be adequate because repeated examinations tend to detect retinopathy missed at earlier examinations. Different reference standards have been used by various studies to compare different methods of screening[365].

### *Sensitivity and Specificity of Examinations*

Tables 2.2.1-2.2.4 document the sensitivity and specificity of ophthalmoscopy and fundus photography[20;22]. Before comparing different screening methods for the detection of DR, the limitations in methodology should be considered. These include sample size variations between studies, the potential for selection bias and the varied experiences of personnel participating in data collection. These factors, along with variations in the reference standard used between studies, can limit generalisability of the diagnostic accuracy studies.

### *Examinations*

#### *1. Slit lamp biomicroscopy*

Slit lamp biomicroscopy with an appropriate lens (e.g. 90D or 78D) after pupil dilation, by an ophthalmologist or optometrist is the currently accepted routine practice to detect DR, and is now preferred to ophthalmoscopy. Scanlon *et al.*[21] validated the slit lamp biomicroscopy performed by an ophthalmologist (termed the ophthalmologists' reference standard) against 7-field non-digital stereo-photography in patients with DR needing ophthalmic referral. Slit lamp biomicroscopy compared favourably with 7-field stereo-photography (sensitivity 87.4%, specificity 94.9%)[21].

#### *2. Direct and indirect ophthalmoscopy*

A systematic review of the effectiveness of ophthalmoscopy in screening for DR found that the sensitivity of detecting any DR by dilated direct ophthalmoscopy alone ranged between 45-98%, and the specificity ranged between 62-100% (Table 2.3.1)[20]. Poor diagnostic sensitivity in detecting PDR was associated with use of a direct ophthalmoscope by a junior hospital physician (13%) and by a physician assistant (20%). There was a trend toward higher sensitivities, however, with more experienced non-eye health professionals. Even in the hands of an experienced ophthalmologist, however, direct ophthalmoscopy is limited by weaknesses inherent to the instrument itself[366].

#### *3. Retinal photography*

**Mydriatic (dilated) retinal photography**

The sensitivity of detecting any DR by dilated (mydriatic) retinal photography ranged between 73% and 96%; the specificity ranged between 68 and 99%. The sensitivity of detecting STR by mydriatic retinal photography was higher (87-97%), with the specificity ranging 83 and92%. A systematic literature review found the most effective DR screening strategy to be the use of mydriatic retinal photography, with the additional use of ophthalmoscopy when photographs could not be graded[20]. These authors showed that mydriatic 45º retinal photographs read by different health care professionals generally reached a sensitivity of at least 80%, a level not consistently reached even

by experienced ophthalmologists using either direct or indirect ophthalmoscopy. However, another study suggested that, despite identifying the occasional patient missed by retinal photography, the addition of ophthalmoscopy would likely increase false positive referrals and detect only a few extra patients requiring laser treatment[367]. Table 2.2.2 provides the technical failure rate, another important practical consideration in assessing test utility.

**Non-mydriatic (undilated) photography**

Recent techniques allow the acquisition of high-quality photographs through undilated pupils and storage in digital format. Non-mydriatic cameras have a number of advantages including eliminating the need for dilating drops, hence facilitating compliance and the ability for non-medically trained personnel to perform the examination[368]. However, limitations include technical failure in persons with small pupils and media opacity. Good macular stereoscopic photographs are difficult to obtain without pupil dilation[369]; and without stereoscopic views, CSME may be difficult to detect when few exudates are present. The Joslin Vision Network Study (52 patients) suggested recent improvement, with only 3% ungradeable for DME[370]. A new technique employing stereoscopic non-mydriatic photography was reported to provide excellent agreement with a dilated ophthalmic retinal examination in a large sample (280 patients)[371].

Compared with 7-field photography using 35mm film, high quality digital non-mydriatic retinal imaging provides positive outcomes in relation to threshold retinopathy requiring referral[23;372] (sensitivity 98%, specificity 90%). Other studies found single non-mydriatic 60º photographs inadequate as a screening procedure for patients with moderate/severe NPDR compared to 7-field stereo-photographs[373].

Tables 2.2.4 shows reported sensitivities and specificities of non-mydriatic camera studies. Some studies showed mydriatic retinal photography to be more sensitive than non-mydriatic photography (81% vs. 61% sensitivity) for detecting moderate NPDR, severe NPDR and PDR[24]. Mydriatic retinal photographs read by ophthalmic assistants, GPs and optometrists achieved sensitivities of 87%, 91% and 89%, respectively[22;366], whereas non-mydriatic retinal photographs read by an ophthalmologist or trained grader generally achieved lower sensitivities, 56% and 60%, respectively[374]. Combined approaches using different non-ophthalmologist examiners may be an effective strategy[23;375-381]. In the UK, such a combined-examiner screening approach increased routine, regular examinations from 45% to over 60%[365].

Studies using newer non-mydriatic digital cameras with 5 overlapping fields (posterior pole + 4 peripheral fields) report favourable diagnostic accuracy for detecting moderate to severe NPDR, but still have 6-11% of photographs assessed ungradeable by at least one observer[382]. Despite a 10% technical failure rate, Harper *et al.*[383] reported the usefulness of non-mydriatic camera in a community-based diabetes screening program in rural Victoria. Murray *et al.* reported a successful non-mydriatic DR screening program performed by Aboriginal health workers and nurses in the Kimberley region, Western Australia[384]. This study reported a technical failure rate of 9% among Indigenous Australians. Phiri *et al*. reported polaroid and digital non-mydriatic cameras were equally effective in detecting referable retinopathy[385]. Non-mydriatic photography is thus very useful in screening for DR, though it does not currently meet the stringent National Institute for Clinical Excellence guidelines[28]. Recent studies suggest this may be changing[370]. Sensitivity >60% may be adequate[364].

***Tele-ophthalmology and tele-screening***

Digital images can be transmitted electronically to a centralised centre for grading. This facilitates examinations for persons living in remote or rural areas. Early tele-ophthalmology studies[386;387] have now led to the development of complete telemedicine screening programs for DR[362;388]. In addition, newly developed automated methods for detecting DR from digital images[389-393] have

improved sensitivity and specificity for detecting H/Ma and Hex. Tele-ophthalmology should not be currently viewed, however, as a substitute for comprehensive eye examinations[362]. Technical considerations were summarised in a 'Practice Recommendations' report[394].

## *Examinations by Different Health Professionals*

### *Physicians*

Significant variability between ophthalmologists and physicians exists in the ability to detect and stage retinopathy[395]. Compared to 7-field photography, physicians using dilated ophthalmoscopy may miss up to 49% of cases of PDR[396]. Further training may improve accuracy and appropriateness of referrals.

### *General practitioners (GPs)*

The ability and accuracy of GPs to detect DR has been reported to range from 41% to 65%[395;397;397-399], though lower sensitivities were found for detecting sight-threatening DR[399]. Appropriate education will dramatically improve GPs' accuracy in detecting retinopathy[400;401], particularly PDR and DME. A number of surveys have assessed how active GPs are in screening their diabetic patients for retinopathy. Unfortunately, 65% of those who screened reported that they never dilated pupils[402-407].

### *Optometrists*

U.K. and Australian studies have found that optometrists had a high sensitivity of detecting evidence of any retinopathy in between 67% and 87% of cases; other studies have indicated higher sensitivity, indicating their improved training[381;397;408-412]. As a group, optometrists correctly referred DME or moderate NPDR in 77-92% of cases[381].

**Table 2.2.1: Diagnostic Accuracy Studies: Screening by slit lamp biomicroscopy or ophthalmoscopy (adapted Hutchinson *et al.*[20] and other studies with >200 subjects)**

| Reference | Study design | Practitioner | Type of screening | Reference standard | Outcome | Sensitivity (%) (95% CI) | Specificity (%) (95% CI) |
|---|---|---|---|---|---|---|---|
| Scanlon *et al.*, 2003[21] | Case series, 239 diabetic patients attending 2 diabetic eye clinics | Ophthalmologist | Dilated slit lamp biomicroscopy | 7-field stereophotography | DR needing referral | 87 (84-92)<br>All were gradable | 95 (92-98) |
| Olson *et al.*, 2003[23] | Case series, 485 diabetic patients attending a hospital based diabetic clinic | 6 Optometrists after training | Slit lamp biomicroscopy | Ophthalmologist's slit lamp biomicroscopy | DR needing referral | 73 (52-88) | 90 (87-93) |
| Gibbins *et al.*, 1998[22] | Case series, 605 diabetic patients from 4 GP group practices | GP<br>Optometrist<br>Optometrist (specialist)<br>GP<br>Optometrist<br>Optometrist (specialist) | Dilated direct ophthalmoscopy | Reading centre assessing 35mm slides | Any DR<br><br><br>STR<br><br> | 63 (56-69)<br>74 (67-81)<br>70 (64-76)<br>66 (54-77)<br>82 (68-92)<br>79 (68-88) | 75 (70-80)<br>80 (75-85)<br>62 (56-68)<br>94 (91-96)<br>90 (87-93)<br>89 (85-92) |
| O'Hare *et al.*, 1996[413] | Case series, 1010 diabetic patients from 11 GP and optometrist practices | GP<br><br>Optometrist | Dilated direct ophthalmoscopy | Ophthalmologist-dilated ophthalmoscopy | DR needing referral | 56<br><br>75 | 98<br><br>93 |
| Pugh *et al.*, 1993[24] | Case series, 352 diabetic patients attending hospital outpatient clinic and medical centre | 10 Ophthalmologists<br><br><br><br>Physician assistant | Dilated direct and indirect ophthalmoscopy<br><br><br><br>Dilated direct ophthalmoscopy | Stereoscopic 7-field photography | Any DR<br><br>NPDR<br>PDR<br>Any DR<br>NPDR<br>PDR | 32 (25-39)<br><br>38 (31-45)<br>43 (1-82)<br>60 (51-68)<br>55 (46-64)<br>20 (1-72) | 97 (93-99)<br><br>98 (94-100)<br>100 (99-100)<br>67 (59-76)<br>66 (58-76)<br>98 (95-99) |
| Lienert, 1989[395] | Case series, 500 consecutive diabetic patients attending hospital general diabetic clinic | GP<br>Diabetologist<br>hospital intern<br>GP<br>Diabetologist<br>hospital intern | Dilated direct ophthalmoscopy | Ophthalmologist-dilated ophthalmoscopy | Any DR<br><br><br><br>PDR<br><br> | 45 (23-69)<br>81 (76-86)<br>64 (58-70)<br><br>50 (13-99)<br>35 (16-57)<br>13 (0-53) | 100 (87-100)<br>95 (92-98)<br>86 (82-91)<br><br>100 (92-100)<br>99 (98-100)<br>100 (99-100) |
| Moss *et al.*, 1985[363] | Cross-sectional survey, 1949 diabetic patients | Ophthalmologist | Dilated direct and/or indirect ophthalmoscopy | Stereoscopic 7-field photography | Any DR<br><br>PDR | 82 (80-84)<br><br>72 (73-86) | 95 (94-96)<br><br>100 (98-100) |

**Outcomes**: **Any DR** - any retinopathy; **PDR** - proliferative diabetic retinopathy; **STR** - sight threatening diabetic retinopathy, **NPDR** - non-proliferative retinopathy, **ME** - macular oedema; **CSME** - clinically significant diabetic macular oedema.

**Table 2.2.2: Diagnostic Accuracy Studies: Screening using retinal photography**

| Reference | Study design | Practitioner | Type of screening | Reference standard | Outcome | Sensitivity (%) (95% CI) | Specificity (%) (95% CI) | Technical Failure Rate (%) |
|---|---|---|---|---|---|---|---|---|
| Olson *et al.*, 2003[23] | Case series, 485 diabetic patients attending a hospital-based diabetic clinic | Experienced retinal photographers | Mydriatic 2-field 50º colour slides | Ophthalmologist's slit lamp biomicroscopy | DR needing referral | 96 (87-100) | 89 (86-91) | 11.9 |
| | | | Mydriatic 2-field 50º red free digital | | | 93 (82-98) | 87 (84-90) | 4.4 |
| Lin *et al.*, 2002[26] | Case series, 197 consecutive diabetic patients attending clinic | Research associate | Single non-mydriatic monochromatic digital photograph | 7-field stereophotography | DR needing referral | 78 | 86 | 8.1 |
| Gibbins *et al.*, 1998[22] | Case series, 605 diabetic patients from 4 GP group practices | GP | Different practitioner assessment of Mydriatic 35mm slides | Reading centre assessing 35mm Mydriatic slides | Any DR | 79 (74-85) | 73 (68-79) | Not reported |
| | | Community optometrist | | | | 88 (83-93) | 68 (62-74) | |
| | | Specialist optometrist | | | | 86 (81-91) | 89 (85-93) | |
| | | Diabetologist | | | | 73 (67-79) | 93 (90-96) | |
| | | GP | | | STR | 87 (77-94) | 85 (81-88) | |
| | | Community optometrist | | | | 91 (79-98) | 83 (79-87) | |
| | | Specialist optometrist | | | | 97 (90-100) | 87 (84-91) | |
| | | Diabetologist | | | | 89 (79-95) | 92 (88-94) | |
| Harding *et al.*, 1995[366] | Case series, 320 diabetic patients attending 4 GP practices | Ophthalmologist clinical assistant | Mydriatic 35mm slides | Slit lamp biomicroscopy by eye specialist | STR | 89 (80-98) | 86 (82-90) | 5.0 |
| Pugh *et al.*, 1993[24] | Case series, 352 diabetic patients attending hospital outpatient clinic and medical centre | Independent grader | Non-mydriatic 35mm colour slides | Stereoscopic 7 field retinal photography | Any DR | 64 (57-71) | 99 (95-100) | Not reported |
| | | | | | NPDR | 64 (56-71) | 97 (93-99) | |
| | | | | | PDR | 25 (1-81) | 100 (99-100) | |
| | | Independent grader | | | Any DR | 72 (66-79) | 96 (92-99) | |
| | | | | | NPDR | 71 (65-78) | 94 (90-97) | |
| | | | | | PDR | 50 (12-88) | 100 (90-96) | |

**Table 2.2.3: Diagnostic Accuracy Studies: Combined ophthalmoscopy and retinal photography**

| Reference | Study design | Practitioner | Type of screening | Reference standard | Outcome | Sensitivity (%) (95% CI) | Specificity (%) (95% CI) |
|---|---|---|---|---|---|---|---|
| Scanlon *et al.*, 2003[414] | Case series, 1549 diabetic patients from GP practices | Nurse technician | Mydriatic 2-field digital + technician ophthalmoscopy | Slit lamp biomicroscopy by ophthalmologist | DR needing referral | 88 | 86 |
| | | | One field non-mydriatic | | | 86 (technical failure 20%) | 77 |
| Pandit *et al.*, 2002[415] | Case series, 609 diabetic patients attending diabetes screening centre in quality assurance audit | Diabetologist | Mydriatic polaroid films and direct ophthalmoscopy | Slit lamp biomicroscopy by ophthalmologist | STR | 83 | 98 |
| | | Trained retinal screeners | | | | 86 | 96 |
| O'Hare *et al.*, 1996[413] | Clinic series, 1010 diabetic patients from 11 GP and optometrist practices | GP | Dilated direct and mydriatic instant prints | Dilated ophthalmoscopy by ophthalmologist | DR needing referral | 60 | 98 |
| | | Optometrist | | | | 88 | 99 |
| Sculpher *et al.*, 1992[416] | Cross sectional survey, 2891 diabetic patients from 3 centres | GP | Dilated direct and non-mydriatic polaroid | Ophthalmoscopy by ophthalmic clinical assistant | STR | 80 | 86 |
| | | Optometrist | | | | 67 | 89 |

**Table 2.2.4: Diagnostic Accuracy Studies: Sensitivity and specificity of non-mydriatic photography**

| Reference | Study Design | Practitioner | Type of screening | Reference standard | Outcome | Sensitivity (%) (95% CI) | Specificity (%) (95% CI) | Level of evidence |
|---|---|---|---|---|---|---|---|---|
| Lin *et al.*, 2002[26] | Case series, 197 consecutive diabetic patients attending large clinic | Research associate | Single non-mydriatic monochromatic digital photograph | 7-field stereophotography | DR needing referral | 78 | 86 | III-2 |
| Siu *et al.*, 1998[25] | Case series, 153 consecutive diabetic patients attending hospital based clinic | Physicians | Dilated direct | Dilated indirect and biomicroscopy (78D) by ophthalmologist | Any DR | 41 (20-62) | 93 (88-97) | III-2 |
| | | Interpreted by experienced ophthalmologist | 45º non-mydriatic | | | 64 (43-85) | 90 (84-96) | |
| Pugh *et al.*, 1993[24] | Case series, 352 diabetic patients attending hospital outpatient clinic and medical centre | Independent grader | Non-mydriatic 35mm colour slides | Stereoscopic 7 field retinal photography | Any DR<br>NPDR<br>PDR | 64 (57-71)<br>64 (56-71)<br>25 (1-81) | 99 (95-100)<br>97 (93-99)<br>100 (99-100) | III-2 |
| | | Independent grader | | | Any DR<br>NPDR<br>PDR | 72 (66-79)<br>71 (65-78)<br>50 (12-88) | 96 (92-99)<br>94 (90-97)<br>100 (90-96) | |
| Buxton *et al.*, 1991[397] | Case series, 3318 diabetic patients attending 3 diabetic centres | Optometrist | Non-mydriatic polaroid | Ophthalmoscopy by ophthalmological clinical assistant | STR | 47 (23-71) | 95 (93-97) | III-2 |

## 2.3 Safety of Pupil Dilation

**Key Points**

- Pupil dilation using 0.5 to 1.0% tropicamide is safe and markedly increases the sensitivity of DR screening, so should be considered mandatory in performing ophthalmoscopy or slit lamp biomicroscopy.
- Two large Australian population studies (MVIP and BMES) showed high levels of patient acceptance for pupil dilation. These and other population studies have also confirmed the safety of pupil dilation.
- Although practitioners should be aware of the potential to induce acute angle closure glaucoma from use of mydriatic drops, its incidence is rare (1 to 6 per 20,000 people) and tropicamide alone has not been reported to cause this.

### *When should the pupil be dilated?*

Ophthalmologists use mydriatic (dilating) eye drops routinely to optimise visualisation in fundoscopy. However, mydriatic eye drops are seldom used by physicians[417;418]. In general medical practice, the most common indication for pupil dilation is screening for diabetic retinopathy, where it increases the sensitivity of screening by over 50%[417]. The possibility of inducing acute glaucoma by mydriasis is often cited by diabetologists and general physicians as a reason for not routinely dilating pupils[400]. It is currently the policy of most medical and diabetes units not to dilate the pupils of patients giving a history of glaucoma of any kind. This advice is reiterated in many authoritative texts[417]. This practice, however, is not evidence-based and denies many diabetic patients an effective examination. Although practitioners should be aware of inducing acute angle closure glaucoma from using mydriatics, its incidence is rare.

Some reports have indicate only small differences in the sensitivity of detecting NPDR from pupil dilation, the sensitivity for PDR is substantially lower without dilation[419]. DME is also much more difficult to detect through undilated pupils. In one study, all cases of DME were missed by diabetologists using undilated ophthalmoscopy[420], an important omission. Pupil dilation is thus essential when performing ophthalmoscopy to screen for DR and should be combined with visual acuity assessment.

### *Adverse effects of pupil dilation*

Reported adverse effects include the potential of acute angle-closure glaucoma (AACG)[421], cardiovascular side effects, plus transient discomfort and blurring. Case reports of allergic contact dermatitis from eye drops are documented[422]. Pupil dilation can also slightly reduce vision and daylight driving performance[423].

Population studies place the risk of AACG caused by pharmacological pupil dilation at 1 to 6 per 20,000 people[27;418;421;424]. There is evidence indicating that narrow angles in isolation, are a poor predictor of the likelihood of mydriatic-induced acute glaucoma[424;425]. In a 4-year review of patients treated for AACG in Birmingham, only 2.6% were due to diagnostic pupil dilation, an approximate risk by diagnostic mydriasis of 1/20,000[421], similar to the population study data[27;417;421;424]. There are no reports of AACG being precipitated by tropicamide used alone. The rate for people being screened for DR is likely to be even lower, given their mostly younger age.

A second potentially important side effect of dilation is increased blood pressure, reported in patients with T1DM, particularly with longer diabetes duration or concurrent use of sympatholytic drugs[426]**.** Other possible cardiovascular side effects have been reported in association with the use of topical phenylephrine[427-429], including myocardial infarction, angina, arrhythmia, hypotension, and

syncope, usually in patients with a history of cardiovascular disease. In view of potential concerns, expert opinion suggests that phenylephrine 2.5% drops are likely to be safer than the routine 10% strength. A combination of 2.5% phenylephrine and 1% tropicamide has been reported to produce substantially more effective pupil dilation than tropicamide alone[430], relevant for patients needing fluorescein angiography or laser treatment.

### *Patient acceptance of pupil dilation*

There are few published data on patient acceptance of pupil dilation. In 2 large Australian eye studies (BMES, MVIP), only 0.3% and 2.0% of participants, respectively, refused mydriatic drops (unpublished). Most previously experienced the effects of pupil dilation. If concerns regarding adverse effects of pupil dilation were commonly held, then greater refusal would be likely. Sunglasses help with the transient increase in glare sensitivity.

## 2.4 Frequency of Examinations and Referral to an Ophthalmologist

**Guidelines**

4. Ensure that all people with diabetes have a dilated fundus examination and visual acuity assessment at the diagnosis of diabetes and at least every 2 years (Level I evidence[14;27]).
5. Screen children with pre-pubertal diabetes for DR at puberty (Level IV[27]).
6. Examine higher-risk patients (longer duration of diabetes, poor glycaemic control, blood pressure or blood lipid control) without DR at least annually (Level I evidence[14]).
7. Examine patients with any signs of NPDR annually or at 3- to 6-monthly intervals, depending on the DR level (Level IV evidence[27]).
8. Refer to an ophthalmologist urgently (within 4 weeks) if there is any unexplained fall in visual acuity, or if there is any suspicion of DME or PDR (Level IV evidence[27;28]).
9. All cases of mild or moderate NPDR should be followed closely to detect signs of sight-threatening retinopathy (Level II evidence[29;30]).
10. Conduct comprehensive eye examinations on pregnant women with diabetes during the 1st trimester and follow women with DR throughout their pregnancy (Level IV evidence[31]).
11. Women with gestational diabetes do not need ophthalmic surveillance after delivery, unless diabetes persists (Level IV evidence[31]).

**Key Points**

- Large, multicentre RCT have shown that timely laser treatment will prevent vision loss from PDR and DME.
- Early detection of sight-threatening retinopathy by regular eye exams is the key to reducing visual loss and blindness from DR.
- Persons with diabetes should have a dilated fundus examination by a trained examiner, with adequate sensitivity and specificity, at the time of diagnosis of diabetes and at least every two years thereafter, if no DR is found.
- Alternately, retinal photographic screening, that may be non-mydriatic, with adequate sensitivity, should be performed. Technical failure should prompt referral for a dilated fundus examination.
- Once DR is detected, further examinations should be conducted annually or at 3-12 monthly intervals depending on the level of DR. Any visual symptoms should prompt a further referral.
- It is important to measure the visual acuity of both eyes, at the time of DR screening.
- Children with pre-pubertal diabetes onset should be screened at puberty, unless other considerations indicate the need for an earlier examination.
- Women with diabetes who become pregnant should have a comprehensive eye examination in the first trimester and, if DR is found, they need close follow-up throughout pregnancy. This does not apply to women who develop gestational diabetes.
- Referral to an ophthalmologist should be urgent (within 4 weeks), if DME or PDR is suspected or if an unexplained fall in visual acuity is recorded.

### *Follow-up for Patients with and without Retinopathy*

T2DM data from the BMES[142], Liverpool DR study[123] and UKPDS indicate incidence rates for any DR in persons with T2DM to be around half (or less) that recorded previously by the WESDR[125;143] and Newcastle studies[127] 15-20 years earlier. The incidence of new PDR or DME more than halved and appears very low for T2DM patients not treated with insulin. It seems likely that these changing incidence rates reflect the better glycaemic and blood pressure control routinely achieved in recent years compared with the past (Level III-2 evidence). Despite such overall improvements, clinicians

still see some poorly controlled diabetic patients making their first presentation with advanced DR after relatively short periods of diabetes.

These trends prompted Younis *et al.* to propose a longer follow-up period for T2DM patients found with no DR[123] (Level III-2 evidence). To be 95% certain of not missing sight-threatening DR, people without DR could be re-screened after 5 years. To avoid a fall in compliance, however, Younis *et al.* suggest that screening every 2-3 years should be reasonable for those without DR. This interval is supported by the UKPDS and BMES data. It seems particularly reasonable for a longer period to be applied to those treated with diet alone because their DR incidence rates are very low. The protocols could be refined to allow more frequent screening for patients at especially high risk. To be 95% certain of not missing STR in T2DM patients with existing mild NPDR, the data from Younis et al. support the current recommendation for a review at least every year for patients with NPDR, or more frequently (4 monthly) once these signs are more severe (Level III-2 evidence)[123].

Younis *et al.* recommendations[123;124] are summarised below (Level III-2 evidence). The following screening intervals were recommended using examinations with high sensitivity and specificity:

| Disease Severity | Frequency |
|---|---|
| No DR in the absence of risk factors | 3 years |
| High-risk patients (using insulin, diabetes >20 years, both) | 1 year |
| Any very early NPDR | 1 year |
| Mild pre-proliferative DR | 4 months |

As 72% of patients in the Younis cohort had no DR, the recommendation away from yearly screening for the major subgroup without retinopathy and no high-risk criteria was likely to significantly reduce costs.

Lengthening screening intervals may risk loss of contact with patients and imply that visual loss is unlikely and of low concern[431;432]. In addition, opportunities to detect other eye conditions more frequent in diabetes (e.g. cataract, glaucoma) would decline. There is also a potential loss of occasions for eye care practitioners to reinforce the importance of glucose control and other risk DR factors. It is thus sensible to continue the previously recommended 2-yearly screening interval for diabetic patients without any DR[1].

This is reinforced by a review of the 10-year Iceland experience (1995-2005) which found biennial screening to be safe and effective[433]. No person progressed from having no retinopathy to STR in less than two years. All patients who developed CSME or PDR had been screened annually before these changes developed.

In the MVIP, 50% of persons with diabetes had not seen an eye care professional in the last 2 years[403]. The efficacy of a screening program depends on patient compliance. The Diabetic Retinopathy Awareness Program in New York, USA examined the factors predicting non-adherence to Diabetes Vision Care guidelines[434]. The factors were younger age, T2DM with or without insulin use, shorter diabetes duration, last eye exam performed by an optometrist or other non-ophthalmologist, less practical knowledge about diabetes, and lack of formal prior diabetes education[434]. A tailored approach to screening intervals and screening frequency may therefore be appropriate for some persons.

Screening strategies depend on the rates of appearance and progression of DR and on risk factors that could influence this. STR is very rare in T1DM patients in the first 5 years of diabetes or before

puberty[435]. Screening in these cases therefore could start at age 12[435]. Over the subsequent two decades, however, almost all T1DM patients develop retinopathy[31]. A significant number of people with T2DM already have DR at diagnosis.

Pregnancy may accelerate the development and progression of DR. Hence, women with diabetes who become pregnant should have a comprehensive eye examination in the first trimester. If DR is present, they should have close follow-up throughout the pregnancy. This does not apply to women who develop gestational diabetes, who do not need to be re-examined unless the diabetes persists[31].

Finally, in view of the frequency[436;437] and ability to treat[438] amblyopia, it is recommended that children should have the vision of both eyes tested following the diagnosis of diabetes to ensure normal baseline vision.

### *Referral to an Ophthalmologist*

Most studies of eye examinations in people with diabetes focus on the detection of early DR. Few studies address which DR level should prompt routine referral to an ophthalmologist. The 1997 Guidelines recommended referral to an ophthalmologist when DR greater than the presence of occasional microaneurysms was found[1]. Few recent data from major studies indicate that this timing of referral to an ophthalmologist needs changing. However, the committee felt that because no clear evidence supported routine referral at a particular DR level, this recommendation should no longer be a guideline.

### *Criteria for Urgent Referral to an Ophthalmologist*

The main objective of DR screening is to detect patients with STR, given the established value of laser photocoagulation treatment in preventing visual loss in such cases. The DRS and ETDRS provide very strong support for the therapeutic benefits of laser treatment. A Swedish report[439] indicated that reasonable long-term retention of vision was possible for all but a few people with T2DM receiving laser treatment (only 6% of those treated) due to chronic complications from DME.

Patients with any level of DME, severe NPDR, or any PDR require prompt care from an ophthalmologist experienced in DR management. Referral is also needed if there is any unexplained loss of vision, or if a screening examination cannot be performed[368;440].

The UK National Institute for Clinical Excellence (NICE) use the following criteria to define the level of urgency of referral[28]:

- Referral to an ophthalmologist within 4 weeks is advised for an unexplained drop in visual acuity, hard exudates present within one disc diameter of the fovea, DME present, or pre-proliferative or moderate NPDR present.
- Referral to an ophthalmologist within 1 week is advised if there are new vessels, vitreous haemorrhage, or rubeosis iridis.
- Emergency referral to an ophthalmologist on the same day is advised if there is sudden, severe visual loss or symptoms or signs suggesting retinal detachment.

Few data support changing the current Australian recommendation[27] of 2-yearly eye exams for persons with diabetes without retinopathy and yearly eye exams once DR is identified. This biennial screening schedule was confirmed in a recent Icelandic study[433]. Evidence since 1996 does not suggest that this recommendation for biennial DR screening needs to be changed.

## 2.5 Role of Fluorescein Angiography in Assessing Diabetic Retinopathy

**Guidelines**

12. Perform FA if diffuse DME is present, and use the angiogram to identify sources of perimacular leakage and non-perfusion, to guide focal and grid laser treatment (level II evidence[32-34]).
13. Use FA to assess signs of likely macular ischaemia (level II evidence[35;36]).

**Consensus Good Practice Point**

3. Use FA in selected patients with PDR, or after PRP therapy for PDR to assess response.

**Key Points**

- Fluorescein angiography (FA) is not appropriate to screen for DR.
- Routine use of FA should be guided by clinical experience, as there is little evidence to provide firm guidelines.
- The presence of CSME is the principal justification for FA in DR patients. It may not be needed to guide treatment if DME is occurring from a well-defined ring of hard exudates or from focal maculopathy. Nevertheless, FA should be performed whenever diffuse macular oedema is present, in order best to identify sources of perimacular leakage and non-perfusion, guiding focal and grid laser treatment.
- FA can determine presence of macular ischaemia.
- FA may be warranted in selected cases of severe NPDR to assess severity of retinal ischaemia, to detect subtle NVE or in assessing patients with PDR before PRP. It may also be warranted in certain cases to determine adequate regression of DR after laser treatment.
- FA has a small risk of significant side effects. Frequent adverse reactions include mild transient reactions that require no medical management such as nausea (5-10%), vomiting (1.3%), dizziness (0.6%), and itching (0.5%).
  Moderate adverse reactions, defined as transient but requiring some medical intervention, include urticaria, syncope, thrombophlebitis or local tissue necrosis from extravasation of injected fluorescein and occur rarely. Severe adverse reactions, such as anaphylaxis or cardiac arrest, were reported in 1:20,000 FA procedures. Deaths occurred in 1:50,000-200,000 FA procedures. A number of FA-related deaths have been reported in Australia.
- It is important to have resuscitation equipment and medications readily available wherever FA is performed.

### Role of Fluorescein Angiography (FA)

Fluorescein angiography (FA) is a useful method for understanding clinico-pathologic changes in the retinal circulation of eyes with DR[441]. It has frequently been used in clinical research studies to document retinal vascular pathology. The ETDRS performed FA on all participants to assess severity and predict progression of DR[36;442]. Given the potential for rare major side effects, routine use of FA in evaluating DR has now been largely abandoned, and this investigation is now reserved principally for the assessment and management of DME. Although with the recent availability of OCT in qualitatively and quantitatively assessing and monitoring DME, the indications for FA have been reduced further. FA is still the only method to assess retinal, and in particular macular, ischaemia.

### Role of FA in Screening and Management of DR

While FA has been shown to detect early retinopathy in eyes classified with no retinopathy on ophthalmoscopy or stereoscopic fundus photographs[443-446], this is an inappropriate use of FA. In the DCCT, 21% of patients classified with no DR on retinal photographs had fluorescein angiographic

signs of DR in 2 standard 30° fields of each eye[443]. FA findings in DR include dye leak, capillary dilation, capillary filling defects, or microaneurysm-like spot capillary dilation[446]. In patients with impaired glucose tolerance, FA may detect incipient retinal microvascular changes, indicating early blood-retinal barrier breakdown before diabetes becomes manifest[447;448]. Fluorescein angiography may detect subtle early retinal vascular changes in diabetic persons without clinical DR. Signs in these patients are minimal and never require laser treatment. Such early detection of DR by FA does not add information for management and should only be used as a research tool. As a research tool, FA is useful in understanding clinico-pathologic changes in the retinal circulation of eyes with DR, in classifying DR[449-451] and to predict progression from baseline FA characteristics[35], particularly patterns of capillary non-perfusion[450;452]. All ETDRS patients had FA to identify sources of leak in patients with DME and to assess the severity of the retinopathy[449]. FA is a standard test in many clinical research studies, particularly RCT, to confirm diagnosis and eligibility of patients, and to document the adequacy of laser treatment[453]. For the ETDRS treatment component, FA was crucial to define the type and source of leak targeted[449;453]. FA was used to assess compliance with treatment protocols[453]. In clinical trials assessing microvascular effects of improved diabetic control, FA has also played an important role in evaluating treatment effects[453;454].

While some authors have suggested that sub-classification of diabetic retinopathy using FA could help to identify subgroups with a worse prognosis or in need of closer follow-up or different management, there is no strong evidence to support this role[455]. FA can be useful in assessing the causes of reduced visual acuity[397].

In eyes with mild NPDR and normal visual acuity, there is no justification for "baseline" FA[456]. Because of the relative frequency of unpleasant side effects and the potential for serious adverse effects[457], as well as cost, FA has no place as a screening test for DR or to evaluate mild NPDR[29;458].

### *Recommendations for Routine FA in Managing DR*

There is no evidence to recommend routine FA for routine assessment of patients with DR. The American Academy of Ophthalmology Preferred Practice Pattern now recommends that FA be used only as a guide for treating CSME, to evaluate causes of unexplained decreased visual acuity, or to identify areas of macular capillary non-perfusion and/or macular oedema[34]. FA occasionally may be useful in identifying suspected but clinically obscure retinal neovascularisation, but not for routine screening of patients without DR or with relatively early NPDR. Table 2.4.1 outlines the AAO recommendations on the use of FA; essentially CSME provides the only current justification for routine FA in patients with DR[34] (Level IV evidence). FA may be useful in some cases of severe NPDR, in order to assess the severity of retinal ischaemia and risk of visual loss (Level IV evidence), as in many cases of PDR.

Many studies including the ETDRS guidelines for laser treatment of DME explicitly state that FA is not needed to guide treatment if macular oedema is occurring from a well-defined ring of hard exudate[459] (Level II evidence). It is current clinical practice in Australia not to perform FA for such patients. Indeed, when the source of oedema is clinically evident to enable accurate focal laser treatment, then the majority of clinicians mostly do not perform FA.

One study, reporting the use of FA in planning laser treatment for DME, found that FA only improved treatment accuracy by 49% to 55%[460], by significantly improving the treatment accuracy of only one of the four retinal specialists studied[460]. The authors suggest that FA may improve treatment-planning accuracy by reducing either over-treatment or under-treatment, and may help clinicians identify ischaemic areas, for which ETDRS guidelines mandate treatment[461]. In a clinic series of 40 eyes from 22 diabetic patients, laser photocoagulation directed at microvascular lesions detected by clinical examination was found to result in complete angiographic control of macular

oedema in 63% of eyes after reaching satisfactory clinical control of the diabetes (Level IV evidence) [462].

**Table 2.5.1: Indications for fluorescein angiography (FA) in diabetic retinopathy**

| Severity of Diabetic Retinopathy | CSME | Indication for FA† | | |
|---|---|---|---|---|
| | | None | Rarely | Usually |
| Normal | No | • | | |
| Mild NPDR | No | • | | |
| | Yes | | | • |
| Moderate NPDR | No | • | | |
| | Yes | | | • |
| Severe NPDR | No | | • | |
| | Yes | | | • |
| PDR | No | | • * | |
| | Yes | | | • |

†Adapted from the American Academy of Ophthalmology[34;463]

* Many ophthalmologists recommend FA to assess the extent of capillary non-perfusion in PDR patients prior to PRP

### *Risks and Complications from Fluorescein Angiography*

FA is generally a safe procedure but serious side-effects occur[464-466]. Although intravenous FA has been used for almost four decades to examine many different chorioretinal disorders, several surveys totalling over 35,000 FA procedures have reported its use to be associated with a small risk of significant side effects[465;467-469] (Level IV evidence). The most frequent adverse reactions associated with FA include mild transient reactions that require no medical management such as nausea (within one minute of the injection (5-10%), vomiting (1.3%), dizziness (0.6%), and itching (0.5%). Moderate adverse reactions, defined as transient but requiring some medical intervention, include urticaria, syncope, thrombophlebitis or local tissue necrosis from extravasation of injected fluorescein[465]. Severe adverse reactions such as anaphylaxis or cardiac arrest have been reported to occur in 1:20,000 FA procedures. Death has been reported following 1:50,000-200,000 angiograms. A number of FA-related deaths have been reported in Australia.

No substantive difference in adverse reaction rates has been reported with different fluorescein concentrations (5%, 10%, 25%), although 10% is the most frequently used. There is a strong impression, however, that common side effects are dose-related, so that previous doses of 10ml of 10% solution (or greater) are now rarely administered, with 2.5 to 5ml of 10% solution now typically administered. Modern digital retinal cameras now provide improved visibility of fluorescein signs, permitting use of even lower doses of dye. Although the incidence of serious allergic reactions is rare, it is strongly recommended that necessary resuscitation equipment and medications are readily available whenever FA is performed. Ipsilateral intravenous fluorescein injection is contraindicated in the setting of compromised lymphatic drainage after arm, breast, or axillary node dissection[470]. Prophylactic use of metoclopramide was reported to significantly reduce the incidence of nausea and vomiting [471], though its use can also be associated with adverse effects.

The Royal Australian & New Zealand College of Ophthalmologists has developed fluorescein angiography guidelines that cover use, side effects and patient consent[472].

### *Oral Fluorescein Angiography*

Several studies assessed the use of oral fluorescein angiography (FA)[473-478], in addition to fundus photography, to identify STR and DME. Oral FA was shown to detect CSME with a sensitivity of 89% and specificity 80%[473]. However, the current practical alternative to FA, OCT, has effectively superseded oral FA because of its improved accuracy in defining and quantifying DME with negligible morbidity.

## 2.6 New Modalities to Assess the Severity of Diabetic Retinopathy

**Key Points**

- Ophthalmoscopy, slit lamp biomicroscopy, fundus photography and fluorescein angiography (FA) have traditionally been used to assess the severity of DR.
- Optical Coherence Tomography (OCT) provides an effective qualitative and quantitative method of examining the eye, particularly in detecting early macular thickening, and also in following progression or regression of macular oedema over the course of treatment. OCT has good reproducibility and accuracy for the measurement of retinal thickness with an axial resolution in the order of 10μm or better with newer instruments. OCT also correlates reasonably with both biomicroscopic examination and FA in CSME.
- Heidelberg Retinal Tomography (HRT) and the Retinal Thickness Analyzer (RTA) are two other modalities that have the potential to provide an indirect measure of retinal thickness in order to quantify diabetic macular oedema. Both techniques have acceptable reproducibility and an axial resolution of around 150μm and 50μm respectively.
- All three new imaging modalities are disadvantaged by image degradation from ocular media opacities such as significant cataract (particularly posterior subcapsular or cortical cataracts, the types seen in diabetes) or vitreous haemorrhage, and by difficulties with small pupils and the relatively high cost of the currently available equipment. To date, all have been assessed only in case series.
- The electroretinogram (ERG) may possibly detect abnormalities at the retinal level before overt DR is evident. As with other imaging instruments, severe media opacities can also interfere with some standard ERG measures, although bright-flash ERG techniques can overcome this to some extent.

Ophthalmoscopy, slit lamp biomicroscopy, fundus photography and FA have traditionally been the recommended methods of assessing the severity of DR. However, each of these methods is limited by subjective interpretation and documented problems with inter- and intra-observer variability in assessing particular signs, particularly diabetic macular oedema (DME) and the overall DR severity.

Visual acuity is not sufficiently sensitive to provide information about the early stages of DR, because acuity may be preserved even in the presence of sight-threatening DR[479]. Lower levels of visual acuity were significantly associated only with definite or substantial retinal thickening[480]. Retinal thickness has only an intermediate to good correlation with logMAR visual acuity ($r = 0.53$ to $0.89$)[480;481].

As DME is one of the principal causes of vision loss in diabetic patients, new techniques have been developed to overcome the issues of subjectivity and reproducibility arising from traditional stereoscopic biomicroscopic or fundus photograph examination. These objective tests include imaging techniques such as Optical Coherence Tomography (OCT), Heidelberg Retina Tomograph (HRT), Retinal Thickness Analyzer (RTA), and such non-imaging techniques as electroretinogram (ERG). Among these, the most promising new modality is OCT.

### *Optical Coherence Tomography (OCT)*

OCT is a non-contact, non-invasive technique using the principles of optical interferometry to image the eye. It is analogous to B-scan ultrasound, but employs light rather than sound[481]. OCT produces cross-sectional images of the retina and optic disc similar to histological sections to an axial resolution of 10 μm or better with newer instruments[482]. OCT images also permit visualisation of intraretinal features found in diabetic retinopathy such as cysts, hard exudates, serous detachments and tractional retinal elevations, sometimes demonstrating vitreous bands[483;484].

Multiple case studies have repeatedly demonstrated that OCT has very good reproducibility and accuracy for the measurement of retinal thickness[480;482;485-488].

Intraretinal abnormalities found in OCT correlate with changes in FA[489-492]. Very early DME morphological changes may be seen better with FA than with OCT, whereas serous detachment of the fovea was seen in OCT but not in FA[491;493]. OCT identification of retinal thickening also correlates well with areas of retinal dysfunction[494]. Morphological studies of DME reveal three OCT patterns: sponge-like thickening, cystoid macular oedema and serous retinal detachment[491;495;496]. Eyes with mild-moderate NPDR are significantly more likely to have sponge-like retinal swelling; while eyes with severe NPDR or PDR are more likely to have serous retinal detachment or vitreofoveal traction[497].

Foveal and extrafoveal retinal thicknesses have also been found from OCT studies to be highly correlated ($r = 0.89\text{-}0.97$)[480;481]. Multiple masked cross-classification studies have reported excellent agreement between the presence of macular oedema on OCT and biomicroscopic examination when foveal thickness was normal (≤200μm) or moderately increased (>300μm), but there was poorer agreement when foveal thickness was only mildly increased (200-300μm)[481;487;488;496;498]. Eyes with subclinical DME may be more likely to progress to CSME, for which laser photocoagulation is usually indicated[498].

Studies have reported differing correlations between OCT-measured retinal thickness and visual acuity. A wide range of visual acuity may be observed for a given degree of retinal oedema. A cross-sectional longitudinal study performed by the Diabetic Retinopathy Clinical Research Network found a modest correlation between OCT-measured centre-point thickness and visual acuity, and a modest correlation of changes in retinal thickening and visual acuity after focal laser treatment for DME[499]. This study did not recommend using OCT retinal thickness measurements as a surrogate for visual acuity.

OCT therefore provides an effective qualitative and quantitative method of examining the eye, allowing screening for early macular thickening, and also following progression or regression of macular oedema over the course of treatment[483;493;500]. It has been incorporated as a routine measure in a number of ongoing RCT of new treatments for DR (e.g. PKC inhibitor or anti-VEGF). The test can be conducted in a few minutes, and examiners certified by a reading centre. Although OCT is a valuable diagnostic tool, it is disadvantaged by image degradation from ocular media opacities such as significant cataract (particularly posterior subcapsular or cortical) or vitreous haemorrhage, difficulties with small pupils, and the relatively expensive cost of the currently available equipment[483].

Fourth-generation ultra-high-resolution OCT (UH-OCT), not yet commercially available, provides a major improvement in axial resolution of approximately 3μm[491].

### *Heidelberg Retina Tomograph (HRT)*

The HRT detects DME by using scanning laser ophthalmoscopy to provide an indirect measure of retinal volume[501]. Although the reproducibility of this technique is acceptable, the resolution achievable is limited to around 150μm. Various reports have found the sensitivity of HRT in detecting macular oedema to be between 58% and 92%[502]. In a cross-classification study of 34 patients receiving RTA and HRT II, the HRT II had a better agreement with clinical assessment of macular oedema than the RTA, and better sensitivity for DME (92% vs. 57%)[502]. The currently available instrument is the HRT II, Heidelberg Engineering, Germany.

### *Retinal Thickness Analyser (RTA)*

The RTA projects oblique laser slits onto the posterior pole to determine retinal thickness. Compared to OCT, the main limitation of RTA arises from greater degradation of images and accuracy from refractive errors, media opacities, and intraretinal lesions such as haemorrhages or exudates[482;493]. This limits its usefulness in patients with diabetes, who typically develop lens opacities relatively early. Reports, including the manufacturer's data, have found results from this instrument to be reproducible and capable of around 50μm resolution. The sensitivity for detecting DME ranges between 69% and 100%[502]. In a study of 55 eyes comparing RTA and OCT[482], retinal thickness measurements were strongly correlated for the two instruments, but systematically slightly lower with RTA.

### *Electroretinogram (ERG)*

ERG is a non-invasive objective method of evaluating retinal function by measuring the bio-electrical response of the retina to visual stimuli. ERG provides an index of retinal electrical activity that can to detect abnormalities at the retinal level at very early stages of disease when there are no visible changes on fundal examination[503]. Several ERG paradigms, such as full-field ERG, focal ERG, multifocal ERG (mfERG), and pattern ERG (pERG), have been used to study associations with DR. As with other instruments, severe media opacities can interfere with some ERG measures, though bright-flash ERG techniques can overcome this to some extent[503].

Early ERG changes may occur in patients with diabetes before development of DR[504;505]. Oscillatory potential and pERG recordings show decreased amplitude and increased latency with increased severity of diabetic retinopathy[503;504]. A longitudinal study of 85 diabetic patients demonstrated the predictive power of ERG by reporting that subjects with normal or greater than normal oscillatory potential amplitudes at the start of the study were less likely to develop PDR over the next 15 years[503;506] (Level III-2 evidence). A study that assessed the relationship between OCT foveal thickness and foveal function measured by mfERG in patients with NPDR and no previous laser treatment found that increased macular thickness (>300μm) was correlated with reduced amplitudes, prolonged implicit times and worse visual acuity[507].

### *Other Techniques*

#### *Colour contrast threshold testing*

Colour contrast threshold testing of tritan wavelengths[508] has also been proposed as a useful method of identifying sight-threatening DR (sensitivity 94% and specificity 95%), particularly when combined with retinal photography. To date, there have been no other comparison studies.

#### *Computerised diabetic retinopathy grading systems*

Computerised systems have also been developed to aid retinal photograph grading for DR signs[390-392;509]. The combination of digital photography and automated image analysis is a research growth area aimed at reducing the burden of DR screening. Currently it is limited by technical failures related to the identification of vessels and artefacts.

# 3. Treatment of Diabetic Retinopathy

## *3.1 Laser Treatment (Photocoagulation) for Diabetic Retinopathy*

**Guidelines**

14. For high-risk PDR, perform PRP as soon as possible (Level II evidence[37;461]).
15. For earlier PDR stages, commence PRP after any maculopathy is stabilised (Level II evidence[37;461]).
16. Consider PRP for severe NPDR, particularly if there is T2DM, poor follow-up compliance, impending cataract surgery, renal disease, pregnancy, severe disease in the fellow eye or evidence of retinopathy progression (Level II evidence)[38].
17. For less severe retinopathy, balance benefits of laser against the small risk of damage to vision from laser treatment (Level II evidence[37]).
18. For all eyes with CSME, apply standard focal/grid macular laser treatment to areas of focal leak and capillary non-perfusion. (Level II evidence[37;39]).
19. For DME not meeting CSME criteria, consider either laser treatment or deferral, depending upon progression of signs, the status of the fellow eye, or ability to follow closely, and warn patients of potential risks (Level II evidence[37;39]).
20. For eyes with both PDR and CSME, but without high-risk PDR, delay PRP until focal or grid macular laser treatment is completed (Level II evidence[37;39]).
21. Review patients closely after completion of laser treatment. If high-risk characteristics do not regress or re-develop, perform additional laser treatment (Level II evidence[37]).
22. Warn patients about the adverse effects of laser treatment (Level II evidence).

**Consensus Good Practice Point**

4. Complete as much PRP as possible before considering vitrectomy surgery, in order to minimise post-operative complications.

**Key Points**

- Multiple RCT, including the DRS and ETDRS, have shown that panretinal photocoagulation (PRP) significantly reduces the risk of severe vision loss (best corrected visual acuity <5/200) from PDR by at least 50%, and that focal or grid laser photocoagulation reduces the risk of moderate vision loss (doubling of the visual angle) from CSME by at least 50%.
- Recommendations of the type and pattern of laser photocoagulation have not changed since the ETDRS reported guidelines in 1987:
    - Apply PRP using 200- to 500-micron burns placed approximately one-half burn width apart, from the posterior fundus to the equator.
    - Apply focal laser photocoagulation using 100-micron laser burns to areas of focal leakage and areas of capillary non-perfusion in the peri-macular region.
    - Apply grid laser photocoagulation using 50-100 micron burns in a grid pattern to areas of diffuse leakage and non-perfusion at the macula.
    - Although treatment is ideally guided by fluorescein angiography, this may not be needed to treat many cases with focal DME. Treatment is unlikely to be beneficial in the presence of significant macular ischaemia.
- ETDRS results were achieved by rigorous application of laser recommendations and close follow-up with re-treatment, as needed.
- Mild, diffuse macular grid laser was shown to have no benefit over routine focal/grid laser, reducing DME and OCT macular thickness less than standard treatment, so is not recommended.
- The following timing of laser treatment is recommended:
    - Patients should be seen at follow-up visits every 1-4 weeks during the course of PRP

and then every 2-4 months thereafter until stable.

- Follow-up of patients with DME should also occur every 2-4 months until stable.

Timely laser photocoagulation currently remains the 'gold standard' therapy for sight threatening DR[510]. In panretinal ('scatter') photocoagulation (PRP), laser burns are placed over the entire retina sparing the central posterior pole and macula. In focal or grid laser, microaneurysms, areas of capillary non-perfusion, and leak in the paramacular region are treated. Multiple RCT, including the DRS[511] and ETDRS[39] and a meta-analysis of trials[512], have shown that PRP significantly reduces the risk of severe vision loss (best correct visual acuity <5/200) from PDR by at least 50% (Level II evidence) and that focal or grid laser treatment reduces the risk of moderate vision loss (doubling of the visual angle) from CSME by at least 50% (Level II evidence). Laser for DME also has a beneficial effect on vision-related quality of life[513].

### *Randomised Controlled Trials of Laser Treatment for Diabetic Retinopathy*

Laser treatment for diabetic retinopathy was assessed in a number of high-quality, well-designed RCT[514], particularly two large U.S. multi-centre trials, the DRS[147;511;515-519] and ETDRS[32;37;39;105;461;520-523]. Both trials had large sample sizes, excellent compliance and adequate follow-up[32]. Two further multi-centre U.K. RCT had a smaller sample size, moderate losses to follow-up, did not provide compliance data and did not analyse by intention to treat[524;525]. Other RCT were relatively small[526-528] or had variable quality[529;530]. Some other studies did not provide enough information to assess study quality. Table 3.1.1, modified from Mohamed et al.[14], summarises these trials.

Despite these differences, the findings of treatment benefit from laser for PDR and DME were highly consistent across all RCT. The strength of the beneficial treatment effects demonstrates that laser photocoagulation is a most effective treatment for diabetic retinopathy. In reporting results from the ETDRS study by patient, rather than by eye[531], Ferris showed that only 1% of study patients who presented with PDR and received laser treatment developed severe visual loss (<5/200) by 5 years.

Although these excellent results from the ETDRS could also have resulted from the aggressive follow-up and close attention to need for re-treatment at each visit, other studies have also confirmed long-term stability of DR after laser[532;533].

### *Laser Audit Studies*

The National Diabetic Retinopathy Laser Treatment Audit was a prospective survey of all ophthalmologists offering laser treatment for DR in the UK[534-536]. The maculopathy paper reported on 546 patients undergoing their first laser treatment for DME without PDR, during a 2-month period in 1995. DME was detected from systematic screening in 65%, from a chance finding in 19%, and from symptomatic presentation in 12%[535]. DME was categorised as predominantly exudative in 70%; 96% of these eyes were treated with standard focal macular laser. For DME that was diffusely oedematous (in 9% of cases), 79% of such eyes were treated with grid macular laser. The most frequently used laser spot size was 100μm, followed by 200μm and then 50μm; this applied to both focal and grid laser. FA was performed before treatment in only 20% of DME cases overall (14% of cases with exudative DME and 34% of cases with diffuse DME). The PDR paper[536] reported on 284 patients undergoing their first PRP for PDR during a 2-month period in 1995. PDR was detected from systematic screening in 47%, from a chance finding in 16%, and was symptomatic in 29%. The authors estimated that, compared to DRS and ETDRS recommendations, at least 33-40% of eyes may have been under treated initially, including 31-39% of eyes with high-risk characteristics. Concurrent DME was present in 30% of those treated for PDR.

In a Danish study of 601 PDR cases, in which 4422 PRP treatment sessions were performed in 1013 eyes, older pre-treatment age, greater number of PRP sessions, and need for vitrectomy predicted a poorer visual prognosis[537].

### *DRS and ETDRS Trials*

The DRS and ETDRS trials assessed three stages of retinopathy: PDR, NPDR and DME, particularly CSME. Each trial included subjects with one or all of these stages, and eyes were randomly assigned to receive laser or to serve as a control. Individual trials identified stages in the natural history of DR at which laser therapy is beneficial.

### *DRS Findings and Recommendations*

The DRS assessed whether PRP, administered by argon laser or xenon arc could improve the prognosis of patients with PDR. Enrolled diabetic patients (either type 1 or type 2) had a broad range of retinopathy severity determined from stereo retinal photographs. PDR was present in at least one eye or severe NPDR was present in both eyes. Both location and severity of new vessels and the presence of preretinal or vitreous haemorrhage were important prognostic factors. The DRS identified a subgroup of patients with "high-risk characteristics" (HRC), any of which predicted a poor visual prognosis: (1) eyes with new vessels on or within one disc diameter of the optic disc (NVD), (2) NVD equal to or exceeding ¼ to ⅓ disc area in extent, (3) any new vessels within one disc diameter of the optic disc and associated with vitreous or pre-retinal haemorrhage, or (4) proliferation elsewhere (NVE) at least ½ disk area in size associated with vitreous or pre-retinal haemorrhage.

After 2 years, focal and scatter PRP was associated with a 50% reduction in development of severe visual loss, in eyes with PDR with or without HRC (26% versus 11% for eyes with HRC, and 7% versus 3% in eyes without HRC). This reduction persisted through 5 years. Even after 15 years, visual outcomes between the two groups still differed substantially. Among surviving DRS participants, visual acuity was 6/12 or better in 58% in argon-treated eyes, compared to 33% for control eyes. Visual acuity of 6/60 or better was maintained in 95% of argon-treated eyes, compared to 58% of control eyes[532].

For eyes with HRC, beneficial effects of laser therapy clearly outweighed risks of harmful treatment effects, which included a small reduction of visual function in 10% and a mild constriction of peripheral visual fields in 5% of treated eyes, impaired night vision, and decreased accommodation. More severe side effects, such as severe central visual loss or peripheral field constriction, were rare. However, for eyes with less severe retinopathy, the DRS did not provide a clear choice between prompt treatment or referral, unless progression to these severe stages occurred. The DRS did not assess effects of focal macular laser in cases of DME or CSME. DRS data indicated that extensive PRP reduced the 5-year risk of severe visual loss by at least 50%[511] in eyes with PDR. However, argon PRP also caused persistent acuity loss of one line in 11% and more than two lines in 3% of patients. Specific treatment complications included inadvertent foveal burn, diminished visual field, increased DME, ciliary block glaucoma, Bruch's membrane rupture, and tractional retinal detachment.

### *ETDRS Findings and Recommendations*

The ETDRS found that focal or grid laser photocoagulation in patients with CSME reduced the risk of moderate visual loss (defined by a doubling of the visual angle) by at least 50% and increased the chances of visual improvement by one or more line. The ETDRS recommended that focal or grid treatment should be considered for eyes with CSME, particularly when the macular centre is involved or threatened[33]. For DME not meeting CSME criteria, there was no difference in visual acuity between treated and untreated patients over 2 years. Therefore, deferral of treatment until

CSME criteria are met appears warranted, assuming close follow-up is possible and PDR is not present[29].

The ETDRS examined the timing of laser treatment for patients with mild to severe NPDR and early PDR. ETDRS investigators recommend that patients with high risk PDR should have PRP as soon as possible. Those with less severe PDR (or severe NPDR) have a lower risk of severe visual loss (3.6%-7.0% in 2 years). Although the risk of damage to vision from laser treatment assumes greater importance, and treatment could sometimes be deferred, in many such cases it should proceed (Level II evidence)[33;36;38]. Treatment was not recommended in eyes with mild or moderate NPDR, provided careful follow-up could be maintained[29].

A later ETDRS analysis examined subgroups of various maculopathy characteristics (capillary closure, severity of leak, extent of DME, presence of cystoid or severity of exudate)[33]. Trends for treatment benefit were reduced for eyes with less extensive retinal thickening, particularly at the centre of the macula. For these eyes, an initial period of close observation could be preferable to immediate treatment, particularly when most leak is close to the centre of the macula, increasing the risk of damage to it from direct treatment or subsequent migration of treatment scars[33].

The ETDRS also examined treatment options for eyes with both PDR and CSME. This issue is important, as PRP can aggravate DME. Delaying PRP until completion of focal laser reduced the risk of visual loss associated with increasing macular oedema. Once focal laser is completed, and a decision is made to initiate PRP, it may be best to limit the treatment in each session, fractionating PRP into a number of sessions. However, in high-risk eyes, delaying PRP until focal laser is completed poses greater risk[29;32].

Rigorous follow-up of treated cases and aggressive, frequent re-treatment if PDR or CSME failed to regress were an integral component of the protocols followed in both the DRS and ETDRS. To achieve comparable results, a similar follow-up approach with re-treatment as necessary is strongly recommended.

### *Other Laser Studies for PDR or Macular Oedema*

A meta-analysis of the DRS and four other RCT[524;525;529;530] of laser therapy for PDR confirmed the effectiveness of PRP[512] (Level I evidence). Based on the 5 RCT, the authors calculated a combined "best estimate" of the relative risk of blindness associated with laser treatment, and concluded that laser treatment reduced the risk of blindness in treated eyes with PDR by 61%. Laser treatment of severe NPDR was supported by findings from a recent small RCT[38].

Other than the ETDRS, a number of other RCT of argon laser treatment for DME have been reported[526;527;538;539]. In these trials, treatment using a small spot size (50-100μm) was applied to areas of focal leakage or microaneurysms, while a grid pattern (100-200μm) was used to treat areas of diffuse leakage[105;526-528;538;539]. Many eyes required multiple treatment sessions. A consistent beneficial treatment effect from laser therapy for DME was found.

### *Patterns of Laser Treatment*

Recommendations of the type and pattern of laser treatment continue to follow ETDRS guidelines[39;540]. These guidelines recommend PRP for patients with high-risk PDR using 500μm burns placed approximately one-half burn width apart, from the posterior fundus to the equator. In routine practice, adequate burns are obtained using settings ranging from 200 up to 500μm. The recommendations for focal and grid photocoagulation are for treatment to areas of macular thickening and capillary non-perfusion leading to CSME. Focal laser photocoagulation involves application of 100μm laser burns to areas of focal leakage (i.e. leaking microaneurysms) and non-perfusion, while grid laser photocoagulation involves application of 50-100μm burns in a grid

pattern to areas of diffuse leakage and non-perfusion[39;461]. No treatment-effect differences were found in RCT between argon blue, green or krypton, or diode laser wavelengths[541].

To minimise PRP-induced exacerbation of CSME, the ETDRS recommends performing focal/grid laser before PRP. However, for patients with concurrent CSME and high-risk PDR, combined focal/grid and panretinal photocoagulation at the first treatment session should be considered[34].

### *Alternate or New Delivery Modalities*

Binocular indirect PRP laser was used in cases with mental, physical or medical conditions which limited conventional contact PRP [542]. This modality was found effective and safe, with over 80% having improved or stable vision (Level IV evidence). A theoretical benefit of sub-threshold diode laser has also been proposed, as this appeared to have an equivalent visual response in treating DME[543], and could also reduce laser scarring[544] or laser scar expansion[543].

A semi-automated patterned scanning laser that delivers multiple very short duration laser burns was also described[545]. Because of its reduced laser exposure, this modality reduces the time and also the discomfort from treatment. Although it is now used in clinical practice[546], comparisons of its long-term effects with traditional instruments are not yet available.

A large 12-month RCT of 'mild macular grid laser' was conducted, in which microaneurysms were not treated directly, but the macula was treated more diffusely (161 eyes). This approach showed no benefit over focal/grid laser (162 eyes) using standard ETDRS technique (Level II evidence). DME, as measured by OCT central macular thickness, was reduced less using this new technique than with conventional therapy[545]. The authors therefore recommended no change in technique following this trial.

### *Side Effects and Complications of Laser Treatment*

The most frequent side effect of laser treatment is discomfort or pain during PRP treatment, which in some cases requires peri-bulbar or sub-tenons anaesthesia. This is minimised using the newer instrument that delivers shorter-duration burns[545].

After treatment, transient blurring of vision for days or weeks, increased glare sensitivity and difficulty with light-dark adaptation are also common[33]. Longer-term visual reduction may occur because of exacerbation of DME in some patients, and a worse visual prognosis after PRP may be seen in patients with pre-treatment parafoveal OCT thickness over 300μm[547]. This effect may be minimised by treatment of any DME prior to commencing PRP, as recommended by the ETDRS[29]. Visual field constriction after PRP[548] could affect driving performance.

There is also a slight risk of damage to the macula from inadvertent foveal laser or from subsequent migration or enlargement of laser treatment scars[33]. This might be more marked with laser using longer wavelengths[549].

Aiello[550] has summarised the complications to include peripheral field constriction, night blindness, internal ophthalmoplegia, mild colour vision changes, inadvertent foveal burn, macular oedema secondary to PRP or heavy focal burn, premacular fibrosis, foveal traction, serous and/or choroidal detachment, acute angle-closure glaucoma, cornea iris or lens burns, retrobulbar haemorrhage associated with anaesthesia, secondary retinal hole and rhegmatogenous retinal detachment, and progression of retinopathy to traction retinal detachment. However, many of these outcomes can develop as part of the natural history of DR.

### *Timing and Follow-up of Laser Treatment*

The decision to initiate laser photocoagulation for DR depends on its stage, presence of co-existing DME and of risk factors for more rapid progression of retinopathy (e.g. T2DM, very poor control, renal disease or pregnancy). The principal aim of laser therapy is to stabilise current visual acuity. It is therefore important that patients with good visual function and DME involving or imminently threatening the centre of the macula be considered for treatment before visual loss occurs, as substantial visual acuity recovery is relatively unusual after treatment[33]. Laser treatment should be considered for pregnant women with severe NPDR, as most will progress to PDR in the post-partum period[311].

Patients should be seen for follow-up every 1-4 weeks during the course of PRP and every 2-4 months thereafter, until stable. Follow-up of DME patients should also occur every 2-4 months. The management recommendations in Table 3.3.1 have been adapted from the ETDRS[33;37;39;105], American Academy of Ophthalmology (AAO)[34;463], International Congress of Ophthalmology (ICO)[551], and the initial NHMRC[27] guidelines.

**Table 3.1.1: Randomised controlled trials of laser treatment for non-proliferative and proliferative diabetic retinopathy and diabetic macular oedema (modified from Mohamed et al.)[14]**

| Study | N | Retinopathy severity | Intervention | Outcome | Comments | Follow up |
|---|---|---|---|---|---|---|
| *Non-Proliferative and Proliferative Diabetic Retinopathy* | | | | | | |
| Rohan et al. Review/Meta-analysis of 5 trials[512] | 2243 | NPDR/PDR (± DME) | Peripheral PRP ± focal laser vs. observation | PRP ↓ risk of blindness in eyes with PDR by 61% (combined "best estimate" based on 5 RCT including Diabetic Retinopathy Study and British Multi-centre Study) | Criteria for study inclusion, quality assessment, baseline comparability & adverse effects of included studies not described | 1-5 yrs |
| Diabetic Retinopathy Study (DRS)[511] | 1742 | Severe NPDR (bilateral) or PDR (± DME | Peripheral PRP ± focal laser vs. observation | PRP ↓ risk of SVL by 52% at 2 yrs<br>90/650 (14%) treated vs. 171/519 (33%) deferred treatment RR 0.42 (0.34-0.53)<br>Eyes with "high risk" features had most benefit (57% ↓ risk SVL) | Decreased VA and constriction of peripheral visual field in some eyes | 5 yrs |
| Early Treatment Diabetic Retinopathy Study (ETDRS)[37;552] | 3711 | Mild –to severe NPDR or early PDR (± DME in both eyes) | One eye of each patient assigned to early PRP ± focal vs. deferral of treatment. | SVL in 2.6% treated vs. 3.7% deferred treatment<br>PRP ↓ risk vitrectomy (2.3% treated vs. 4% deferred)<br>↓ risk of SVL or vitrectomy 4% with early photocoagulation vs. 6% in deferred group. | Eyes assigned to deferral of PRP did not receive any focal laser for any coexistent DME, until the positive results of macular treatment were released | 5 yrs |
| British Multi-centre study[525] | 107 | PDR (bilateral symmetrical) | Xenon-arc laser photocoagulation vs. observation | PRP ↓ risk of blindness 5% vs. 17% observed RR 0.29 (0.11-0.77). Patients with NVD at entry had greatest difference. Treated eyes becoming blind had less treatment than eyes retaining vision. | Large loss to FU (28%): only 77 completed the 5-yr follow-up.<br>No intention-to-treat analysis | 5-7 yrs |
| British Multi-centre Study[524] | 99 | NPDR | Peripheral xenon arc laser vs. observation | PRP ↓ visual deterioration 32% treated vs. 55% controls<br>RR 0.49 (0.32-0.74) | Large loss to FU<br>No intention-to-treat analysis | 5 yrs |
| Lövestam-Adrian[38] (2003) | 81 | Severe NPDR and PDR in type 1 diabetes patients | All participants treated with PRP.<br>One randomly selected eye per patient entered into study. | 35% (14/40) eyes treated for severe NPDR developed NV. VH less frequent in treated eyes with severe NPDR vs. PDR (2/40 vs. 12/41; p=0.007). ↓ vitrectomy for VH in eyes treated for severe NPDR (1/40 versus 6/41; p = 0.052).<br>↓ visual impairment in eyes treated for severe NPDR compared to PDR (4/40 vs. 10/40; p = 0.056). | Time point for PRP not randomly assigned.<br>Adverse outcomes not assessed.<br>Inclusion/exclusion criteria, blinding, intention-to-treat analysis not specified.<br>Coexistent CSME treated with macular laser. | 2.9 ± 1.5 yrs |
| Hercules et al.[530] | 94 | Symmetrical PDR involving optic disc | PRP vs. observation | PRP ↓ risk of blindness 7% (7/94) compared to 38% (36/94) RR 0.19 (0.09-0.41) | Incomplete masking<br>No intention-to-treat analysis. | 3 yrs |

| *Diabetic Macular Oedema* | | | | | | |
|---|---|---|---|---|---|---|
| ETDRS[105] | 2244 | Bilateral DME (mild-to-moderate NPDR) | Focal argon laser (754 eyes) vs. observation (1490 eyes). | Treatment ↓ moderate visual loss (RR 0.50 (0.47-0.53)).<br>Benefits most marked in eyes with CSME, particularly if the centre of the macula was involved or imminently threatened (Subgroup analysis). | | 3 yrs |
| DRCR network[545] | 323 | DME<br>No previous treatment | Modified ETDRS laser (162 eyes) vs. mild grid laser (161 eyes) | No significant difference in OCT central macular thickness or visual acuity (Treatment ↓ CMT 88μm in the modified ETDRS group vs. 49μm in the mild macular grid laser group, p=0.04) | | 1 yr |
| Olk et al.[527] | 92 | Diffuse DME ± CSME | Modified grid argon laser vs. observation | Treatment ↓ risk of moderate visual loss 50–70%. Loss of VA reduced compared with no treatment at 1 yr (RR 0.84) and at 2 yrs (RR 0.78, CI 0.60-0.96) | | 2 yrs |
| Interim report of a multi-centre controlled study[528] | 76 | Bilateral symmetrical DME | Xenon-arc laser vs. observation | 8 treated vs. 18 control eyes blind.<br>Prognosis was best in those with initial VA ≥ 6/24 | Only 44 patients at 2 yrs, and 25 after 3yrs | 3 yrs |

Trials with less than 75 subjects excluded.

DME = diabetic macular oedema; CSME = clinically significant macular oedema; PRP = panretinal laser photocoagulation; VA = visual acuity; VF = visual fields; MVL = moderate visual loss; SVL = severe visual loss; VH = vitreous haemorrhage; NPDR = non-proliferative diabetic retinopathy, NV = neovascularisation; NVD = neovascularisation of the disk; PDR = proliferative diabetic retinopathy; RR = risk reduction; CI = confidence interval (95%); BP = blood pressure.

**Table 3.1.2: Summary of diabetic retinopathy management recommendations (adapted from the AAO, ICO, ETDRS and NHMRC guidelines)**

| Retinopathy Stage | CSME[¶] | Focal/Grid laser | Panretinal laser | Follow-up (months) |
|---|---|---|---|---|
| Normal | No | No | No | 24 |
| Minimal NPDR | No | No | No | 12 |
| Mild NPDR | No | No | No | 12 |
| | Yes | Yes[*†] | No | 2-4 |
| Moderate NPDR | No | No | No | 6-12 |
| | Yes | Yes[*†] | No | 2-4 |
| Severe NPDR | No | No | Sometimes[§] | 2-4 |
| | Yes | Yes[‖] | Sometimes[§] | 2-4 |
| Proliferative DR | No | No | Usually[§] | 2-4 |
| | Yes | Yes[‖] | Usually[§] | 2-4 |
| High risk proliferative DR[‡] | No | No | Yes | 2-4 |
| | Yes | Yes[‖] | Yes | 2-4 |

[*] Deferral of photocoagulation for a brief period of medical treatment may be considered in cases of hypertension or fluid retention associated with heart failure, renal failure, pregnancy or other causes that may aggravate DME.
[†] Deferral of CSME treatment is an option when the centre of the macula is not involved, visual acuity is excellent, close follow-up is possible, and the patient understands the risks.
[§] Treatment should be considered especially in patients with T2DM, poor follow-up compliance, impending cataract extraction, renal disease, pregnancy, and severe disease in the fellow eye.
[‖] To minimise PRP-induced exacerbation of macular oedema, focal photocoagulation is suggested prior to PRP.
[¶] CSME (Clinically Significant Macular Oedema) is defined by the ETDRS as either:

- Thickening of the retina at or within 500μm of the centre of the macula; or
- Hard exudates at or within 500 microns of the centre of the macula associated with adjacent retinal thickening; or
- A zone or zones of retinal thickening one disc area or larger, any part of which is within one disc diameter of the centre of the macula.

[‡] High-risk features of PDR include either:

- New vessels within one disc diameter of the optic nerve head that are larger than ⅓ disc area; or
- Vitreous or preretinal haemorrhage associated with less extensive neovascularisation on or within one disc diameter of the optic disc; or
- Neovascularisation elsewhere in the retina greater than one disc diameter from the optic disc margin at least ½ disc area in size.

## 3.2 Role of Vitrectomy in Managing Diabetic Retinopathy

**Guidelines**

23. Consider vitrectomy within 3 months for T1DM patients with severe vitreous haemorrhage in eyes suspected to have very severe PDR (Level II evidence[40-42]).
24. Also consider early vitrectomy for eyes with severe PDR, not responding to aggressive and extensive PRP (Level II evidence[40;42]).
25. Consider vitrectomy to relieve macular or other retinal traction in advanced PDR cases, in an attempt to salvage some vision (Level IV evidence[42-44]). Such cases, if left untreated, will mostly develop severe visual loss or blindness.
26. Consider vitrectomy in eyes with chronic or diffuse DME that is non-responsive to laser treatment (Level III-1 evidence)[45-48], or if related to vitreomacular traction (Level III-1 evidence).
27. Warn patients about the adverse effects of vitrectomy surgery (Level II evidence[40;49]).

**Consensus Good Practice Point**

5. Use OCT to confirm the presence and severity of DME and to monitor its response to treatment.

**Key Points**

- The Diabetic Retinopathy Vitrectomy Study (DRVS) was a multi-centre RCT that evaluated indications and timing of pars plana vitrectomy for management of advanced DR.
- The indications and rationale for vitrectomy established by the DRVS still guide therapy, but the thresholds for performing surgery are lower as a consequence of improved surgical results, improvements in vitreoretinal instrumentation and technique, and the introduction of ancillary modalities or modified techniques.
- Early vitrectomy for treatment of vitreous haemorrhage secondary to DR was found highly cost-effective in a cost-utility analysis using DRVS results.
- The benefits of early vitrectomy for non-resolving severe vitreous haemorrhage were less for type 2 diabetes.
- Vitrectomy was found in small RCT to benefit chronic or diffuse DME.
- OCT is valuable to confirm and quantify DME, and to confirm traction and its response to surgery.
- Vitrectomy, possibly combined with inner limiting membrane peeling, in selected eyes with thickened or taut posterior hyaloid has been found to facilitate more rapid resolution of DME and improvement in visual acuity.
- Combined cataract surgery (phacoemulsification and insertion of a posterior chamber intraocular lens) with vitrectomy has been shown to result in earlier visual rehabilitation by avoiding need for later cataract surgery.
- Complications from vitrectomy include recurrent vitreous haemorrhage, endophthalmitis, glaucoma, retinal tear or detachment, rubeosis iridis, and premature development of cataract.
- Adjunctive intravitreal anti-VEGF therapy (particularly with bevacizumab) is currently widely used prior to vitrectomy to induce new vessel regression and reduce haemorrhage.

Vitreous contraction is an inherent late component of PDR[553] and results in sequelae that affect vision, including vitreous haemorrhage and traction retinal detachment involving the macula. Vitrectomy may provide significant benefit for these stages or for other PDR complications[554;555]. The most common indications for diabetic vitrectomy are[554;556]:

1. severe non-clearing vitreous haemorrhage,
2. traction retinal detachment recently involving the macula,

3. combined traction and rhegmatogenous detachment,
4. progressive fibrovascular proliferation,
5. rubeosis iridis and vitreous haemorrhage, with opacity preventing adequate laser.

RCT for vitrectomy in DR are listed in Table 3.2.1. No large RCT were conducted to identify indications or timing of vitrectomy for complications of DR until the Diabetic Retinopathy Vitrectomy Study. This landmark multi-centre RCT, conducted by the U.S. National Eye Institute, aimed to evaluate indications and timing of pars plana vitrectomy for the management of advanced DR[40;41]. It was designed to evaluate risks and benefits of performing early pars plana vitrectomy in eyes with advanced PDR. The DRVS comprised three trials: two were RCT of early vitrectomy for advanced PDR[40;41] or for severe non-clearing vitreous haemorrhage[40;41], and the third was a natural history study of severe PDR with conventional management[557]. The DRVS was a well-conducted RCT, providing Level II evidence, though some design criticisms have been made[558]. An increasing role for vitrectomy in managing chronic or diffuse DME is the main change to indications for vitrectomy since the DRVS[559-562].

Need for vitrectomy surgery was reported by the ETDRS[552], as a 5.3% 5-year cumulative vitrectomy rate. Vitreous haemorrhage was the indication in 54% of cases and retinal detachment in 46%. Significant improvement was observed in post-operative visual acuity after vitrectomy.

The DRVS included patients with visual acuity ≥3/60 (20/400) and either: (1) severe neovascularisation and fibrous proliferation; or (2) fibrous proliferation and moderate vitreous haemorrhage; or (3) moderate neovascularisation, severe fibrous proliferation, and moderate vitreous haemorrhage. The DRVS divided these patients into a group that underwent early vitrectomy and a group whose treatment was deferred; and reported that the group undergoing early vitrectomy achieved visual acuity ≥6/12 in 25% at the 4-year follow-up, compared to 15% in the deferred treatment group[40]. The benefits of early vitrectomy were more pronounced in patients with type 1 diabetes (36% vs. 12% for early vitrectomy compared to deferral), but were not statistically significant for patients with type 2 diabetes[40;41] (Level II evidence).

DRVS authors concluded:

1. Early vitrectomy provides a greater chance for prompt recovery of visual acuity in eyes with recent severe vitreous haemorrhage, and is most useful for patients without useful vision in the fellow eye. Early vitrectomy should be offered to such patients with little regard to retinopathy severity or type of diabetes (Level II evidence).
2. For patients with type 1 diabetes, particularly those in whom severe vitreous haemorrhage occurred after a shorter duration of diabetes, early vitrectomy provides a greater chance of recovering good visual acuity, with benefit evident for at least four years. DRVS findings support early vitrectomy in eyes known or suspected to have very severe PDR, as a means of increasing the chance to restore or maintain good vision[41] (Level II evidence).

The DRVS was conducted before recent improvements in surgical techniques, including endolaser, certain bimanual techniques and perfluorocarbon, so the DRVS results must provide only general guidelines for the current surgical management of DR. Therefore, early vitrectomy for type 2 diabetic patients with severe non-clearing vitreous haemorrhage should probably be considered, particularly if active neovascularisation is present[34]. Early vitrectomy for treatment of vitreous haemorrhage secondary to DR has been found to be highly cost-effective in a cost-utility analysis using DRVS findings[563].

Vitrectomy techniques are most useful for removing media opacities (e.g. vitreous haemorrhage and associated debris) which prevent accurate diagnosis and monitoring. By allowing concurrent intra-operative endolaser treatment[564], vitrectomy may also permit necessary laser treatment to be

completed in eyes with advanced DR[565;566]. Vitrectomy also permits the re-attachment of retina detached by traction.

There is an increasing trend to combine cataract surgery (phacoemulsification and insertion of a posterior chamber intraocular lens)[567] with vitrectomy[568]. One case-control study and one large case series examined combined surgery and concluded that this procedure prevents a second operation for post-vitrectomy cataract, allowing earlier visual rehabilitation[568;569] (Level III-2 evidence).

Increasing use for vitrectomy in managing cases of chronic or diffuse DME non-responsive to focal laser treatment has been the principal change to surgical indications[559-562;570-575]. However, to date, the few RCT of vitrectomy for DME (Table 3.2.1) have relatively small sample size and short follow-up, with inconsistent results[45-48].

Optical Coherence Tomography (OCT) is extremely valuable in confirming and quantifying DME[576;577], in assessing the presence of posterior hyaloid traction in such patients[44;578], and in documenting reduced DME after vitrectomy[560;576;579;580].

Vitrectomy surgery is often combined with peeling of the internal limiting membrane, because many eyes are found to have a thickened or taut posterior hyaloid[559]. Multiple case series[43;581-583] and one randomised trial[559] comparing vitrectomy with membrane peeling to control, appear to show that vitrectomy facilitates a more rapid resolution of DME and improvement in visual acuity (Level II evidence), though not all studies have confirmed this[578]. A small study that randomised one eye to vitrectomy with removal of the internal limiting membrane, and the fellow eye to grid laser, reported better results in the vitrectomy group[560] (Level III-I evidence). The recent introduction of new medical and intravitreal therapies may have reduced the need for such surgery.

Finally, vitrectomy has been attributed with stabilising further development of the proliferative process in DR through several mechanisms. First, it removes the anatomical scaffold for ingrowth of fibrovascular tissue into the eye, including epimacular membrane[584]. Second, vitrectomy relieves traction on retinal vessels to improve blood flow and reduce leakage from these vessels. Third, vitrectomy may relieve retinal hypoxia in ischaemic areas of the retina and prevent accumulation of vasoactive cytokines and growth factors such as VEGF[585].

The indications and rationale for vitrectomy, established by DRVS, have not changed substantially in recent years (Table 3.4.1), but the thresholds for performing surgery are lower due to improved surgical results from improvements in vitreoretinal instrumentation and technique[34;42;565] and the introduction of ancillary modalities[586-588] or modified techniques[589]. Many diabetic vitrectomy patients need fellow-eye surgery[590]. The role of vitrectomy in managing DR was reviewed by Smiddy and Flynn[42], and is summarised in Table 3.2.2, together with visual outcomes from vitrectomy in diabetic patients.

A recent review of post-vitrectomy visual outcomes and associated clinical variables revealed that 50-89% of participants who underwent vitrectomy had achieved some improvement or stabilisation of visual acuity, while 20-81% of participants achieved final visual acuity of at least 15/600[591] (Level III-3 evidence). Reports have also shown that the postoperative improvement of vision is generally retained[592;593] (Level III-3 evidence).

The DRVS also described many well-reported complications from vitrectomy[40;41](Level II evidence). The most frequent short-term post-operative complication is recurrent vitreous haemorrhage[594-596]. This was reported to be frequent in eyes with iris neovascularisation and in patients with lower extremity amputations, and to be reduced by anti-hypertensive therapy before vitrectomy[597]. The premature development of cataract is the most common long-term complication

[593;598;599]. Other important complications are rubeosis iridis with secondary glaucoma, endophthalmitis, retinal tears, and retinal detachment.

A number of reports have documented the long-term effects of vitrectomy on vision in diabetic eyes[593;600-602]; 5-10 years after vitrectomy, 42%-75% of patients maintain stable and useful visual acuity. Those with good short-term results after surgery tend to remain stable[592;593]. The causes of significant visual loss include cataract, neovascular glaucoma, progressive traction retinal detachment, macular scarring, rhegmatogenous retinal detachment and preretinal macular fibrosis[593;603]. Accelerated cataract is a frequently reported complication of diabetic vitrectomy[598;604], with significant cataract seen in 20-25% of eyes within 6 months[598]. A number of studies have examined the survival after vitrectomy for diabetic retinopathy; 5-year survival rates have ranged from 75%[605] to 85%[606].

More recently, adjunctive intravitreal anti-VEGF therapy (particularly with bevacizumab) has become widely used prior to vitrectomy to induce new vessel regression and reduce intra- and peri-operative haemorrhage[607].

**Table 3.2.1: Randomised controlled trials of vitrectomy surgery for proliferative diabetic retinopathy and diabetic macular oedema (modified from Mohamed et al.[14])**

| Author | Diagnosis | Intervention | N | Outcome | Comment | Follow up |
|---|---|---|---|---|---|---|
| **Proliferative Diabetic Retinopathy** | | | | | | |
| Diabetic Retinopathy Vitrectomy Study[40;49] | Recent severe diabetic vitreous haemorrhage reducing VA ≤ 5/200 at least 1 month | Early vitrectomy vs. deferral of vitrectomy for 1 year. | 616 eyes | Early surgery ↑ recovery of VA ≥10/20 (25% vs. 15% deferred group)<br>Trend for more frequent loss of LP with early surgery (25% vs. 19%).<br>Greatest benefit ↑ VA ≥10/20 in Type 1 DM with more severe PDR (36% vs. 12% deferred group) and proportion losing LP was similar (28% vs. 26%) | | 4 yrs |
| Diabetic Retinopathy Vitrectomy Study[40;49] | Advanced PDR with fibrovascular proliferation, and VA ≥10/200 | Early vitrectomy vs. conventional management | 370 eyes | Early surgery ↑ proportion of eyes with VA≥10/20 (44% vs. 28% conventional treatment)<br>No difference in proportion having loss of vision to light perception or less. | Most benefit in patients with very advanced PDR. No benefit in group with less severe NV | 4 yrs |
| **Diabetic Macular Oedema** | | | | | | |
| Yanyali et al. (2006)[45] | Bilateral DME unresponsive to grid laser photocoagulation | Vitrectomy with removal of the internal limiting membrane (ILM) randomly in one eye | 20 eyes of 10 patients | Surgery ↓ CMT by 165.8 ± 114.8μm vs. 37.8 ± 71.2μm in untreated eye (p=0.016).<br>Vitrectomy ↑ VA by ≥2 lines in 4 (40%) vs. 1 (10%) – not significant | | 1 yr |
| Thomas et al.[46] | DME (VA≤6/12) unresponsive to laser with no associated traction. | Vitrectomy + ILM peel vs. further macular laser. | 40 eyes | Vitrectomy ↓ CMT by 73μm (20%) vs. 29μm (10.7%).<br>Vitrectomy ↓ mean BCVA by 0.05 logMAR vs. ↑ 0.03 logMAR in controls -- not significant | 18% loss to FU | 1 yr |
| Dhingra et al.[47] | DME (VA≤6/12) unresponsive to laser with no associated traction or ischaemia | Vitrectomy + ILM peel vs. observation | 20 eyes of 20 patients | Vitrectomy ↓ mean CMT (250.6 ± 56.8μm vs. 450 ± 40μm controls).<br>No significant change in logMAR VA | Masking unclear | 1 yr |
| Bahadir et al.[48] | Diffuse CSME | Vitrectomy + ILM peel (17 eyes) vs. vitrectomy without ILM peel (41 eyes) | 58 eyes of 49 patients | No significant difference between groups in VA outcome.<br>VA ↑ in both groups (0.391 ± 0.335 in Vity/ILM and 0.393 ± 0.273 logMAR, p>0.01) | Randomisation & masking unclear. $HbA_{1c}$ & baseline BP not reported. | 1 yr |

CMT = central macular thickness; DME =diabetic macular oedema; VA = visual acuity; ILM = internal limiting membrane; OCT = optical coherence tomography; PPV = pars plana vitrectomy; LP = light perception; IOP = intraocular pressure; FU = follow up; CSME = clinically significant macular oedema; BP = blood pressure;

**Table 3.2.2: Summary of current indications for vitrectomy in diabetic retinopathy (adapted from Smiddy[42])**

| | |
|---|---|
| **Media Opacities** | |
| 1. | Non clearing haemorrhage |
| 2. | Vitreous |
| 3. | Subhyaloid/premacular |
| 4. | Anterior segment neovascularisation with posterior segment opacity |
| 5. | Cataract preventing treatment of severe PDR |
| **Vitreoretinal Traction** | |
| 1. | Progressive fibrovascular proliferation |
| 2. | Traction retinal detachment involving the macula |
| 3. | Combined traction and rhegmatogenous retinal detachment |
| 4. | Macular oedema associated with taut, persistently attached posterior hyaloid |
| **Post-vitrectomy complications** | |
| 1. | Vitreous haemorrhage/ghost cell glaucoma |
| 2. | Traction or rhegmatogenous retinal detachment |
| 3. | Anterior hyaloid fibrovascular proliferation |
| 4. | Fibrinoid syndrome: extensive fibrinous membrane cross-linking of the vitreous |
| 5. | Epiretinal membrane |

**Table 3.2.3: Summary of post vitrectomy visual acuity outcomes (adapted from Smiddy[42]**

| **Indication for vitrectomy** | **Visual acuity outcome** | | |
|---|---|---|---|
| | **Improved** | **≥6/60** | **No light perception** |
| Vitreous haemorrhage | 59-83% | 40-62% | 5-17% |
| Fibrovascular proliferation | 70% | 70% | 11% |
| Traction retinal detachment | 59-80% | 21-58% | 11-19% |
| Combined traction and rhegmatogenous retinal detachment | 32-53% | 25-36% | 9-23% |

## 3.3 Medical and Ancillary Therapies for Diabetic Retinopathy

**Guidelines**

28. Strive to achieve optimal glycaemic control ($HbA_{1c}$ levels less than 7%) in all patients with diabetes in order to reduce the development and progression of DR (Level I evidence) [13;14].
29. Consider adjunctive blood-pressure-lowering therapy in patients with DR. Any lowering of systolic and or diastolic blood pressure is beneficial. In patients with DR, aim to keep systolic BP <130 mm Hg (Level I evidence)[50-53].
30. Consider lowering blood lipids to reduce diabetes macrovascular complications and to reduce progression of DME (Level II evidence)[18;54].
31. Consider lowering blood lipids in patients with extensive hard exudate deposition (Level III-3 evidence)[55-57].
32. Consider using intravitreal triamcinolone (IVTA) for selected cases of DME that persists after focal/grid laser treatment (Level II evidence)[58].
33. Also consider IVTA in selected cases for extensive macular hard exudate deposition, or as an adjunct to PRP for PDR (Level III-3 evidence) [59-64].
34. Warn patients having IVTA about the high incidence of secondary intraocular pressure rise, development of posterior subcapsular cataract, risk of intraocular infection, and the need for treatment of these adverse effects, as well as recurrence of the DME (Level II evidence)[58].

**Key Points**

- Trials of blood-pressure-lowering therapy in diabetes suggest the importance of hypertension/ blood pressure as a major modifiable risk factor for DR. It is unclear from the trials whether a threshold exists beyond which further lowering of blood pressure no longer influences DR progression.
- Benefits on DR may also be seen from the use of anti-hypertensive agents in people with diabetes and normal blood pressure levels.
- The renin-angiotensin system and angiotensin converting enzyme (ACE) are expressed in the eye, may independently affect VEGF expression, and are involved in the pathogenesis of DR. ACE inhibitors, used in managing blood pressure, have been evaluated for effects on DR.
- Lisinopril was shown to reduce DR progression in a 2-year RCT (Level II evidence). Other larger trials are ongoing. The UKPDS, however, did not find an ACE inhibitor superior to a beta blocker in its effect on DR. Blood pressure reduction alone may be the important parameter in determining progression of DR.
- Disordered blood lipids may increase the risk of macular hard exudate deposition and CSME. Fenofibrate reduced the need for laser treatment in a large diabetes cardiovascular trial. Studies to date suggest a potential role for fibrates or statins in managing DR, particularly in patients with extensive hard exudate deposition.
- ETDRS data showed that aspirin did not increase the risk of vitreous haemorrhage or exacerbate the severity or duration of vitreous or preretinal haemorrhage.
- Protein kinase C (PKC) plays a major role in hyperglycaemia-induced microvascular dysfunction in diabetes and DR. One PKC inhibitor, ruboxistaurin, has been the subject of 3 large RCT. Two trials showed benefit in reducing risk of moderate visual loss, but not on progression of DR or progression to DME. The third trial failed to demonstrate a reduced need for laser with this drug. Further trials are ongoing. Overall, there is insufficient evidence to recommend use of ruboxistaurin.
- A pathogenic role for aldose reductase in DR is likely. However, trials of aldose reductase inhibitors (ARIs) to reduce severity or progression of retinopathy have not shown benefit and have been limited by toxicity of the agents tested.
- Elevated growth hormone levels have been associated with accelerated DR. A small trial of a somatostatin analogue (Octreotide) compared to conventional therapy showed a reduced need

for PRP laser and progression. Use of this therapy may be limited by its high maintenance cost.

- A pathogenic role for advanced glycation end-products (AGEs) in DR is likely. AGE inhibitors such as aminoguanidine are currently being evaluated in trials.
- Human trials have shown benefits from use of steroid agents in treating DME. Because of the transience of most steroid agents (e.g. cortisone), depot steroid agents such as triamcinolone, have been used.
- Intravitreal triamcinolone (IVTA) is widely used in managing DME that persists despite focal/ grid laser treatment. A small 2-year Australian RCT demonstrated benefit from IVTA on OCT macular thickness and visual acuity . Repeated injections are frequently needed, at around 6-monthly intervals.
- IVTA may also be used in treating patients with massive hard exudates deposition or as an adjunct to PRP for PDR.
- Frequent adverse ocular effects from IVTA include elevated intraocular pressure and glaucoma and development of posterior subcapsular cataract, often needing surgery.
- Unresolved issues include the ideal triamcinolone dosage, need for additional post-IVTA focal/grid laser, duration of repeat therapy, and concerns regarding the formulation in current use.
- Anti-Vascular Endothelial Growth Factor (VEGF) drugs, administered by repeat intravitreal injection, offer great promise in managing both PDR (including iris new vessels) and DME. Their use is accompanied by acceptably low rates of serious adverse ocular effects (less than from IVTA). Repeated applications are needed, and their long-term safety is not known.
- For PDR, anti-VEGF agents (particularly bevacizumab) are currently widely used as an adjunct to laser treatment and prior to vitrectomy surgery. For these two indications, RCT evidence is lacking. For DME, there is accumulating RCT evidence of benefit.
    - Pegaptanib (Macugen) has been shown to reduce OCT macular thickness and visual loss due to DME.
    - Bevacizumab (Avastin) is currently the most widely used anti-VEGF agent for DR; it reduces OCT macular thickness, and PDR activity and severity, and improves visual acuity. There are unresolved concerns regarding its systemic safety.
    - Ranibizumab (Lucentis) may have similar effects.
    - Ovine hyaluronidase (Vitrase) has been shown to accelerate the clearing of vitreous haemorrhage in PDR.

Many pharmacologic agents have been assessed in clinical trials designed to prevent the development or progression of DR, or as adjuncts to laser photocoagulation[608;609]. The mainstay of current treatment involves risk factor reduction by controlling blood glucose, blood pressure and serum lipids[610;611]. Lipid lowering therapies have been assessed in only relatively few trials to date[54;55] and case-control studies[306].

Potential alternative therapeutic approaches that directly target diabetic microvascular complications include antiplatelet agents, advanced glycation end product (AGE) inhibitors, aldose reductase inhibitors (ARIs), protein kinase C (PKC) inhibitors, angiotensin converting enzyme (ACE) inhibitors, corticosteroids, particularly intravitreal triamcinolone, together with vascular endothelial growth factor (VEGF) inhibitors and other agents.

This field has been summarised in many reviews[608;609;612;612-615]. Monitoring the methods for trials of medical therapy in DR have also been described[616]. The introduction of OCT has facilitated the assessment of new therapies for DME. Table 3.3.1 (adapted from Mohamed et al.[14], summarises RCT of various medical interventions in DR.

As covered in Section 1.6, clinicians should strive to achieve optimal glycaemic control for all patients with diabetes, in order to reduce the development or progression of DR (Level I evidence)[13;14].

### *Blood Pressure Lowering Therapies*

Although epidemiological studies do not suggest that blood pressure is as consistently important as glycaemic control for the incidence and progression of DR, RCT of blood pressure lowering medications indicate that blood pressure is a major modifiable risk factor. However, it is unclear from the trials whether there is a threshold effect beyond which further blood pressure lowering no longer influences DR progression. Table 3.3.2 summarises these RCT data. UKPDS findings are further described in Section 1.6. Clinicians should consider adjunctive blood-pressure-lowering therapy in all patients with DR. Any lowering of systolic and or diastolic blood pressure is beneficial. In patients with DR, aim to keep systolic BP <130 mm Hg (Level I evidence)[50-53].

The Appropriate Blood Pressure Control in Diabetes (ABCD) trial[51] randomised 470 people with T2DM and hypertension to receive intensive or moderate blood pressure control. No difference in DR progression was observed over 5 years, and there was no difference between treatment with nisoldipine compared to enalapril. Poorer glycaemic control, shorter follow-up and lower baseline blood pressure levels compared with the UKPDS could explain the lack of efficacy.

Benefits from using antihypertensive agents may also be seen in people with diabetes with normal blood pressure. In another ABCD trial arm[52], intensive blood pressure control significantly reduced DR progression over 5 years compared to moderate blood pressure control among 480 patients with type 2 diabetes without hypertension.

### *Specific Agents: Angiotensin-Converting Enzyme (ACE) Inhibitors*

The renin-angiotensin system is expressed in the eye[180-182], including expression of ACE[182;183]. Patients with DR have elevated levels of intraocular and serum ACE, prorenin and angiotensin II, which are correlated with disease severity[180;181;184]. Angiotensin II regulates angiogenesis via growth factors such as VEGF[184;617] and enhances vascular permeability and oxidative stress. ACE inhibitors or angiotensin II type 1 ($AT_1$) receptor blockers[183] were shown to inhibit new retinal vessels in rats with retinopathy of prematurity, were postulated to protect against DR progression[618;619], and may independently reduce VEGF expression[617].

One such blocker was evaluated for its effects on DR progression in the EURODIAB Controlled Trial of Lisinopril in Insulin-Dependent Diabetes Mellitus (EUCLID) study[53], on DR progression in 530 normotensive, normoalbuminuric patients with T1DM. Lisinopril reduced DR progression by 50% and progression to PDR by 80% over 2 years (Level II Evidence). Blood pressure changes did not appear to account for the ACE inhibitor treatment effect on DR[53]. Study limitations were differences in baseline glycaemic levels between groups (treatment group had lower $HbA_{1c}$, even though adjusted for in analyses) and relatively short follow-up of only 2 years.

Another smaller RCT of captopril[620] suggested that ACE inhibitors may have additional benefits on DR progression independent of blood pressure lowering. In the 4-year MICRO-HOPE RCT, need for laser therapy was reduced by 16% by use of ramipril, another ACE inhibitor. The relative risk reduction of laser therapy, overt nephropathy, or dialysis was modest at 16%, p=0.036[618] (Level II evidence).

This was not confirmed by the UKPDS[50], which compared an ACE inhibitor (captopril) to a beta blocker (atenolol), or by the ABCD trial[51;52]. These trials did not find ACE inhibitors superior to

other blood pressure medications, and suggested that the effect of the blood pressure reduction itself may be the more important parameter than its therapy[621].

Whether newer blood pressure medications have additional beneficial effects may become evident from two large ongoing RCT. The Action in Diabetes and Vascular Disease (ADVANCE) and ADVANCE Retinal Measurements (AdRem) trials are evaluating an ACE inhibitor-diuretic (perindopril-indapamide) combination on DR incidence[622;623]. The DIabetic REtinopathy Candesartan Trial (DIRECT) is assessing whether the angiotensin-II receptor blocker candesartan can prevent development and progression of DR in both T1DM and T2DM[183;624-626].

### *Lipid-lowering Therapies*

There is growing evidence that disordered lipid levels in many diabetic patients may increase the risk of retinal and macular hard exudate deposition, with associated CSME and permanent macular damage[17;117;627;628]. The potential for lipid-lowering therapy (with fibrates or statins) as an adjunct to the medical management of DR or to laser treatment in cases with DME has been examined and is being explored in other studies. An early RCT of clofibrate in DR demonstrated a reduction in retinal hard exudates, but no effect on vision[55]. In the large Fenofibrate Intervention and Event Lowering in Diabetes[54] among 9,795 participants with T2DM, those on fenofibrate therapy were significantly less likely than controls to need laser treatment, 3.6% vs. 5.2% (Level II evidence). This, however, was not the principal endpoint of the trial and the indications for laser were not reported.

A small RCT of simvastatin in 50 patients with T2DM, DR and hyperlipidaemia showed some benefit on vision and in the DR appearance in treated vs. control eyes[18], but the number of events was small (Level II evidence).

The Collaborative Atorvastatin Diabetes Study (CARDS), a RCT of 2,830 patients with T2DM, did not find any benefit from atorvastatin in reducing DR progression[629]. Limitations were a lack of photographic grading of DR and substantial missing data. A small non-randomised trial of atorvastatin showed reduction in hard exudate deposition and subfoveal lipid migration (Level III-2 evidence)[19]. Ongoing RCT, such as the Atorvastatin Study for Prevention of Coronary Endpoints in NIDDM (ASPEN)[630] will also evaluate effects of atorvastatin on DR, while ACCORD-EYE[631], will assess the extent to which combined glycaemic, blood pressure and lipid control will alter the course of DR.

These studies suggest a potential role for fibrates or statins in managing DR[57], particularly for the small subgroup of patients who rapidly develop hard exudate plaques at the macula with consequent rapid and severe loss of central acuity[56].

In summary, clinicians should consider lowering blood lipids to reduce diabetes macrovascular complications and to reduce progression of DME (Level II evidence)[18;54], or in patients with extensive hard exudate deposition (Level III-3 evidence)[55-57].

### *Antiplatelet Agents*

The ETDRS did not find that regular aspirin treatment (650 mg/day) prevented the development or progression of DR[632] or the risk of visual loss, or vitreous/ pre-retinal haemorrhage[633] (Level II evidence). This finding was despite animal studies suggesting that aspirin inhibited development of retinal haemorrhages[634] and reduced breakdown of the blood-retina barrier[583].

Benefits of antiplatelet therapy (aspirin or dipyridamole or both) were shown from slower development of DR or FA changes in the DAMAD Study[635]. Reduced microaneurysm progression was documented over a 3-year period in the Ticlopidine Microangiopathy of Diabetes (TAMAD)

Study[636] (level II evidence). Use of this medication was limited, however, by development of neutropenia, diarrhoea and rashes.

Importantly, ETDRS data showed that aspirin did not increase the risk of vitreous haemorrhage, or need for vitrectomy,[632] nor did it exacerbate the severity or duration of vitreous or preretinal haemorrhage[633] (Level II evidence). The safety of aspirin for cardiovascular risk reduction in the presence of DR has been confirmed[637] (Level II evidence).

### *Anticoagulants*

Results from the GUSTO-I trial confirmed the rarity of ocular haemorrhages in patients with diabetes who had thrombolytic therapy. The trial involved 40,000 patients enrolled at 1,081 centres presenting to hospital with an acute myocardial infarct; only one patient of the 15% with diabetes developed an ocular haemorrhage. The authors concluded that DR should not be considered a contraindication to thrombolysis[638] (Level III-3 evidence).

### *Protein Kinase C (PKC) Inhibitors*

A large body of evidence now indicates that protein kinase C (PKC) plays a major role in hyperglycaemia-induced microvascular dysfunction in diabetes. Increased flux through the polyol pathway and generation of AGE and oxidative species result in the generation of diacylglycerol, a physiologic activator of the PKC pathway[175]. PKC is a family of related enzymes which function as signalling components for a variety of growth factors, hormones, neurotransmitters and cytokines[176]. PKC activation results in numerous cellular changes that lead to basement membrane thickening and changes in vessel permeability and/or blood flow, and so is linked to the pathophysiology of DR. Although the activity of multiple PCK isoforms is increased in vascular tissues in the diabetic state, studies suggest that the PKC-beta isoform is preferentially activated[176-178]. PKC-beta is also an integral component of cellular signalling by VEGF, the mediator of ocular neovascularisation. In addition, PKC-beta is credited with increasing endothelial permeability[175].

A wide array of PKC inhibitory compounds with varying degrees of isoform selectivity are now being assessed because of their potential to arrest DR progression[179;614]. Ruboxistaurin is the most selective oral inhibitor for the PKC-beta isoform developed to date, and appears to have very little effect on unrelated enzymes[176]. Other PKC inhibitors include: (a) Rottlerin, which inhibits the delta PKC isoform with some selectivity but also inhibits other important enzymes, including protein kinase A and calmodulin; (b) Indolocarbazoles, which also inhibit multiple PKC isoforms as well as non-PKC enzymes; and (c) PKC412, which potently inhibits VEGF and multiple PKC isoforms as well as VEGF and PDGF receptor components.

In animal models, ruboxistaurin blocked vascular complications of diabetes, including abnormalities in retinal blood flow, neovascularisation and VEGF-mediated effects on permeability[639-641]. Phase I studies of ruboxistaurin were conducted using single and multiple doses in various patient populations[176]. They showed that the compound is similarly readily bioavailable with a low frequency of adverse events, between placebo and treatment groups[176;642]. A preliminary small phase II RCT demonstrated a 30% reduction in retinal vascular leak[643].

Three Phase III RCT (PKC-DRS[644], PKC-DRS2[645] and PKC-DMES[646]) have been reported (Table 3.3.1). The first trial involved 252 subjects with moderate to severe NPDR, randomised to ruboxistaurin (8, 16 or 32 mg/day) or placebo. Over 3 years, ruboxistaurin significantly reduced risk of moderate visual loss (MVL), but not DR progression[644]. The second 3-year trial included 685 subjects with similar severe NPDR[645]. Ruboxistaurin treatment had no significant effect on progression to sight-threatening DME, but reduced development of sustained MVL by 40% (6.7% of ruboxistaurin subjects developed 15-letter VA loss vs. 9.9% in placebo, p=0.005). Ruboxistaurin also reduced the need for laser and increased the likelihood of visual improvement[645]. The third 2.5-

year trial included 686 subjects with 'pre-maculopathy', DME signs further than 300µm from the macular centre and mild to moderate NPDR, randomised to ruboxistaurin (4, 16 or 32 mg/day) or placebo. This trial aimed to determine whether ruboxistaurin would delay progression of DME and the need for focal/grid laser treatment. Although the primary endpoint was not reached, there was a suggestion of benefit from the highest dose (32mg)[646]. Long-term kidney outcomes were also not influenced by ruboxistaurin[211].

In summary, PKC inhibition held substantial promise as a potentially useful medical therapy for early DR[179]. However, the phase III ruboxistaurin RCT suggested only possible modest benefit in delaying DME and associated visual loss (Level II evidence), but no definite benefit when the risk of visual loss was more imminent. Subsequent studies have not been completed.

### *Aldose Reductase Inhibitors (ARIs)*

High blood glucose increases polyol pathway activity and an accelerated apoptosis of pericytes. This effect on pericytes may be crucial in the development of DR. Pericytes have been shown to synthesise TGF ß and inhibit proliferation and migration of vascular endothelial cells. Loss of pericytes would thus contribute not only to vasodynamic changes in early DR stages, but also to neovascularisation in PDR[164].

Aldose reductase is an integral enzyme in the polyol pathway and catalyses the reduction of glucose to sorbitol. Its inhibition was shown to arrest pericyte impairment[164;165]. Hyperglycaemia-induced increased aldose reductase activity also results in a build-up of sorbitol, thought to cause osmotic damage to vascular cells[161]. A study of 611 people with type 2 diabetes and 73 controls reported increased DR prevalence with increasing red cell aldose reductase[647]. Other studies have confirmed this relationship.

Many ARIs were developed and some showing benefit in animal models were evaluated for treatment of DR[165;648]. Clinical trials of ARIs to prevent or reduce DR (sorbinil and tolrestat), however, were disappointing[177;649;650]. The Sorbinil Retinopathy Trial demonstrated no effect on DR progression, and significant hypersensitivity limited its use[650].

### *Growth Hormone Suppression (Octreotide)*

Marked elevation of growth hormone (GH) level has been associated with accelerated DR, a mechanism postulated to explain the development of DR during puberty. It was observed that GH-deficient subjects with dwarfism who are diabetic did not develop macrovascular or microvascular complications. Patients with pituitary infarction were also noted not to develop DR. The magnitude of GH hyper-secretion has been correlated with severity of DR[651], though the underlying mechanisms are not completely understood[652]. Evidence points to peptide growth factors being involved in the cascade of events leading to neovascularisation. Early reports before the advent of laser treatment, indicated benefits from pituitary ablation (hypophysectomy) for treatment of severe ("florid") PDR, with a dramatic response in some cases[653].

Treatment of severe PDR using somatostatin antagonists to inhibit or suppress pituitary GH secretion has been proposed[654]. A small (n=23) RCT of the somatostatin analogue octreotide reduced need for laser photocoagulation in NPDR or early PDR[651]. The incidence of disease progression to severe PDR was lower in the active treatment group than in those receiving conventional treatment[651] (Level II evidence). These findings would need to be validated in larger trials, as this therapy has a high annual maintenance cost.

### *Advanced Glycation End-product (AGE) Inhibition*

During normal ageing, proteins are irreversibly modified by blood sugars, and elevated blood glucose accelerates this protein modification. Glucose binding to protein side chains results in the

formation of non-functional products termed advanced glycation end-products (AGE)[655]. AGE formation damages cells by impairing the function of many proteins including extracellular structural proteins such as collagen[170]. AGEs also alter cellular function by binding to receptors (RAGE)[656], producing a cascade of cellular signalling events leading to protein kinase C activation[170]. People with diabetes have markedly higher serum AGE levels than those without diabetes[171]. RAGE gene promoter polymorphisms are associated with DR[656], and interactions between AGEs and RAGE induce VEGF production[626]. There is thus evidence for a pathogenic role of AGEs in the initiation and progression of DR[655;657].

Use of compounds, such as aminoguanidine, to inhibit AGE formation is being investigated for DR. Aminoguanidine binds irreversibly to reactive intermediates of early glycated end products, preventing AGE formation and AGE-induced protein cross-linking[171]. Animal studies showed reduced AGE accumulation, retinal microaneurysms and pericyte loss[177;634;649]. An RCT (ACTION II) was initiated, principally for nephropathy, with a secondary aim to assess DR. Promising phase III results were reported[171], but anaemia may limit use[658]. Renin-angiotensin blockade might also benefit DR by inhibiting AGEs and suppressing RAGE[626].

### *Intravitreal Corticosteroid Therapy, Including Triamcinolone*

Corticosteroids, given locally or systemically, are potent anti-inflammatory and anti-angiogenesis agents[659-662]. Steroids reduce extravasation from leaking blood vessels, inhibit proliferation of fibroblasts and formation of granulation tissue[663] and inhibit VEGF production by human vascular cells[664]. Steroids can reduce both the production and stability of VEGF mRNA, and thus function as VEGF inhibitors. Vitreous VEGF levels were nearly undetectable, with reduced DME, one month after intravitreal triamcinolone[665].

Cortisone was shown to be safe when injected into the vitreous in animal models during the 1980s[666]. Human trials concluded that intravitreal steroids may be a useful adjunctive therapy for DME [667]. While cortisone itself is washed out of the eye within 24 hours after a single intravitreal injection, depot forms (e.g. triamcinolone acetate, IVTA), provide continuous exposure for considerably longer periods, with absorption occurring over 2 to 6 months, [666]. Use of IVTA in managing retinal diseases was recently reviewed[668]. Two key studies are shown in Table 3.3.3.

After early reports by Jonas and others[663;666;667;669-674], IVTA is now widely used in treating DME,. Many RCT have demonstrated improvement in vision and in the morphology of DME, particularly rapid reduction in OCT macular thickness[675;676] after IVTA[58;677-681;681-684]. However, most of these studies had relatively small participant numbers and short follow-up. Substantial adverse effects from IVTA include infection[685;686], glaucoma and posterior subcapsular cataract[58;687-690]. No toxic effects on the ERG were demonstrated[691].

In the Australian RCT[58], eyes with persistent DME were randomised to receive IVTA 4mg or sham injection (saline subconjunctival injection); 56% of 34 IVTA treated eyes had a visual acuity improvement of at least 5 letters compared with 26% of 35 placebo treated eyes over 2 years, p=0.007. Overall, IVTA treated eyes had twice the chance of improved visual acuity and half the risk of further loss. However, many eyes required repeated injections (mean 2.6), significant intraocular pressure elevation was documented (at least 5mm Hg in 68% of treated eyes vs. 10%), and 55% of treated eyes needed cataract surgery. Thus, while this study demonstrated significant efficacy of IVTA for persistent DME (Level II evidence), larger RCT are needed to provide further data on long-term benefits and safety.

Substantial benefit from use of IVTA in patients with extensive hard exudate deposition, a particularly difficult DME complication, was documented in 2 non-comparative case series[59;60] (Level III-3 evidence). IVTA may have an independent beneficial effect on neovascularisation[692]

and has been recommended as an adjunct to PRP for PDR[61;62], particularly when this is associated with DME[63], and it may help to prevent PRP-induced exacerbation of DME[64].

IVTA has a number of unresolved issues. First, the ideal triamcinolone dose remains unclear, with a suggestion of more prolonged benefit from higher doses up to 8 months, compared to the usual duration up to 6 months[683;693;694]. Studies by Jonas[681] have used around 20mg (though the effective dose may be lower[695]), whereas most others[58] have injected 4mg. Second, although IVTA is frequently given to eyes refractory to laser treatment[696;697], it is unclear whether subsequent laser is helpful once the DME has settled following IVTA. One study suggested an improvement in OCT macular thickness with laser in such eyes, but no further improvement in visual acuity over IVTA alone[684]. Another trial found no incremental benefit from IVTA in combination with focal laser[698]. Third, although the response to subsequent injections appears relatively similar to the first[58;699], the potential duration of repeat therapy is unknown. Fourth, reported studies have used the Kenalog (Upjohn) triamcinolone preparation, marketed in Australia as KenacortA40 (Bristol-Myers Squibb). Concern has been expressed that this contains toxic solvents, including benzyl alcohol, that could have caused the sterile (non-infectious) endophthalmitis cases reported after IVTA[685;686;695]. A preservative-free preparation is becoming available[700].

Intravitreal or retinal implants may permit extended drug delivery. A surgically implanted intravitreal fluocinolone acetonide (Retisert, Bausch & Lomb) was evaluated in 97 DME patients randomised to receive either implant or standard care (laser or observation)[701]. After 3 years, DME had resolved in 58% of implant eyes and 30% of controls, $p<0.001$, with an associated improvement in visual acuity. However, the risk of cataract and glaucoma appeared to be higher than with IVTA, with 5% requiring implant removal to control glaucoma. An injectable biodegradable intravitreal dexamethasone extended-release implant (Posurdex, Allergan) was evaluated in a small RCT with improvements in visual acuity and OCT macular thickness over 6 months[702]. Almost 50% of the eyes in this study had macular oedema from other causes (retinal vein occlusion, uveitis, post cataract surgery). A larger Phase III RCT of Posurdex for DME is ongoing.

Posterior subtenons injection of triamcinolone is a potentially safer form of administration. Although this had a demonstrable effect on DME[703;704], its efficacy appeared reduced by comparison to IVTA in two small RCT[705;706].

In summary, IVTA appears to be an effective therapy for recalcitrant DME that has failed to respond to focal/grid macular laser treatment (Level II evidence). IVTA has a predictable though manageable adverse event profile, particularly elevated intraocular pressure and posterior subcapsular cataract. Recurrent DME is frequent after around 6 months, which is the other main limitation of this therapy. Repeat injections can be given with similar effect. Further laser therapy applied before recurrent DME occurs may be an appropriate measure to enhance long-term effects.

### *Intravitreal Vascular Endothelial Growth Factor (VEGF) Inhibitors*

VEGF is one of the most important factors contributing to the initiation of abnormal vessel growth and vascular leakage in the retina and is a principal therapeutic target for DR[707]. Angiotensin II stimulates the secretion of VEGF by vascular smooth muscle cells, mesangial cells and pericytes. These cells have receptors for angiotensin II which stimulate cell growth and upregulate VEGF mRNA expression[184]. The induction of VEGF requires hyperglycaemic or oxidative conditions[203].

Studies indicate increased retinal VEGF production in patients with PDR and altered expression patterns of VEGF receptors[201]. VEGF is clearly implicated in the pathogenesis of both diabetic neovascularisation[176;184;204;708] and DME[206].

RCT are currently evaluating the three commercially available agents that suppress VEGF (pegaptanib, ranibizumab and bevacizumab), as treatment for DME. Pegaptanib (Macugen, Pfizer) targets the 165-isoform of VEGF-A[709], and was introduced for treatment of neovascular AMD[710]. A RCT of 172 patients with DME randomised to repeated intravitreal pegaptanib or sham injection showed that treated eyes were more likely to have improvement in visual acuity of at least 10 letters (34% vs. 10%, p=0.03), reduced macular thickness (p=0.02), and need for focal laser treatment (p=0.04) after 36 weeks[711] (Table 3.3.3), together with regression of neovascularisation in PDR cases[712] (Level II evidence). A Phase III RCT, comparing pegaptanib to sham intravitreal injections, with the option of 'rescue' laser treatment after 3 months, is underway.

Ranibizumab (Lucentis, Genentech), targets all VEGF-A isoforms and was also developed to treat neovascular AMD[713;714]. Ranibizumab has been evaluated for DME in pilot studies[206;715] and is being evaluated in the RESOLVE study, a phase-II RCT, comparing ranibizumab to sham intravitreal injections, with the option of 'rescue' laser treatment after 3 months.

Bevacizumab (Avastin, Genentech) also targets all VEGF-A isoforms, and is approved for the treatment of disseminated colorectal cancer but is not currently licensed for intraocular use. Bevacizumab, however, has been widely used off-label in the treatment of PDR[716-718], iris new vessels[719;720], and DME[721-724], because of its relative low cost. Non-comparative studies show some efficacy in the treatment of these three conditions (Level III-3 evidence).

Case reports and small case series describe rapid regression of PDR following intravitreal bevacizumab[716-718;721;725;726]. The specific role for bevacizumab in treatment of DR is not established. However, it may be a very useful adjunctive treatment before laser or vitrectomy surgery for PDR, and in patients with vitreous haemorrhage[716]. It also has a potentially important role as an adjunct to laser in the management of iris new vessels in patients with severe DR[719-721].

A 3-month phase 2 RCT compared 2 doses of intravitreal bevacizumab (1.25mg and 2.5mg) to focal laser treatment, and to combined laser and bevacizumab therapy[727]. This showed that intravitreal bevacizumab can reduce DME in some eyes (greater reduction in OCT central macular thickness than from laser), Level II evidence. Given the short duration, this study, however, was not designed to determine whether this treatment was beneficial. A 3-year phase 3 RCT comparing the effects of laser treatment, intravitreal bevacizumab, and combined intravitreal bevacizumab and laser or sham injection on DME is planned by the U.S. National Institutes of Health.

Nevertheless, considerable clinical experience using becacizumab to treat DME has now been gained across the world, and both bevacizumab and ranibizumab certainly appear to have greater ocular safety than IVTA, with no concerns regarding cataract or glaucoma. There are concerns, however, regarding the systemic safety of bevacizumab[728], and this agent does not penetrate the retina as well as ranibizumab, which is a smaller molecule[729]. No RCT comparing bevacizumab therapy to sham intravitreal injections has yet been reported.

### *Other Therapeutic Approaches*

#### *Ovine Hyaluronidase (Vitrase)*

An ophthalmic injectable formulation of highly purified ovine hyaluronidase (Vitrase, Ista) was developed and a large multi-centre Phase-III RCT (1125 patients) compared Vitrase to sham injection[730;731]. This trial demonstrated modest benefit for the higher dose (55 IU) in accelerating clearing of vitreous haemorrhage and debris, which occurred as early as months 1 and 2. No serious safety issues were identified[731], but the medication is not yet available.

**Table 3.3.1: Randomised controlled trials evaluating blood-pressure-lowering therapies in diabetic retinopathy (adapted from Mohamed et al.[14])**

| Study | N | Diabetes Type | Intervention | Outcome | Comments | Follow-up |
|---|---|---|---|---|---|---|
| United Kingdom Prospective Diabetes Study (UKPDS)[50] | 1148 | Type 2 DM with hypertension (mean BP of 160/94mm Hg) | Tight BP control (<150/85mm Hg) vs. less tight BP control (<180/105 mm Hg<br><br>(Randomised to beta-blocker or angiotensin-converting enzyme (ACE) inhibitor) | IT ↓ risk of progression DR (≥2 ETDRS steps) by 34% (99% CI; 11%-50%, p=0.004)<br>IT ↓ risk VA loss 3 ETDRS lines by 47% (7% to 70%, p=0.004)<br>IT ↓ risk of laser photocoagulation by 35%. (p=0.02)<br>IT ↓ risk of >5 MA (RR, 0.66; p<.001), Hex (RR, 0.53; p<.001), and CWS (RR, 0.53; p<.001) at 7.5 yrs. | Observational data suggest 13% ↓ in microvascular complications for each 10mm Hg ↓ in mean systolic BP.<br><br>No difference in outcome between ACE inhibitor and beta-blockade | 8.4 yrs |
| Appropriate Blood Pressure Control in Diabetes trial (ABCD)[51] | 470 | Hypertensive Type 2 DM (mean baseline DBP >90mm Hg) | Intensive BP control (aiming for a DBP of 75) vs. moderate control (DBP 80-89 mm Hg) | No difference in progression of DR between IT (mean BP 132/78) and CT (mean BP 138/86). | No difference in progression of DR with nisoldipine vs. enalapril. | 5.3 yrs |
| Appropriate Blood Pressure Control in Diabetes trial (ABCD)[52] | 480 | Normotensive Type 2 DM (BP <140/90 mm Hg) | Intensive (10 mm Hg below the baseline DBP) vs. moderate (80-89 mm Hg) DBP control | IT (mean BP 128/75mm Hg) ↓ progression of DR compared to CT (mean BP 137/81mm Hg) (p=0.019). | Results were the same regardless of the initial antihypertensive agent used | 5.3 yrs |
| The EURODIAB Controlled Trial of Lisinopril in Insulin-Dependent Diabetes Mellitus (EUCLID)[53] | 325 | Normotensive and normoalbuminuric Type 1 DM | Lisinopril treatment | Lisinopril ↓ progression DR (2 ETDRS steps) by 50% and ↓ progression to PDR by 80%. | Concern about possibility of inadequate randomisation (Lisinopril group had lower $HbA_{1c}$ levels) | 2 yrs |

DM = diabetes mellitus, BP = blood pressure, DM = diabetes mellitus, NPDR = non proliferative diabetic retinopathy, $HbA_{1c}$ = glycosylated haemoglobin A levels, IT = intensive treatment, CT = conventional treatment, DR = diabetic retinopathy, PDR = proliferative diabetic retinopathy, NPDR = non-proliferative diabetic retinopathy, RR = relative risk, MA = microaneurysm; Hex = hard exudates; DBP = Diastolic blood pressure;

**Table 3.3.2: Randomised controlled trials of various medical therapy interventions in diabetic retinopathy (adapted from Mohamed et al.[14])**

| Author | Diagnosis | Intervention | N | Outcome | Comment | Follow-up |
|---|---|---|---|---|---|---|
| Fenofibrate Intervention and Event Lowering in Diabetes (FIELD study)[54] | Type 2 DM Total cholesterol 3 - 6.5 mmol/L and no lipid lowering Rx at baseline | Fenofibrate vs. placebo | 9795 | Treatment ↓ reported need for retinal laser photocoagulation (5.2% vs. 3.6%, p=0.0003). | Not main endpoint. Large loss of data. Severity of DR, indication for laser & the type of laser (focal or panretinal) not reported | 5 yrs |
| ETDRS[632] Chew et al.[633] | Mild-to-severe NPDR or early PDR | Aspirin 650mg/day vs. placebo | 3711 | VH in 32% aspirin vs. 30% placebo, p = 0.48)*. No difference in the severity of vitreous/preretinal haemorrhages (p= 0.11)* or rate of resolution (p = 0.86) | Aspirin had no effect on DR incidence/progression, VH, or need for vitrectomy. | 3 yrs |
| The DAMAD Study Group[635] | Early diabetic retinopathy (Type 1 and Type 2 DM) | Aspirin (330mg tds) alone vs. Aspirin + dipyridamole (75 mg tds) vs. placebo | 475 | Aspirin alone and aspirin+dipyridamole ↓ mean yearly increases in MA on FFA (Aspirin-alone group (0.69 ± 5.1); aspirin + dipyridamole (0.34 ± 3.0), placebo (1.44 ± 4.5) (p=0.02) | 10% of patients lost to follow-up. | 3 yrs |
| The Ticlopidine Microangiopathy of Diabetes study (TIMAD)[636] | NPDR | Ticlopidine hydrochloride (antiplatelet agent) vs. placebo | 435 | Treatment ↓ yearly MA progression on FFA (0.23 ± 6.66 vs. 1.57 ± 5.29; p=0.03). Treatment ↓ progression to PDR (p =0.056)* | Adverse reactions included neutropenia (severe in one case), diarrhoea, and rash. | 3 yrs |
| Cullen et al.[55] | Exudative diabetic maculopathy | Atromid-S (clofibrate) | | ↓ hard exudates but no statistical improvement in VA | Lacked power. | 1 yr |
| The PKC-DRS Study Group[644] | Moderately severe to very severe NPDR (ETDRS severity level 47B - 53E, VA ≥20/125 and no previous scatter photocoagulation) | Ruboxistaurin RBX (8, 16, or 32 mg/day) vs. placebo | 252 | No significant effect on DR progression. 32 mg RBX delayed occurrence of MVL (p = 0.038) and SMVL (p = 0.226)*. In multivariable Cox proportional hazard analysis, RBX 32 mg ↓ risk of MVL vs. placebo (hazard ratio 0.37, 95% CI 0.17-0.80, p = 0.012). | RBX ↓ of SMVL was seen only in eyes with definite DME at baseline (10% RBX vs. 25% placebo, p = 0.017). | 36-46 months |
| PKC-DRS2 Study Group[645] | Moderately severe to very severe NPDR (ETDRS severity level 47B - 53E, VA ≥20/125 and no previous scatter photocoagulation) | Ruboxistaurin 32mg/day vs. placebo | 685 | No significant effect on DR progression. Treatment ↓ risk of sustained MVL (5.5% treated vs. 9.1% placebo, p=0.034) | | 3 yrs |

| | | | | | | |
|---|---|---|---|---|---|---|
| PKC-DME Study[646] | DME > 300µm from centre. (ETDRS severity level 20 – 47A, VA ≥75 ETDRS letters and no previous laser) | Ruboxistaurin 32mg/day | 686 | No significant effect on progression to sight threatening DME or need for focal laser. | Variation in application of focal laser between centres. 32mg RBX reduced progression of DME vs. placebo in secondary analysis (p=0.054 unadjusted) | 3 yrs |
| The Sorbinol Retinopathy Trial[650] | Type 1 diabetic | Oral sorbinil 250mg vs. placebo | 497 | No significant effect on DR progression (28% sorbinil vs. 32% placebo; p=0.344)*. | Hypersensitivity reaction in 7% sorbinil treated group. | 41 months |
| Grant et al.[651] | Severe NPDR or early non-high-risk PDR | Max tolerated doses octreotide (200-5,000µg/day subcutaneously vs. conventional treatment | 23 | Treatment ↓ progression to high risk PDR needing PRP (1/22 eyes treated vs. 9/24 controls, p<0.006) Octreotide ↓ progression DR (27% vs. 42% controls; p=0.0605)*. | Thyroxine replacement therapy needed in all treated patients | 15 months |

VH = vitreous haemorrhage; NPDR = non proliferative diabetic retinopathy, NV = neovascularisation; NVD = neovascularisation of the disk, PDR = proliferative diabetic retinopathy, DME = diabetic macular oedema, PRP = panretinal laser photocoagulation; RR = risk reduction; MVL = moderate visual loss, SVL = severe visual loss; Hex = hard exudates, BP = blood pressure, * = Not significant.

**Table 3.3.3: Randomised controlled trials conducted for at least 36 weeks, of intravitreal therapies for diabetic macular oedema (adapted from Mohamed et al.[14])**

| Author | Diagnosis | Intervention | N | Outcome | Comment | Follow-up |
|---|---|---|---|---|---|---|
| Gillies et al.[58] | DME and impaired vision that persisted or recurred after laser treatment. | Intravitreal triamcinolone acetonide (TA) injections (4mg) vs. subconjunctival saline placebo | 43 (69 eyes) | TA ↑BCVA ≥ 5 letters (56% vs. 26%; p = 0.006).<br>TA ↑ Mean VA by 5.7 letters (CI, 1.4-9.9) vs. placebo<br>IOP elevation ≥ 5mm Hg in 23/34 (68%) vs. 3/30 (10%) untreated eyes (p<0.0001).<br>Cataract surgery in 54% vs. 0% controls (p<0.0001).<br>2 TA eyes required trabeculectomy.<br>1 case of infectious endophthalmitis | Data for 60 of 69 (87%) eyes of 35 of 41 (85%) patients. | 2 yrs |
| Pearson et al.[701] | DME | Sustained release fluocinolone acetonide intravitreal implant (Retisert) vs. standard care (randomised 2:1 ratio) | 197 | Implant ↓ DME (no oedema in 58% vs. 30% standard care; p<0.001)<br>Implant ↑ improvement in CMT<br>Trend ↑ VA with implant (VA ↑ ≥3 lines in 28% vs. 15%, p<0.05*)<br>Cataract surgery in 95% of phakic implanted eyes | ↑ IOP in 35%<br>28% required a filtering procedure and 5% explanted to manage IOP. | 3 yrs |
| Cunningham et al.[711] | DME | Intravitreal Pegaptanib (0.3mg, 1mg, 3mg) injections vs. sham (randomised 1:1:1:1) | 172 | Pegaptanib ↑ VA for 0.3mg (20/50 vs. 20/63 p=0.04)<br>Larger proportion treated with 0.3mg gained 10 letters (34% vs. 10%, p=0.003); or 15 letters (18% vs. 7%, p=0.12).<br>Mean central retinal thickness decreased by 68 microns with 0.3mg vs. 4 microns with sham, p=0.02<br>Laser needed in fewer subjects on pegaptanib (for 0.3 mg, 25% vs. 48%, p=0.04) | Endophthalmitis in 1/652 injections, not associated with severe visual loss | 36 weeks |

CMT = central macular thickness; DME = diabetic macular oedema; VA = visual acuity; ILM = internal limiting membrane, OCT = optical coherence tomography; PPV = pars plana vitrectomy; LP = light perception; IOP = intraocular pressure; FU = follow up; * = not significant; CSME = clinically significant macular oedema; BP = blood pressure; $HbA_{1c}$ = glycosylated haemoglobin

## 3.4 Management of Cataract

**Guidelines**

35. Carefully assess DR in patients with significant cataract. Attempt to treat any DME with focal/grid laser, before cataract surgery, if possible (Level III-3[65]).
36. Once DR is stable, consider cataract surgery to improve vision in diabetic patients. If cataract is moderate to advanced, consider surgery to adequately assess need for laser or to permit laser (Level IV[66-68]).

**Consensus Good Practice Point**

6. Consider delaying cataract surgery until DR and DME signs are stabilised.

**Key Points**

- Diabetes is associated with an increased risk of both cataract (particularly cortical and posterior subcapsular cataract) and cataract surgery.
- Vitrectomy in diabetic patients is associated with earlier onset of cataract and need for cataract surgery.
- Cataract surgery may be needed to adequately assess need for laser and to permit laser treatment to be completed.
- Cataract surgery may also lead to substantial visual improvements in diabetic patients.
- The visual outcome after cataract surgery in people with diabetes depends on the severity of pre-operative DR and presence of DME. Asymmetric retinopathy progression can occur in the operated eye, and the risk of rubeosis iridis or neovascular glaucoma increases after cataract surgery.
- Pre-operative DME and active PDR are strong predictors of a poor visual result.
- Although modern cataract surgical techniques show consistently improved visual outcomes in diabetic patients, a systematic review of case series and clinical trials consistently demonstrated worse visual results from cataract surgery in persons with than without DR.
- Progression of DR after cataract surgery is correlated with diabetic control at the time of surgery and the presence of T2DM and PDR at baseline.
- While no RCT have examined timing of laser treatment in relation to cataract surgery, current opinion recommends that adequate laser treatment of significant DR be completed before cataract surgery.
- Current opinion also recommends consideration of intravitreal triamcinolone (or bevacizumab) on the same day as cataract surgery in patients with DME to reduce progression.
- Diabetic patients develop posterior capsule opacification (PCO) earlier and with greater magnitude than do non-diabetic patients; but no correlation has been found between PCO and stage of DR, duration of diabetes, or HbA1c level.
- In relation to visual acuity or DR progression, no important differences exist between phacoemulsification and extra-capsular cataract extraction (ECCE).

### *Cataract in Diabetes*

Many studies have postulated an association between diabetes and cataract or examined this question in population-based or clinic samples[732-739]. Two early population surveys, the Framingham Eye Survey[740] and the Health and Nutrition Examination Survey (HANES)[741], showed a marked excess prevalence of cataract and cataract surgery in persons with diabetes aged less than 65 years; significant OR 4.6 and 3.3, respectively, for the two studies. The HANES showed significantly increased odds of cataract (OR 2.5) for ages older than 65 years, although this was not found in Framingham (OR 1.0).

The BMES (1992-4), an Australian cross-sectional survey of 3654 persons, reported that diabetes was independently associated with cortical and posterior subcapsular (PSC) cataract and a higher prevalence of cataract surgery in people aged 55-74 years. However, only PSC (OR 1.8) and past cataract surgery (OR 2.5) remained significantly associated with diabetes after adjustment for known cataract risk factors[742]. BMES incidence data confirmed the diabetes association with incident PSC cataract but not with cortical cataract[743]. Cortical cataract incidence was significantly greater, however, in pre-diabetic subjects.

Cross-sectional findings from the Beaver Dam Eye Study[744] and the POLA Study[745], indicated associations between diabetes and both cortical and PSC cataract, while the Barbados Eye Study[746] reported an association only with cortical cataract. Many studies, including case reports and population surveys, have also found associations between diabetes and all lens opacities[733], very early or rapid-onset cortical opacities[747-749], and cataract surgery[750-752]. Among 653 consecutive cataract surgical procedures in persons aged 60 years or older at Westmead Hospital in Sydney, 28% gave a diabetes history, a much higher proportion than seen for healthy patients at this age[753]. DR was an independent predictor of cataract surgery in a Taiwanese population[754].

Vitrectomy surgery for diabetic retinopathy was associated with an increased risk of cataract requiring surgery in a small series of 50 cases[755]. Another clinic series of 223 cases reported that combined phacoemulsification, insertion of PC-IOL, and pars plana vitrectomy for DR complications achieved good results, avoiding a second procedure for post-vitrectomy cataract[568].

### *Visual Outcome from Cataract Surgery in Diabetes*

Diabetes-related cataract is strongly associated with the duration of diabetes, as is DR. A significant relationship was reported between cataract surgery and retinopathy severity in T1DM, but not T2DM[750]. An important issue is that cataract surgery may be needed to provide an adequate assessment of the need for retinal laser, or to permit its completion[66;756].

### *Does Diabetes Adversely Influence Visual Outcomes from Cataract Surgery?*

The visual outcome following cataract extraction in diabetes varies by the severity of pre-operative retinopathy and the presence of DME, particularly CSME. A systematic review defined the relation between pre-operative retinopathy and post-operative vision[65] (Level III-2 evidence), and included 10 case-series reports that adequately defined retinopathy and visual outcomes. A diminishing proportion of eyes achieved 6/12 or better vision after cataract surgery, from 87% of eyes with no retinopathy to 41% of eyes with both NPDR and DME. No eyes with active PDR achieved this visual acuity post-operatively[65]. A prospective trial reported a substantial adverse effect of CSME and to a lesser extent severity of DR at the time of surgery, on postoperative visual acuity (Level III-I evidence)[68]. Pre-operative DME and active PDR are thus strong predictors of a poor visual result. Diabetes may substantially worsen the visual outcome after cataract surgery, because of asymmetric retinopathy progression in the operated eye[757], possibly by affecting the blood-aqueous barrier[758] or by altering concentrations of angiogenic growth factors[759].

Case series using phacoemulsification cataract surgery report consistently better visual outcomes in diabetic patients than previously[67;68;760;761] (Level IV evidence). Mittra et al.[67] retrospectively examined 150 eyes of 119 patients and reported that diabetic eyes had a significant improvement in visual acuity post-operatively at all levels of pre-operative DR; 53% of treated PDR cases achieved a visual acuity of 6/12 or better. One study of 132 diabetic patients reported no post-operative DR progression[761]. Despite this comparatively recent improvement, cataract surgical results overall are worse in the presence of significant DR.

In an ETDRS report[762], cataract surgery improved visual acuity (Level II evidence. However, more severe DR at baseline and poorer pre-operative visual acuity predicted a visual acuity worse than 6/30 after cataract surgery. Importantly, no statistically significant long-term post-operative DME risk was documented. The authors acknowledged important limitations from using studies such as the ETDRS to assess risk factors because of their highly selected patient sample.

### *Progression of Diabetic Retinopathy after Cataract Surgery*

A retrospective study examined progression of DR after phacoemulsification cataract surgery[67] (Level IV evidence) and revealed faster retinopathy progression in association with NPDR and PDR at baseline, and a weaker but significant association with surgical inexperience. In addition to baseline DR, other studies reported that DR progression correlated with diabetic control at the time of surgery, as assessed by the level of $HbA_{1c}$[760;763]. Asymmetric progression of NPDR in the operated eye has been shown in many[757;764] but not all[760;761;763;765] studies. In one study[764], DR progression occurred in 85% of operated eyes compared to only 15% of non-operated eyes (Level III-2 evidence). OCT appears to be a sensitive indicator of DME after cataract surgery; a 22% DME incidence was measured using OCT[766]. In these cases, mean foveal thickness increased by 202μm after one month, and was associated with around one line loss of visual acuity.

A retrospective study[767] and a number of prospective studies[761;764] have evaluated different types of surgery in people with diabetes. In general, there are few significant differences in visual acuity or retinopathy progression between phacoemulsification and extra-capsular cataract extraction (ECCE). A prospective case series of 75 patients[764] also found no significant difference between phacoemulsification and ECCE. However, this study showed that preoperative DME and poor renal function were important predictors of DR progression.

Some authors have proposed combining intravitreal triamcinolone (IVT) injection on the same day as phacoemulsification cataract surgery[768] in patients with DME in order to reduce DR progression.

### *Other Complications Associated with Cataract Surgery*

People with diabetes also appear to develop posterior capsule opacification (PCO) earlier and with greater magnitude than do non-diabetic patients[769]. A prospective case-control clinic study of consecutive diabetic and non-diabetic patients showed substantial PCO progression in the late post-operative period (18 months or later) among those with diabetes. However, there was no significant correlation of PCO value with the stage of retinopathy, duration of diabetes, or $HbA_{1c}$[770] (level III-2 evidence).

Rubeosis and neovascular glaucoma may complicate cataract surgery in some diabetic patients[771;772], particularly those with active PDR[771] and those not previously treated by PRP[773].

## 3.5 Consideration of Special Groups in Managing Diabetic Retinopathy

**Guidelines**

37. Conduct annual screening for Aboriginal or Torres Strait Islander groups with diabetes (Level IV evidence[69]).

**Key Points**

- The prevalence of diabetes in Aboriginal and Torres Strait Islander communities is between 2-and 4-fold higher overall than in non-Aboriginal communities.
- Australians in rural and remote communities experience considerably higher hospitalisation due to diabetes than in metropolitan areas, which demonstrates the need for improved diabetes care services.

### *Aboriginal and Torres Strait Islander communities*

Higher diabetes prevalence rates in Aboriginal and Torres Strait Islander communities were documented previously in a population based study[774]. Estimates by the International Diabetes Institute for the Office for Aboriginal and Torres Strait Islander Health Services, Canberra, 1998 indicate between 2-and 4-fold overall higher diabetes prevalence in aboriginal than in non-aboriginal communities[775]. The epidemiology of this disease along with geographical and cultural differences pose challenges relating to screening, treatment and follow-up in the Aboriginal and Torres Strait Islander communities.

A study[776] in the Lower Top End of the Northern Territory provided cross-sectional data on DR in the Aboriginal population. A total of 234 people with diabetes were examined in 1993 and 243 in 1996. The frequency of retinopathy was 18% in 1993 and 21% in 1996. The respective findings for CSME were 8% and 6%. A 2005 study in the Kimberley region using non-mydriatic photography reported a DR prevalence of 21%, including 1% PDR and 3% CMSE among 1318 Aboriginal Australians with diabetes[384]. The technical failure rate of 9% was lower than that previously reported[777;778].

The importance of DR screening and treatment was emphasised in the Commonwealth of Australia publications "Specialist Eye Health Guidelines for Use in Aboriginal and Torres Strait Islander Populations" (2001)[6] and "Review of the Implementation of the National Aboriginal and Torres Strait Islander Program" (2003)[69;779].

Annual screening and urgent treatment of STR using portable lasers are strategies currently employed to manage DR in Indigenous Australians

### *Rural communities*

Australians in rural and remote communities experience considerably higher hospitalisation due to diabetes than in metropolitan areas, which demonstrates the need for improved diabetes care services[780]. In a pilot, mobile screening program for the early detection of diabetic eye disease conducted in rural Victoria, actual costs of screening were measured and applied to a permanent model[780]. The screening procedure included a test of visual acuity and non-mydriatic fundus photographs that were graded by an ophthalmologist. The cost per participant, (included establishment and an estimate of operating costs) if 80% examination compliance to guidelines for diabetic retinopathy was achieved through mobile screening, was AU$41 per participant. This was competitive with Medicare rebate costs for examinations. Costs were attributed to staff salaries, film, program promotion, rental, equipment maintenance and repairs, stationery, postage and telephone. However, sensitivity analyses revealed that the number of people presenting for

screening had the largest impact on the cost per participant, with the cost rising to AU$65 when screening at 60% efficiency.

A study in an isolated First Nations cohort with diabetes in northern Ontario, Canada modelled the cost-effectiveness of retinopathy screening by travelling retina specialists versus retinal photography with a portable digital camera (50° photos) that were concurrent over 5 years.[781] The camera program was more cost-effective, maintaining the highest number of sight years and was cheaper than the specialist-based program. The savings were realised through lower personnel and transportation costs. The camera system was found cost-effective even with screening percentages as low as 65%.

# 4. Costs of Diabetic Retinopathy

## *4.1 Costs of Diabetes, Diabetic Retinopathy and its Management*

**Key Points**

- Diabetes accounts for about 3% of the total health care costs in most countries.
- The 2000-01 cost of diabetes in Australia was estimated at $784 million, 1.7% of health expenditure. Average health expenditure on diabetes was $1469 per known (self reported) case of diabetes, or $42 per Australian.
- UKPDS and DCCT data show that intensive diabetes therapy is more expensive, but has justifiable long-term benefits on complications, including DR, from an economic perspective.
- Preventive/screening programs targeted at DR are not only highly cost effective, but also cost saving.

Relatively few published data exist on the direct cost of DR to the Australian community. Such costs can be derived in part from studies of the costs of diabetes and general studies of the costs of diabetes-related complications. In these *Guidelines*, costs are in Australian dollars unless otherwise specified.

Where possible and appropriate, cost-effectiveness studies were appraised according to NHMRC criteria (Table 4.1.1)[10]. These 12 criteria are listed in Appendix 3.

### *Costs of Diabetes*

Diabetes imposes a substantial cost burden on the community, though such costs are difficult to assess with certainty. Once diagnosed with diabetes, a person will have the disease for life. Thus, costs will depend on the age at diagnosis and are higher for individuals who develop T1DM during childhood than for persons who develop T2DM at age 50[782].

#### *Australian Data*

In 2005, the Australian Institute of Health and Welfare estimated the costs of diabetes in Australia for 2000-01: $784 million or 1.7% of total health expenditure[783]. The cost of diabetes ranked 15$^{th}$ out of around 200 disease groups. Average health expenditure on diabetes was $1469 per known (self reported) diabetes case, or $42 per Australian. The Australian Government and people with diabetes spent $204 million on antidiabetic drugs and diabetes testing reagents. Insulin accounted for 60% of the antidiabetic drug expenditure. The 2003 DiabCost study estimated that average annual cost per person with T2DM was $5360[784] and that estimated that the excess cost attributable directly to diabetes in Australia is approximately $1 billion.

#### *International Data*

Diabetes is estimated to account for at least 3% of the total health care costs in most countries[782]. The estimated medical expenditure and lost productivity as a consequence of diabetes in the US is US$132 billion. The American Diabetes Association (ADA) noted that this was likely an underestimate of the true burden of diabetes in the US because it omits such intangibles as pain and suffering, care provided by non-paid caregivers, and the higher healthcare-service usage by people with diabetes (e.g. optometry, etc.)[785]. A Canadian study estimated the total economic burden from diabetes and its chronic complications as US$4.8-5.2 billion in 1998[786].

Raikou and McGuire performed a systematic literature review of the economics of T2DM screening and treatment[787]. They reported that a Swedish study by Henricksson et al. found hospitalisation and drug costs accounted for 42% and 27% of the total cost, respectively. Drug costs for insulin-treated

persons were twice as high as in those treated with oral anti-diabetic agents. For individuals with microvascular complications alone, the annual costs were of the same magnitude as for those with no complications. Costs for individuals with both microvascular and macrovascular complications were approximately 3 times higher than the costs for those without complications[787]. Brown et al. found that the annual costs of a US diabetic population were approximately double those of matched case-controls[787]. Evans et al. estimated that patients with diabetes accounted for around 8% of the UK drugs budget: and of this, 90% was attributable to patients with T2DM [787].

Brandle et al. reported the median annual direct medical costs in a random sample of 1364 persons with T2DM who were members of a Michigan health maintenance organisation[788]. The costs for persons with diet-controlled T2DM, body-mass index of 30 and no microvascular, neuropathic, or cardiovascular complications were US$1704 for white men and US$2104 for white women. A body mass index increase of 10, treatment with oral antidiabetic or antihypertensive agents, diabetic kidney disease, cerebrovascular disease, and peripheral vascular disease were each associated with cost increases of 10-30%. Insulin treatment, angina and myocardial infarction were each associated with cost increases of 60-90%. Dialysis was associated with 11-fold higher costs.

Many authors have used computer models to predict lifetime diabetes health events[789-792] to determine the frequency of screening intervals, treatment, and their cost effectiveness.

### *Cost-effectiveness of Intensive Therapy in Types I and II Diabetes*

Studies have examined the cost-effectiveness of a variety of interventions for diabetes such as weight loss, antihypertensive medication, and intensive use of insulin regimes, compared to conventional therapy[787;793-795].

The DCCT found that intensive therapy may slow the progression of the microvascular complications of T1DM[270]. In a 10-year follow-up of insulin dependent T2DM, intensive insulin therapy reduced the risk of progression of retinopathy by 67% and photocoagulation by 77% relative to conventional therapy[795] (Level II evidence). Although intensive therapy was more expensive, it became cost-effective in treating T1DM when the costs of complications were included. For T2DM, savings made generally offset the increased expenditure[796].

A study based on the UKPDS population[793] concluded that intensive therapy significantly increased treatment costs but substantially reduced the cost of complications and increased the complication-free interval. As in the DCCT analysis, it concluded that increased treatment costs would be offset by a reduced cost of complications (Level II evidence). Population data from the Netherlands demonstrated that intensive glycaemic control and intensive eye care shortened the duration of blindness in type 1 diabetes by 0.76 years and 0.53 years, respectively[797]. A study using US incidence data estimated that the incremental cost per QALY* (quality-adjusted life year) gained by intensive therapy of T2DM was US$16,000, which is in the range of interventions generally considered cost-effective[794].

Thus several population-based cost-effectiveness studies show that intensive therapy is more expensive but has justifiable long-term economic benefits[793;795;796]. These three studies are appraised according to the NHMRC criteria in Table 4.2.1, and represent robust analyses. Although intervention studies have established that intensive glycaemic control can prevent the microvascular complications of diabetes, this is rarely achieved in clinical practice[798]. Successful models of care

* QALY estimates are derived from cost utility analyses, in which treatment outcomes are scaled to constructs called utilities. These attempt to express the overall effect of a disease on the patient in a continuous scale ranging from perfect health to death. The incremental utility score comparing treatment to no treatment is multiplied by the estimated remaining years of life. The difference is the QALYs gained. Division by the incremental cost provides the cost/QALY.

should focus on strategies that promote and maintain improved self-care behaviour[798]. This report suggested that the message about benefits of tight glycaemic control needs to be refocused from the patient's perspective, e.g., in terms of increasing personal freedom.

### *Costs of Diabetic Retinopathy and Eye Disease*

Authors in this area acknowledge the difficulties in assessing the costs of diabetic eye disease, because diabetes typically causes multiple morbidities. How should diabetes health-care costs be attributed when a patient suffers from retinopathy, nephropathy and hypertension? Is it possible to calculate the cost of maintaining vision? Should the costs of managing hypertension also be attributed, as this treatment reduces the risk of DR?

#### *Australian Data*

The Access Economics Report "Economic Impact and Cost of Vision Loss in Australia" in 2004 estimated the overall cost of visual impairment in Australia at $9.8 billion ($1.8 billion in direct medical costs, $3.2 billion for indirect costs of visual impairment, and $4.8 billion for suffering and premature death)[799]. However, this study did not separate out the cost for DR. A further Access Economics Report "Investing in Sight: Strategic Interventions to Prevent Vision Loss in Australia" in 2005 addressed the cost-effectiveness of two-yearly eye examinations and sustainable funding for retinal photography for people with diabetes[800]. Data presented in this report, however, did not permit appraisal using NHMRC criteria[10].

An Australian paper reported the direct financial costs of blindness to the government and community, including the cost of concessions, but did not include financial costs due to loss of productivity[801]. A hypothetical case was presented of a working-age person with DR and severe visual impairment. High cost estimates were calculated using figures for a married person with 2 dependent children. Costs for a typical adult with DR were $17701, but this ranged from a low of $9669 to a high of $26720 using figures from Centrelink[801].

A second Australian study used 7-year Medicare data( 1993-99) to compare the patterns of healthcare utilisation among persons with diabetes who received their first laser photocoagulation treatment in 2000 with persons who had never received this treatment[802]. The authors reported that persons who received laser were significantly less likely to have attended a GP or specialist, or be tested for $HbA_1C$ or HDL-cholesterol. Women were at a higher risk of STR. Reasons for this were not elucidated.

#### *International Data*

The calculations of total costs are complex and must include the costs of illness (direct, indirect, and intangible costs), treatment and other economic costs[796]. Rein and others estimated that in 2004 the total financial cost of major visual disorders among US residents aged 40 years or older was US$35.4 billion: US$16.2b in direct medical costs, US$11.1 billion in other direct costs, and US$8 billion in productivity losses[803]. The direct medical cost of DR was US$493 million.

Javitt et al. (1996) found that screening and treatment of eye disease in patients with diabetes in the US cost US$3190 per QALY[804]. This average cost represented a weighted average (based on prevalence of disease) of the cost-effectiveness of detecting and treating diabetic eye disease in those with T1DM (US$1996 per QALY), those with T2DM using insulin (US$2933 per QALY) and not using insulin (US$3530 per QALY)[804]. A review by Klonoff and Schwartz estimated that in 1998 each sight-year gained cost US$2613 per American patient[805]. They calculated that the cost per sight-year gained was US$2735 for T2DM versus US$1635 for T1DM[805], higher than the likely cost from another study[806]. At similar levels of visual acuity loss, reduction in quality of life was relatively similar whether due to DR or to age-related macular degeneration[807].

A community-based study among persons with T2DM in Taiwan with only a 56% response rate reported that the overall mean utility value associated with DR was 0.92 ± 0.12 (95% CI 0.91-0.93)[808]. Thus, persons with T2DM were willing to trade about 8% of their remaining life in return for being free of the disease. In a multiple linear regression analysis, older age and more severe degrees of DR decreased the utility values[808].

### *Cost-effectiveness of Treating Diabetic Retinopathy*

There are no published cost-effectiveness studies evaluating specific treatments for diabetic retinopathy. Smiddy at al. report that the cost per line of vision saved was US$5458 for DME laser, US$594 for panretinal photocoagulation, and US$2984-4178 for diabetic vitrectomy[809].

One report stratified 17 widely practised interventions to decrease complications of diabetes according to their economic impact[805]: (1) clearly cost saving, (2) clearly cost-effective, (3) possibly cost-effective, (4) not cost-effective, or (5) unclear. The authors systematically evaluated 10 DR studies and concluded that DR interventions (eye care) were clearly cost saving[364;419;420;458;810-815]. Of the 17 interventions, only DR interventions and pre-conception care of diabetic women to reduce the incidence of foetal malformation were cost–saving. Interventions with an unclear economic impact included blood pressure control, blood lipid control, and $HbA_{1c}$ measurement.

## 4.2 Costs and Cost-effectiveness of Diabetic Retinopathy Detection

**Consensus Good Practice Point**

7. Screen for DR as part of the systematic and integrated care of people with diabetes, where possible.

**Key Points**

- Despite the high level of efficacy, clinical effectiveness and cost-effectiveness, problems remain with screening and treatment compliance.
- The cost of non-mydriatic retinal photography by non-medically trained staff, with photograph grading by an ophthalmologist in a 2-year mobile community-based DR screening program in rural Victoria, was similar to Medicare rebate costs for eye examinations.
- A cost-minimisation analysis revealed that telemedicine was cheaper than conventional examination (ophthalmoscopy) at higher patient numbers, but that this technology was hampered by a relatively high technical failure rate (around 10%) and the difficulties in reliably detecting DME.

Raikou and McGuire note controversy over the cost effectiveness of screening for DR[787]. Early studies were criticised for utilising suboptimal screening methods and not using opportunistic screening as a comparison. Differing assumed prevalences of DR in a study make comparisons difficult [787], but studies suggest overall that systematic screening alone, as well as combined screening and treatment programs, are cost-effective.

Table 4.2.1 shows appraisal of four screening studies[781;816-818] using NHMRC criteria[10]. Application of these appraisal scores (i.e. --, +, ++) will give some impression of the potential cost effectiveness of improving glycaemic control, treatment interventions and screening for DR, using the list of shadow prices in Appendix 3.

### *Australian Data*

There are few available data on direct costs of DR screening tests. Lee et al. evaluated an eye care model for people with diabetes in rural areas[780]. Actual costs from a pilot project that involved mobile screening in rural Victoria were presented. The program conducted community-based screening of people with diabetes for DR using non-mydriatic retinal photography. Non-medically trained staff took photographs that were graded by an ophthalmologist. Costs were categorised as either establishment or operating costs. Establishment costs consisted of the purchase of equipment for the program, which included the camera, carrying case and table, the DCA 2000 Analyser, a station wagon, one portable and one desktop computer, software and a printer. Operating costs included staff salaries, participant recruitment costs, equipment maintenance and repair, vehicle running costs, telephone, fax, printing, translations and interpreters, Polaroid film, stationery, and overheads. The cost per participant, if 80% compliance to DR examination guidelines was achieved, was $41 per participant. This compared favourably with Australian Medicare rebate costs for eye examination. As well as detecting DR, screening could also be assumed to detect other vision-threatening conditions such as glaucoma. Analyses by the University of Melbourne, Department of Ophthalmology had reported the cost savings in Australia that would flow from screening programs using different levels of coverage[27].

### *International Data*

Javitt et al. show that preventive/screening programs targeted at DR not only result in significant US Medicaid/Medicare cost savings, but are also highly cost-effective health investments for society[794;804;805]. A Canadian rural study concluded that a portable retinal camera was a cost-

effective means of screening for DR in isolated communities[781]. No studies have assessed the minimum period and nature of the training needed for technicians to obtain adequate quality mydriatic or non-mydriatic retinal photographs.

O'Hare et al. claimed a cost of £12.50 ($33) per patient screened for DR with retinal photography, and an estimated cost of £1,100 ($2,895) per patient whose sight is saved[413]. However, after problems with the costing were addressed, the true cost of adding retinal photography was £10,938 ($28,785) per patient whose sight is saved[819]. A Liverpool, UK, study evaluated the cost-effectiveness of systematic screening for sight-threatening DR in a target population of 5000 diabetic patients[817]. This study concluded that replacing existing *ad hoc* programs with systematic screening for DR was justified; because systematic screening identified an estimated 502 cases at a per-case cost of £209 ($523), while the *ad hoc* program identified 346 cases at a per-case cost of £289 ($723). The incremental cost of completely replacing the *ad hoc* program was £32 ($80) per additional case identified.

A study conducted in parallel in two geographically and logistically identical populations in the UK[820] compared the clinical and cost effectiveness of screening by a trained optometrist using slit lamp biomicroscopy compared to digital photography (non-mydriatic camera) following tropicamide instillation. Compliance with both screening models in their first years was equally poor at around 50% (Level III-2 evidence). Optometric screening detected significantly higher rates of early retinopathy and maculopathy. The sensitivity for optometrist examination was 75% compared to 80% for imaging. The cost per screened patient was £24 ($60) for optometry compared to £29 ($72) for digital photography. However, the cost-effectiveness of the two models in the first year was poor due to the relatively low compliance rates.

Screening was most cost-effective when applied to the youngest age groups who had the most QALYs to gain, and to ethnic minorities who have a higher incidence of the disease[787].

Computer-simulated models find diabetic screening and treatment highly cost-effective[804;816;821]. Such models incorporate a number of assumptions including prevalence, incidence and natural history of diabetes and DR, screening sensitivity and specificity, patient compliance, and treatment efficacy. Davies et al. modelled screening strategies to determine cost-effectiveness in a population of 500,000[821]. Standard methods of screening save up to 50% of the sight years potentially lost. An idealised gold standard program using mydriatic seven-field photography reported by an ophthalmologist save up to 85% of sight years potentially lost. Screening by a mobile camera (one photo reviewed by a diabetologist) gave the lowest cost of sight years saved (£2842)[821]. It is less effective to screen type 2 than type 1 diabetes patients, but type 2 patients contributed to almost three-quarters of the sight years saved. These results indicate that it appears more cost-effective to continue to screen outside an ophthalmology clinic until treatment is needed.

### *Cost-effectiveness of Different Screening Intervals*

Annual retinal screening for diabetic patients without prior DR may not be warranted[816]; every 2 years is currently recommended in Australia. Using a theoretical Markov model, stratified by age and the level of glycaemic control, Vijan et al. assessed the marginal cost-effectiveness of various screening intervals (every year, 2-yearly or 3-yearly) for people aged 40 years or older with T2DM[816]. Patients in the high-risk group ($HbA_{1c}$ 11%) cost an additional US$40,530 ($58,000) per QALY gained, while those in the low-risk group ($HbA_{1c}$ 7%) cost an additional US$211,570 ($302,000) per QALY gained. The authors concluded that annual screening would still be beneficial for 'younger' patients with poorly controlled diabetes, but was not as beneficial in 'older' patients. Patients at low risk would also not need annual examinations. This study, strongly criticised by Javitt[822], had a number of weaknesses, including an inability to firmly define the utility value for blindness. Quantification of utility values associated with varying degrees of visual loss would

allow more precise ophthalmic cost-effectiveness analyses[822;823]. The study was also criticised by Fong et al.[431] who suggest the need to better understand the total value of eye screening exams, the potential indirect effects of less frequent exams, and patient preferences, before adopting a less frequent screening schedule than the present annual schedule recommended in the US. Before adopting new guidelines for screening intervals in individuals with T2DM, the effectiveness of screening in achieving a significant reduction in vision loss from DR in persons with T2DM should be demonstrated[432].

A study of youths aged 21 or less with T1DM at least three years found that annual screening for DR from age 10, 3-5 years after diagnosis (ADA recommendations), was not cost-effective[824]. A general ophthalmologist or optometrist detected 3/130 cases of DR using ophthalmoscopy through dilated pupils. Two of these cases were not later confirmed by a retinal specialist. If screening of all patients had followed the ADA recommendations and commenced after 3 or 5 years of T1DM, the total eye examination cost, excluding transportation costs and time lost from work and school, would have been US$96,615 or US$67,170 respectively. This study concluded that the current ADA recommendations for DR screening are not cost-effective for paediatric T1DM patients who maintain strict glycaemic control with intensive insulin therapy. The authors however did not recommend a more cost-effective screening frequency in youths.

### *Costs of Telemedicine*

Numerous studies report that among persons with diabetes, compliance with eye screening remains a problem, despite high levels of efficacy, clinical effectiveness and cost-effectiveness[818]. Tele-ophthalmology aims to increase accessibility to screening while reducing costs. A Norwegian study examined the costs of telemedicine screening for DR[825]. Specially trained nurses performed non-mydriatic digital retinal photography on 42 diabetic patients, and these images were then sent to an eye specialist. A cost-minimisation analysis showed that for low patient numbers telemedicine was more expensive than conventional ophthalmoscopy by an eye specialist, but that at higher patient numbers, telemedicine was cheaper. For example, at 200 patients per annum, telemedicine cost NKr971 ($200) and conventional examinations cost NKr1440 ($300) per patient. The break-even point occurred at 110 patients per annum (Level IV evidence). Telemedicine was a cost-effective way of evaluating DR in prison inmates with T2DM when the number of inmates with diabetes exceeded 500 (Level IV evidence) [826].

Whited et al. modelled the cost effectiveness of non-mydriatic digital tele-ophthalmology screening versus traditional clinic-based ophthalmoscopy examinations with dilated pupil to detect PDR[818]. They found that in most modelled scenarios, non-mydriatic digital tele-ophthalmology screening was more effective and less costly. In Scotland, modelled automated grading within the national screening program for diabetic retinopathy was considered a cost-effective alternative to manual grading[827].

**Table 4.2.1: Appraisal of Economic Evaluation Studies of treatment and/or screening for diabetes and diabetic retinopathy, according to 12 NHMRC criteria[10]**

| Study | Main Findings | 1 Study question well defined | 2 Health care options clear | 3 Appropriate Study used | 4 Effective health care options | 5 Cost estimate baseline popn | 6 All costs identify-ied | 7 Costs – accurate measure | 8 Costs – credible measure | 9 Differential timing | 10 Incremental analysis | 11 Sensitivity analysis performed | 12 Modeling techniques clear |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Glycaemic control** | | | | | | | | | | | | | |
| Cost-effectiveness of intensive control in T2DM (UKPDS41) Gray et al, 2000[793] | Intensive control increased Rx costs but reduced cost of complications and increased time free of complications | ++ | + | ++ | ++ | - | **Direct only** | ++ | + | + | ++ | + | ++ |
| Health benefits & cost effectiveness of Rx T2DM with goal of normoglycaemia. Eastman et al 1997[794] | Incremental cost effectiveness of Rx T2DM to achieve normoglycaemia $19000 per QALY | ++ | ++ | ++ | **duration HbA1c, minority** | ++ | ++ | + | + | ++ | -- | + | ++ |
| Cost effectiveness of intensive control in T2DM (Kumamoto Study) Wake et al 2000[795] | Multiple injections vs. conventional Rx decreased risk of DR progression by 67% and laser Rx by 77% | ++ | + | + | ++ | + | **Direct only** | + | + | ++ | -- | + | + |
| **Overall Interventions** | | | | | | | | | | | | | |
| An economic analysis of interventions for diabetes. Klonoff et al 2000[805] | Review 10 studies. Screening, eye care clearly cost saving; $3500 to $7000 per QALY saved | ++ | ++ | + | ++ | -- | + | **Review** | **Review** | ++ | -- | + | + |
| Cost effectiveness of glycaemic control & eye care in DR. Polak et al 2003[797] | Both glycaemic control & eye care complementary in shortening duration of blindness | + | -- | + | **?**+ | -- | **?**+ | + | **?**+ | + | -- | -- | **?**+ |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Screening for Diabetic Retinopathy** | | | | | | | | | | | | | |
| Cost-utility analysis of screening intervals for DR in T2DM. Vijan et al 2000[816] | Annual screening not warranted. 2nd yearly adequate; cost $58000 per QALY saved | ++ | ++ | + | ++ | -- | -- | + | + | -- | ++ | + | ++ |
| Cost effectiveness of screening for sight threatening diabetic eye disease. James et al 2000[817] | Systematic screening justified. Incremental cost of replacing opportunistic program $50/pt | ++ | ++ | + | ++ | -- | -- | + | + | -- | + | + | + **no modeling** |
| Cost effectiveness of DR screening in James Bay, Ontario. Maberley et al 2003[781] | Screening with non mydriatic camera vs. specialist visits; $4000 vs. $10000 per sight year or $15000 vs. $37000 per QALY saved | ++ | + | ++ | ++ | -- | + | ++ | + | ++ | + | ++ | + |
| Modelled economic analysis of digital tele-ophthalmology for detecting PDR. Whited et al. 2005[818] | A non-mydriatic tele-ophthalmology system was more cost effective than clinic-based exams in detecting PDR. | ++ | + | ++ | ++ | + | + | + | + | ++ | + | ++ | + |
| Cost effectiveness of automated grading in UK national DR screening program. Scotland et al 2007[827] | Automated grading of DR from digital photographs compared to manual grading was less costly and similarly effective. | ++ | -- | + | + | -- | ++ | + | + | ?+ | -- | ++ | + |
| **Specific Therapies for DR** | | | | | | | | | | | | | |
| Cost effectiveness of early vitrectomy for treatment of vitreous haemorrhage in DR[563] | Cost utility Markov model examined cost per QALY from early vs vitrectomy deferral | ++ | + | ++ | ++ | -- | ++ | + | + | -- | -- | ++ | ++ |

**Scores ++ criterion well addressed + criterion partly addressed -- criterion not well addressed or unclear**

$ amounts expressed in $AUD, where possible.
QALY = Quality adjusted life year; DR = diabetic retinopathy; PDR = proliferative diabetic retinopathy; T2DM = type 2 diabetes mellitus; Rx = treatment; pt = patient

# Appendix 1 – Committee Membership

**Membership of the Working Party**

| | |
|---|---|
| A/Prof Justin O'Day (Chair) | Ophthalmologist, Melbourne, Chair of previous Diabetic Retinopathy NHMRC Guidelines committee |
| Dr Ralph Audehm | General Practitioner |
| Dr Daryl Guest | Optometrist, Tasmania |
| Mr Robert Guthrie | Consumer Representative |
| Prof Janet Hiller | Adelaide Health Technology Assessment, University of Adelaide |
| A/Prof Jill Keeffe | Centre for Eye Research Australia, Melbourne |
| Mr John Kilmartin | Credentialed Diabetes Educator |
| Dr Mark McCoombe | Ophthalmologist, Melbourne |
| Dr. Andrew Magennis | General Practitioner Advisor |
| Ms Tracy Merlin | Adelaide Health Technology Assessment, University of Adelaide |
| Prof Paul Mitchell | Ophthalmologist, University of Sydney |
| Peter Montgomery (retired from Committee 2007) | Optometrist, Brisbane, National Treasurer of the Optometrists Association of Australia |
| Dr Pat Phillips | Endocrinologist, Adelaide |
| Prof Tien Wong | Ophthalmologist, University of Melbourne |
| **Consultant Writers**<br>Prof Paul Mitchell<br>Dr Suriya Foran<br><br>Prof Tien Wong<br>Dr Brian Chua<br>Dr Ilesh Patel<br>Dr Elvis Ojaimi | Department of Ophthalmology, University of Sydney, Westmead Hospital, Sydney |
| Secretariat<br>Mr Chris Thorpe | Executive Officer, Australian Diabetes Professional Organisations (ADPO), Canberra |

# Appendix 2 – Methods: Process Report of the Literature Review

A systematic review of all literature published and referenced between 1996 and 31 August 2007, was undertaken by the Technical Writer, assistants and members of the Committee.

The following data sources were search for all the questions set by the Committee:

- MEDLINE, EMBASE, CINAHL
- the Cochrane Database of Systematic Reviews and the Cochrane Library
- unpublished studies sought from Review Group members.

The following search terms and their combinations were used to search the databases for relevant literature for this literature review.

| Search Terms and Keywords | Number of articles |
|---|---|
| Diabetes or Diabetes Mellitus | 121076 |
| Diabetic retinopathy | 8434 |
| Prevalence | 520094 |
| Incidence | 560836 |
| Risk factor(s) | 248217 |
| Grade or Stage | 222518 |
| Screening | 1257867 |
| Management | 531868 |
| Laser | 73564 |
| Fluorescein angiogram | 5217 |
| Optical Coherence Tomography or OCT | 5625 |
| Heidelberg Retinal Tomograph or HRT | 4598 |
| Retinal Thickness Analyzer or RTA | 1142 |
| Vitrectomy | 4274 |
| Cost or cost effective or cost benefit | 182922 |

Articles identified from the search term/ keyword search were further screened for suitability by reviewing the title and abstract. If the article was considered as suitable for deeper review, then the whole article was read and appraised using the systematic checklist defined below. Manual search of the reference lists from these selected articles were also examined for articles of interest for inclusion in this literature review.

**Exclusion criteria:**

Articles reviewed were excluded if they:

did not address the pre-specified research questions
were published in a language other than English
had results that were updated in subsequent publications
had inappropriate or poor study design
involved basic science research

**Inclusion criteria:**
Selection of articles appropriate for inclusion in this literature review was dependent on the pre-determined research questions set by the Panel of the Retinopathy Subcommittee of the Australian Diabetes Society. The questions are listed in Section A.

***1) Epidemiology of diabetic eye disease***

| Selection criteria | Inclusion criteria |
|---|---|
| Population | Australian<br>International |
| Outcome | Prevalence<br>Incidence<br>Trends<br>Risk factor identification |
| Study Design | Prevalence and trend data: cross-sectional surveys, consecutive case series, extrapolated data using United Nations' population estimates<br>Incidence: cohort studies<br>Risk factors: cohort studies, case-control studies, cross-sectional surveys |
| Search period | All articles published between 1996 and August 2007 |
| Language | English |

***2) Grading of diabetic retinopathy***

| Selection criteria | Inclusion criteria |
|---|---|
| Population | International |
| Outcome | Grading or staging of DR severity |
| Study Design | RCTs or systemic reviews of RCTs |
| Search period | All articles published between 1996 and August 2007 |
| Language | English |

International ophthalmic society guidelines and an internationally-agreed consensus to simplify the grading of DR are referenced.

***3) Detection of diabetic retinopathy***

| **Selection criteria** | **Inclusion criteria** |
|---|---|
| Population | International<br>Australian |
| Outcome | Sensitivity and Specificity of available DR screening tests<br>Cost/cost effectiveness/cost benefit of DR screening tests<br>Criteria for referral to an Ophthalmologist from DR screening |
| Study Design | Sensitivity/Specificity: cross-classification between screening test and gold standard or systemic review of this study design or diagnostic case-control study or study of diagnostic yield.<br>Cost: case series, economic modeling using population data<br>Criteria for referral: RCT, cohort study, cross-sectional study, case series, or systematic review of these study designs |

***4) Management of diabetic retinopathy***

| Selection criteria | Inclusion criteria |
|---|---|
| Population | International<br>Australian |
| Outcome | Effectiveness of laser treatment in managing DR<br>Benefit from fluorescein angiography in managing different types/severity levels of DR<br>Effectiveness of vitrectomy techniques at different stages of DR<br>Benefit from new/alternative therapies for DR<br>Impact of cataract surgery on the development/progression of DR or diabetic macular oedema |
| Study Design | RCT, cohort study, cross-sectional study, case series, systematic reviews of all study designs |
| Search period | All articles published between 1996 and August 2007 |
| Language | English |

***5) Management cost of diabetic retinopathy***

| Selection criteria | Inclusion criteria |
|---|---|
| Population | International<br>Australian |
| Outcome | Cost analyses for management of DR |
| Study Design | RCT, cohort study, cross-sectional study, case series, systematic reviews of all study designs, economic modelling using population data |
| Search period | All articles published between 1996 and August 2007 |
| Language | English |

In all parts of this literature review, we attempted to comment on the levels of evidence and quality of evidence of the articles used according to NHMRC established guidelines[27].

# Appendix 3 – Methods: Appraisal of Economic Evaluation Studies

The NHMRC Handbook: How to compare the costs and benefits: evaluation of the economic evidence provides a 12 point checklist for appraising economic evaluation studies[10]. The checklist questions listed below formed the basis of our appraisal of these studies.

1. Was the study question well defined?
2. Were appropriate health care options chosen and clearly described?
3. Was an appropriate study type used?
4. Was the effectiveness of the health care options established?
5. Were the cost estimates related to baseline population risk?
6. Were all the relevant costs and consequences identified for each health care option?
7. Were the costs and consequences measured accurately?
8. Were the costs and consequences valued credibly?
9. Was differential timing considered?
10. Was incremental analysis performed?
11. Was a sensitivity analysis performed?
12. Were modeling techniques used in a clear and reasonable way?

The Handbook also provides a table of 'shadow prices' (see below), with which to compare the results of the Economic Evaluation Studies of treatment and/or screening for diabetes and DR (Table 4.2.1).

Assessing evidence using shadow prices (in 2001)

| Ranking of evidence on costs | Ranking of evidence on effects | |
|---|---|---|
| | High | Low |
| Strong | Recommend if:<br>< $70,000 per life-year<br>Do not recommend if:<br>> $100,000 per life-year | Recommend if:<br>< $30,000 per life-year<br>Do not recommend if:<br>> $70,000 per life-year |
| Weak | Recommend if:<br>< $30,000 per life-year<br>Do not recommend if:<br>> $70,000 per life-year | Recommend if:<br>< $30,000 per life-year<br>Do not recommend if:<br>> $30,000 per life-year |

Differences in health gains are often measured in terms of the expected number of Quality Adjusted Life Years (QALYs) that patients receiving a new management option could expect to gain over their remaining lifetime compared to the standard management option. QALYs are a measure of health that adjust life expectancy for an individual by their quality of life during those years. This is done through the use of utility weights that are attached to the time in different health states over the course of an individual's expected remaining life span. As perfect health has a utility weight of 1.0 (or 100%), then if a person lives for 4 years with health judged to be 50% as good as perfect health, followed by 5 years with health only 80% as good as perfect health, then whilst that individual has lived for 9 years, they have only gained 6 QALYs. Therefore, any quality adjustment of a life year is likely to lower the absolute value of QALYs gained and thus will *increase* the overall shadow price or threshold with which to recommend that management option. It is possible that quality adjustment of a life year will result in a lower absolute value of the QALY gained, resulting in an *increase* in the overall shadow price or threshold for recommending that treatment option.

# Appendix 4 – Process for Development of the Guidelines

The NHMRC Clinical Practice Guidelines for the Management of Diabetic Retinopathy (NHMRC June, 1997: ISBN 0 642 27260 3) were originally developed by an expert group convened by the NHMRC, and were undertaken in accordance with the NHMRC document: 'Guide to the Development, Implementation and Evaluation of Clinical Practice Guidelines' (NHMRC, 1999).

In 2003, the Retinopathy Committee of the Australian Diabetes Society requested that the guidelines be reviewed and updated. This was agreed by NHMRC under the overview of Prof Janet Hiller and Ms Tracy Merlin. The review and update of the previous guidelines was written by Prof Paul Mitchell and others as listed.

***Terms of Reference***

Aim: The Australian Diabetes Society Working Group will update the current National Health and Medical Research Council (NHMRC) *Management of Diabetic Retinopathy: Clinical Practice Guidelines* (Retinopathy Guidelines) so that the evidence base underpinning the Guidelines is current and contains all the key information.

The Working Party is to:

- carry out a literature search to identify the evidence base research required to update the Retinopathy Guidelines.
- write a synopsis of the evidence and grade the research according to NHMRC evidence criteria.
- write a revised Retinopathy Guidelines incorporating the necessary new information.
- ensure that the revised Retinopathy Guidelines are available on the internet and information regarding its availability is disseminated through currently available channels, including newsletters distributed to the Australian Diabetes sector, and also through newsletters of consumer and professional associations.

***Composition of the Guidelines Review Group***

The NHMRC recommends that guidelines are developed by a multi-disciplinary panel that is representative of all stakeholders, as this can impact on the effectiveness of implementation. The Guidelines Review Group selected groups involved in the pathways for diabetic retinopathy screening and treatment.

The following stakeholders were represented:

- ophthalmologists
- optometrists
- diabetes physicians/ endocrinologists
- diabetes educators
- general practitioners
- consumers
- public health physicians/ epidemiologists
- guidelines reviewers

A comprehensive range of expertise was present within this group, who were members of the following organisations, but did not act as representatives of these orgaisations: the Royal Australian & New Zealand College of Ophthalmologists (RANZCO), the Optometrists Association of Australia (OAA), the Royal Australasian College of Physicians (RACP), the Royal Australian College of General Practitioners (RACGP), the Australian Faculty of Public Health Medicine (AFPHM) and Diabetes Australia.

***Process Followed***

After agreement with the NHMRC, an initial face-to face meeting of the Guidelines Review Group was held. This identified key steps, including:

- review of the literature and development of recommendations, based on a series of questions set by the Committee (A)
- agreement on terminology
- identifying key measures for disseminating the guidelines
- development of principles for implementing the guidelines

The Guidelines Review Group met on multiple occasions and by teleconference.

***Consultation***

At the outset, key stakeholders were advised of the guideline development process. After completion of the final draft of the guidelines by the Guidelines Review Group, an advertisement was placed in the Australian newspaper of 13 December, 2007. The closing date for submissions was 18 January, 2008. It was also put on the Australian Diabetes Society website and was notified to all members. Copies were sent to all University Departments of Ophthalmology and Optometry, Commonwealth and State Departments of Health, the Royal Australian & New Zealand College of Ophthalmologists, the Optometrists Association of Australia, the Royal Australian College of General Practitioners, the Royal Australasian College of Physicians, the Royal Australasian College of Surgeons, the Royal Australian College of Nursing and Vision 2020 Australia, and to consumers via Diabetes Australia.

***Submissions Received***

**Table A4.1. Submissions Received from Public Consultation and Responses to these**

| Submission Received From | Title/position | Comment summary | Response |
|---|---|---|---|
| Dr Joe Chackman | Executive Director, Optometrists Association Australia | 1. Previous guidelines poorly accepted by optometrists for 2 reasons: specified pupil dilation, which optometrists already practised, and recommended the referral to ophthalmologists of patients with very early DR. New guidelines do not correct this. Little recognition of optometrists as the main practitioners screening for DR.<br>2. Medicare Item number for examination of people with diabetes by optometrists<br>3. Recommends modifications to Guidelines 10 & 11.<br>4. Date correction.<br>5. Typographical error.<br>6. Few 'optometric' references.<br>7. Recommendations 10, 11 – concern with References 18, 19, 20. | 1. Compliance issue now acknowledged in Foreword. Optometry clearly has a pivotal role in detection and monitoring DR, but other clinicians are also involved.<br>2. This was previously considered, but a detailed coverage of Medicare funding for particular examinations was considered beyond the scope of the Guidelines.<br>3. Guidelines 10 & 11 now changed. See above response to Dr D Cockburn.<br>4. Corrected.<br>5. Corrected.<br>6. Schmid reference was already included in 2007 Guidelines. Many optometric references were already included.<br>7. Guidelines 10 & 11 now changed and now do not refer to these references. |
| Dr D Cockburn | Optometrist | 1. Guideline 11 for referral of patients with mild DR is | 1. Most studies of eye exams in people with diabetes focus on detection of early DR. |

| | | | |
|---|---|---|---|
| | | impractical and would substantially reduce optometrists current contribution to monitoring of DR.<br>2. Statement that GP's are mostly unable to monitor for DR. Recommends separate guidelines for optometrists and GPs. | Few studies actually address which DR level should prompt routine referral to an ophthalmologist. The 1997 Guidelines recommended ophthalmic referral when DR greater than presence of microaneurysms was found[1]. Few recent data from major studies indicate that this timing of referral to an ophthalmologist needs changing. However, the committee felt that because no clear evidence supported routine referral at a particular DR level, this recommendation should no longer be a guideline. Guidelines 10 & 11 are therefore now modified to not specify a DR level at which referral of people with diabetes should occur, except to specify which patients need urgent referral.<br>2. Proposal not accepted by the Committee, despite acknowledging that subsequent publications will target separate groups. |
| Dr Sally Cockburn | GP | 1. Failure to properly evaluate existing guidelines or recommend ongoing evaluation.<br>2. Failure to properly analyse or make recommendations on best use of multidisciplinary clinical resources.<br>3. Issues with evidence base for referral criteria recommendations.<br>4. Failure to properly address question of national screening program. | 1. The 1997 Guideline evaluation research is now included, summarised and referenced in the Foreword. The evaluation criteria for existing and future guidelines were considered to be beyond the ToR, but will be the subject of subsequent longer-term evaluation. The comment regarding a change in questions posed from 1997 were also beyond the ToR of the current guidelines.<br>2. The Guidelines strongly recommend that all clinicians involved in the care of people with diabetes (e.g. optometrists, GPs, specialist physicians, ophthalmologists) are active in the detection and management of DR. No preference is made for any particular group.<br>3. Guidelines 10 and 11 now amended (see below).<br>4. While a national screening program of asymptomatic people with diabetes appears attractive, its need, proper resourcing and implementation would require more accurate data on current screening rates, and specific direction from the NHMRC and Department of Health and Ageing. |
| Ms. Christine Cooper | | 1. Date change needed on page 1. | 1. Amended. |
| Dr S Couzos | Public Health Officer, National Aboriginal Community Controlled Organisation | 1. Capitalise indigenous.<br>2. Suggested additional references.<br>3. Suggested adding "National guide to a preventive health assessment…".<br>4. Suggested inclusion of Medicare chronic disease care plans. | 1. Done where appropriate.<br>2. Some additional references added [384], one already included[144].<br>3. This document did not address DR and was therefore not included.<br>4. Not included as outside Terms of Reference (ToR). |
| Dr Catherine Dunlop | Ophthalmologist, Newcastle | 1. Vision testing in children with diabetes to detect amblyopia. | Now incorporated in Section 2.4 |
| Prof Alex Harper | Ophthalmologist, Melbourne | 1. Clarification of focal and grid EDTRS laser nomenclature.<br>2. Incorrect mean number of injections. | 1. Although the possibility of using term "direct" to describe focal treatment was considered, it was felt that the terms "focal" and " grid" are well understood by |

| | | | |
|---|---|---|---|
| | | 3. Reference to the Australian triamcinolone formulation | ophthalmologists and the use of a relatively new term may lead to confusion.<br>2. Number corrected.<br>3. Australian formulation now included |
| Dr Alex Hunyor | Ophthalmologist, Sydney | 1. Suggest removing recommendation to consider IVTA for persistent DME.<br>2. Suggest removing guideline to also consider anti-VEGF therapy in this circumstance.<br>3. Suggest addition of RANZCO Guidelines for FA.<br>4. Suggest modified wording of the OCT description.<br>5. ERG description not relevant<br>6. Concern re addition of 'inner limiting membrane peeling'.<br>7. Role of FA.<br>8. Minor edit.<br>9. Diabetic macular oedema p34.<br>10. Use of oedema and edema.<br>11. 'Minimal NPDR'.<br>12. Pupil dilation.<br>13. Driving after pupil dilation.<br>14. Use of FA in assessing DR.<br>15. Minor edits.<br>16. '…other retinal traction'.<br>17. DRVS findings.<br>18. Iris neovascularisation comment.<br>19. Vitrectomy with ILM peeling.<br>20. Recent FIELD findings (Nov 2007). | 1. This has been left, given the evidence in support, but 'selected cases' has been added.<br>2. In order for consistency with the key points, and unavailability of pegaptanib in Australia, this guideline has been removed, as suggested.<br>3. Incorporated as suggested.<br>4. Changed as suggested.<br>5. This has been left for completeness, as it is under-emphasised as a means of assessing DR.<br>6. Text modified. References suggested already included but now added to discussion of this topic.<br>7. Text modified but statement retained after Committee discussion.<br>8. Completed.<br>9. This is left unchanged as full definition is provided in Table 2.1.1.<br>10. We have opted to use UK spelling, but as the US abbreviation is in such common use, this is used throughout and explained in the List of acronyms.<br>11. This is retained, as it is a useful link with the previous classification.<br>12. Text modified slightly.<br>13. Text modified.<br>14. Guideline changed as suggested. This was a Consensus Good Practice Point only.<br>15. Corrected.<br>16. Committee elected to retain this.<br>17. Error corrected.<br>18. This comment and reference are now removed, in view of the change in surgery.<br>19. This statement has already been changed.<br>20. This strongly supportive Lancet reference was just outside the review period so cannot be included. |
| Ms Paula Katilinic/ Prof Fiona Stapleton | Optometrists, School of Optometry University of NSW | 1. A number of references omitted.<br>2. Redundancy.<br>3. Asks which grading system should be used by practising optometrists.<br>4. Yearly compared to 2-yearly examinations.<br>5. ATA reference. | 1. Two of the four listed are now included, the other two were regarded as superseded by other literature.<br>2. Key points and guidelines are listed in the beginning and again in the body of the document.<br>3. Different grading approaches permit either lesion or referral severity based assessments. There was no intention to select one over another.<br>4. This issue is covered in detail. Routine 2-yearly examinations for people with diabetes and no DR were recommended in the previous Guidelines and no evidence since suggests a need to change this recommendation.<br>5. This reference was previously considered generic and over-technical, but is now |

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| | | | included for completeness. |
| Assoc Prof Jonathon Shaw/ Prof Paul Zimmet | Deputy Director/ Director International Diabetes Institute, Melbourne | 1. Amend prevalence of DR p22.<br>2. Target $HbA_1C$ and BP p22.<br>3. Text on p 26 on lisinopril.<br>4. Missing word p27.<br>5. Suggest more recent reference.<br>6. Figure 1 out of date. | 1. Amended.<br>2. Both now applied to people with diabetes.<br>3. Amended as suggested.<br>4. Corrected.<br>5. Reference and estimates updated.<br>6. Figure deleted. |
| Professor Hugh Taylor AC | Ophthalmologist, University of Melbourne | 1. Use of inconsistent nomenclature with regards to minimal and mild DR.<br>2. Clarification of recommendations for use of International Council of Ophthalmology and World Health Organisation grading.<br>3. Reference suggested. | 1. Amendments made to table 3.1.2 page 87, and elsewhere<br>2. Both the International Clinical Diabetic Retinopathy and Diabetic Macula Edema Disease Severity Scale and to the World Health Organisation grading system are covered. The first is a lesion based grading approach, while the second is a referral priority grading approach. Both these simplified scales a useful, but one is not recommended over the other.<br>3. Reference already included[141] |

**Table A4.2 Submissions Received at Peer Review and Responses to these**

| Submission Received From | Title/ position | Comment summary | Response |
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| NHMRC Council | | Requested removal of non-evidence based recommendations. | Initial guidelines table split into Table I (Evidence based guidelines, level I to IV intervention evidence) and Table II (Consensus Good Practice Points). Key points now incorporated in Table III. |
| Professor Doug Coster | | General comments. | Agree with comments. No response needed. |
| Professor Ian Constable | | 1. Use of intravitreal triamcinolone superseded by use of bevacizumab for DME particularly in younger phakic patients, level of evidence.<br>2. Need to recommend annual screening, use of portable laser systems and immediate laser treatment upon diagnosis in indigenous populations.<br>3. Use of triamcinolone or bevacizumab prior to cataract surgery for DME where laser not possible.<br>4. Use of anti-VEGF treatment for management of DR undervalued. Particularly, rapid therapeutic effect of bevacizumab on severe PDR, and, widespread use of Avastin prior to vitreoretinal surgery for advanced PDR with traction detachment.<br>5. Beneficial effects of shorter duration laser burns for PRP. | 1. This section of text modified to reflect clinical practice. An additional small RCT included (DRCRnet).<br>2. Urgent treatment with portable laser now mentioned.<br>3. Added.<br>4. This section has been expanded. Traction detachment references not included as outside review period. Key point added to Vitrectomy section. Most references within review period.<br>5. This is already covered. Suggested reference (November 2007) outside review period. |
| Professor Tim Davis | | 1. Clarification of guideline 2.<br>2. Screening age in T1DM.<br>3. DR screening for women with | 1. This does not seem necessary, given the revisions undertaken in Section 2.4.<br>2. This recommendation was the subject of |

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| | | gestational diabetes.<br>4. $HbA_{1C}$ levels.<br>5. Transient worsening of DR with rapid tight control.<br>6. Targets for lipid parameters.<br>7. BP control: ADVANCE trial findings.<br>8. Blood lipid control: FIELD trial findings.<br>9. Protective effect of smoking.<br>10. Pupil dilation for angle closure glaucoma patients on miotic drops.<br>11. Protein kinase C inhibitors.<br>12. Growth hormone suppression.<br>13. Intravitreal corticosteroid therapy and effect on glycaemic control. | considerable discussion, and is supported by the concept of introducing eye screening early in the course of diabetes. Children with pre-pubertal diabetes are recommended to have examinations from puberty. While type 1 diabetes can develop later in life, type 2 can develop early in life. Differentiating between types 1 and 2 for retinopathy screening was not considered useful.<br>3. The guidelines for gestational diabetes and pregnancy are now made consistent with the text statements.<br>4. The recent ACCORD data were outside the review period. However, this suggestion is appropriate – amended to target of '7.0 mmol/L or below'.<br>5. Section added to cover this phenomenon.<br>6. Target levels now added, as in the Evidence Based Guidelines for management of type 2 diabetes mellitus: Part 7 – Lipid Control in type 2 diabetes.<br>7. ADVANCE paper just outside review period.<br>8. FIELD paper just outside review period.<br>9. More detailed discussion of this non-intuitive finding does not seem appropriate as other studies have not shown this.<br>10. This small subgroup of patients are likely to be receiving ophthalmic care so specific recommendations unnecessary. Patients detected to have an angle closure tendency are rarely on miotic drops long term as iridotomy treatment is routine. After iridotomy, pupils can be dilated safely.<br>11. Final paragraph in section modified. Some studies are still ongoing.<br>12. Sentence added in section, possible mechanism already described.<br>13. No data found. IVTA dose only 10% of usual rheumatologic dose. |
| Dr Kathryn Antioch | | 1. Levels of evidence.<br>2. Questions set by the committee.<br>3. Cost effectiveness.<br>4. Editing issues.<br>5. Typographical errors. | 1. As the new NHMRC additional levels of evidence are still at stage 2 consultation, it was not felt appropriate to incorporate them at this time. However, this will be a valuable post-release project.<br>2. Although not explicit under the 'Questions set'…, the Committee directed the developers to explore cost effectiveness issues.<br>3. .As suggested, the NHMRC Table of shadow prices is now added to Appendix 3, and is also referred to in the text describing Table 4.2.1.<br>4. DRVS cost utility analysis now also evaluated using 12-point criteria in Table 4.2.1. Other editing issues corrected.<br>5. Corrected. |
| Professor James Best | Chair of the NHMRC Research | 1. Consensus statements used for some recommendations<br>2. Any need for further optometric | 1. Consensus evidence changed to 'Good practice points' as suggested.<br>2. One of the reviewers was an optometrist and |

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| | Committee | review<br>3. Suggests removal of paragraph under heading "Non-English-speaking background" as appears to contravene principle of evidence-based guidelines. | felt issues were adequately presented, following the major responses made to the public consultation. Further review could create unnecessary delay.<br>3. Paragraph and recommendation deleted. |
| Dr Alex Gentle | Senior Lecturer, Dept. Optometry and Vision Sciences, University of Melbourne | 1. Redundant acronyms.<br>2. Cite source publications.<br>3. Citation redundant + redundant point.<br>4. Inconsistent citation.<br>5. Repetition of dot point.<br>6. Remove inconsistent term: very severe PDR.<br>7. Remove term “soft exudates”.<br>8. Impaired glucose tolerance.<br>9. Clarification.<br>10. Clarification.<br>11. $HbA_{1C}$ clarification.<br>12. Repetition.<br>13. HOORN acronym.<br>14. Typographical error.<br>15. Slit lamp biomicroscopy does not specify pupil dilation.<br>16. Inconsistent spelling.<br>17. Repetition of word.<br>18. Inappropriate placement of paragraph.<br>19. Comment on timing of referral to ophthalmologist.<br>20. OCT sensitivity and specificity.<br>21. Inconsistent capitalisation.<br>22. Inconsistent capitalisation.<br>23. Inconsistent spelling.<br>24. Typographical error.<br>25. Missing reference to table in text.<br>26. Repetition.<br>27. Missing numbers. | 1. Acronyms listed on p8 and redefined again at the beginning of a section.<br>2. Corrected, where possible. In some cases, a large number of publications were used as source documents, and in these cases, referral was made to the previous NHMRC Guidelines.<br>3. Citation removed; redundant point removed.<br>4. Citations removed for consistency.<br>5. Repetitive dot point removed from summary.<br>6. Corrected<br>7. Agree cotton wool spots describes pathogenesis better, however soft exudates retained in conjunction with CWS because of historic use.<br>8. Reference authorship corrected. Adding recommendation for people with IFG is beyond scope of these guidelines, which address persons with diabetes.<br>9. Sentence changed as suggested.<br>10. Sentence modified. Two papers factual. No contra-indication as pericyte contractility not only cause of increased resistance.<br>11. Initial statement changed. However, this refers to diagnosis of diabetes, rather than ongoing monitoring of risk for progression.<br>12. Repetitive section deleted.<br>13. Hoorn not acronym, corrected.<br>14. Corrected.<br>15. Pupil dilation included.<br>16. Corrected to dilation throughout.<br>17. Corrected.<br>18. Paragraph moved to new section.<br>19. Comment noted.<br>20. No good OCT sensitivity and specificity values for DR were available within the review period. No data support use of OCT for baseline monitoring of early DR. A reference (outside the review period: Browning AJO 2008) showed that OCT in eyes with subclinical DME did not predict progression to CSME.<br>21. Corrected.<br>22. Oedema consistently used in text, abbreviated to ‘E’ in DME and CSME in line with common use. See List of Acronyms.<br>23. Corrected.<br>24. Corrected<br>25. Table now referenced in text.<br>26. We feel this minor repetition justified.<br>27. Table reformatted. |

***Incorporation of Comments Received***

The Guidelines Review Group considered all comments received during the consultation period (up to January 2008) and amended the guidelines as appropriate (upper table). These amended guidelines were sent for peer review (April 2008). Further amendments (lower table) were then made after considering these comments. This final version was submitted to the NHMRC for consideration of ratification on 5 June 2008.

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