

Guidelines for the Prevention and Management of Diabetic Retinopathy and Diabetic Eye Disease in India

Version 1, June 2019

LONDON
SCHOOL of
HYGIENE
& TROPICAL
MEDICINE



THE QUEEN ELIZABETH
DIAMOND JUBILEE TRUST



INDIAN
INSTITUTE OF
PUBLIC HEALTH
HYDERABAD

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KNOWLEDGE TO ACTION
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INDIAN
INSTITUTE OF
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HYDERABAD

Indian Institute of Public Health – Hyderabad

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Foreword



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 स्वास्थ्य अनुसंधान विभाग
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Message for Diabetic Retinopathy Guidelines

I am pleased to know that the Public Health Foundation of India and the London School of Hygiene and Tropical Medicine have facilitated the development of technical guidelines to prevent visual impairment and blindness from diabetic eye disease in India. There are an estimated 75 million people with diabetes in India and this number is expected to increase significantly in the next few decades. That is why these guidelines are a timely value addition for the country.

The objective of the guidelines is to document evidence-based guidance for management of diabetic eye disease including the need for effective management of diabetes and risk factors for the causation and progression of diabetic eye disease. The scope of the guidelines is tailored to the prevention and management of diabetic eye disease with specific emphasis on vision threatening diabetic retinopathy. The guidelines were made possible by consensus opinion of a representative panel of endocrinologists, ophthalmologists and public health professionals in India. The guidelines offer context-specific advice for managing the increasing prevalence of diabetes and its complications in India.

I am confident that the guidelines will help in improving evidence-based practice not only in India but also other low and middle income countries which are facing an epidemic of diabetes.

Professor Dr. Balram Bhargava

Director General, Indian Council of Medical Research



International Diabetes Federation

Foreword

It gives me great pleasure to introduce the national guidelines for the prevention and management of diabetic eye disease with a specific emphasis on vision threatening diabetic retinopathy. I understand that the process took three years of deliberations of an expert panel of endocrinologists, ophthalmologists and public health specialists constituted with support from the Public Health Foundation of India and the London School of Hygiene and Tropical Medicine. The guidelines have been developed using the available evidence on prevalence of diabetes and diabetic retinopathy, associated risk factors and successful interventions at the clinical and population level. Efforts have been made to capture evidence available from India and South Asia wherever possible, though the quantum of evidence from high income countries is much more at present. These recommendations will go a long way in saving and salvaging eyes and lives of people with diabetes especially in south Asian Region of the globe.

IDF south East Asian region hosts the second largest population of Type 2 diabetes in planet earth and has an exponential rise of type 1 diabetes as well. I congratulate the technical experts and the writing group led by Prof Clare Gilbert, Dr. TP Das and Prof Nikhil Tandon for this great initiative and am sure that the guidelines will be used extensively in India and other countries in South and South East Asia.

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Foreword

The Guideline Development Group has prepared extensive evidence-based guidelines on diabetic retinopathy (DR) which includes recommendations about the awareness, early detection by screening, clinical investigations and treatment for the prevention of vision loss from *Diabetic Retinopathy and Eye Disease in India, Version 1, June 2019*. The teamwork involved in creating this impactful research is commendable. The guidelines include analysis of research from other countries and guidelines laid down by the International Council of Ophthalmology.

India is fast emerging as the diabetes capital of the world, the projection is expected to increase to 72 million by 2030. The guidelines assume special importance because it has taken the awareness levels and approaches adopted by the caregivers as well as the care receivers. Diabetic Retinopathy caused visual impairment is not only a social problem but a major economic threat to economically backward groups since the impairment cripples them financially by obstructing them from performing their profession/trade. Therefore, research, intervention and formulation of guidelines at regional and national levels is imperative.

The stakeholders in the health system – ophthalmologists, physicians, endocrinologists, community physicians, policy makers and service planners – involved in the prevention of visual loss due to diabetic retinopathy can easily adopt the guidelines. This well researched document can help in overcoming the same and act as a crucial component of Universal Health Coverage; it could also be adopted as a template for the various stakeholders battling Diabetic Retinopathy in the South East Asia Region.

The All India Ophthalmological Society is spearheading a national DR screening plan to implement the diabetic retinopathy program in India (ARC Pan India DR Project – *Jyot Se Jyotjalo* – Stop Blindness) and these guidelines are therefore very timely.

Prof. Dr. S Natarajan, MD

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GUIDELINE DEVELOPMENT

Scope and purpose

The scope of the Guidelines is wide, and includes recommendations for the following: the prevention of diabetic retinopathy in people with diabetes; approaches to the early detection of diabetic retinopathy by screening and opportunistic examination; clinical investigations for the diagnosis of retinopathy, and clinical management of the different types and stages. The Guidelines also include recommendations for the management of cataract in people with diabetes with respect to the prevention and management of diabetic retinopathy. It does not include the primary prevention of diabetes, the control of risk factors for other complications of diabetes, nor vision rehabilitation.

The purpose of the Guidelines is to provide recommendations to relevant audiences, anticipating the likely increase in the incidence of visual impairment and blindness from diabetic retinopathy as the diabetes “epidemic” in India continues and matures. The Guidelines are intended for a wide audience, including policy makers and service planners and a wide range of health care professionals who provide services for people with diabetes and eye care at all levels in the health system.

Given the wide scope of the Guidelines, many of the recommendations are for practice, in relation to clinical management and for public health. These technical Guidelines are supported by Operational Guidelines which go into more detail about how a programme for the control of visual loss from diabetic retinopathy can be implanted through integration into the health system in India.

Background

Many of the recommendations for practice in relation to screening were informed by a recent programme which was supported by the Queen Elizabeth Diamond Jubilee Trust, UK. In this programme screening for diabetic retinopathy at the primary level was integrated into 51 facilities for patients with diabetes attending non-communicable diseases clinics in 10 States.

During the programme almost 60,000 people with diabetes were screened, 6% of whom were treated for vision threatening retinopathy. Several members of the Guideline Development Group were actively involved in this programme which ran from 2014 to 2019. The development of guidelines was recommended by the National Diabetic Retinopathy Task Force, which was established by the Government of India in 2014. Members of a Technical Expert Group, which was established by the Task Force, contributed to the development of the guidelines. The Trust, which supported Technical Expert Group meetings, played no role in the development of these Guidelines.

Stakeholder involvement

The Guideline Development Group comprised physicians, ophthalmologists, community physicians, policy makers and public health professionals from the Government of India’s health system and non-government service providers, and from schools of public health in India and the UK. It did not include the perspectives of primary level health care professionals or patients.

Methods used to search for evidence

A rigorous literature search was undertaken by an Information Scientist, Cochrane Eyes and Vision Group, using extensive search terms. The terms included other countries in Asia to provide regional evidence if this was not available for India. Systematic reviews, with or without network analyses, were preferentially used to formulate the recommendations whenever available. The literature was searched for additional and more recent evidence during development, as required.

Formulating the recommendations

The following levels of evidence were used:¹

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

Guidelines from other countries and those produced by the International Council of Ophthalmology were reviewed. The balance of benefits and harms were also taken into consideration.

In India there is considerable variability in the level of services for eye care between and within the government, private and not-for-profit sectors. Some centres provide subspeciality retina services and are fully equipped to provide the full range of investigations and management options for diabetic retinopathy. Other centres provide general

eye care, which includes conditions of the retina, and lack some of the expertise or equipment to implement the full range of treatments. The Guidelines take account of this variability. As many of the newer treatments for diabetic retinopathy require extensive and frequent follow up, the recommendations also allow clinicians to recommend the optimum treatment which reflects a particular individual's circumstances.

The development of evidence based guidelines is a crucial component of Universal Health Coverage, and Dr Alarcos Cieza, Coordinator, Blindness and Deafness Prevention, Disability and Rehabilitation at the World Health Organization said "the team in India are to be congratulated on developing these guidelines, which is an important step in developing essential packages of care for diabetes and its complications in India. I am confident that other countries will be motivated to use them following the example of its implementation in India".

A limitation of the Guidelines is that for many of the recommendations there was little high quality evidence from studies undertaken in India. Some of the recommendations for practice are more conservative than elsewhere, as patients with diabetes are often diagnosed late or do not attend regular follow ups. In addition, in India there is a different phenotype, such as higher rates and severity of dyslipidemia, which may influence the pathophysiology and natural history of diabetic retinopathy as well as responses to treatment.

Processes involved in Guideline development

A National Task Force for Diabetic Retinopathy was established in 2014.

A Technical Expert Group to develop the National Guidelines for Diabetic Retinopathy and Eye Diseases was established by the National Task Force in 2015.

Five meetings of the Technical Expert Group have been held in which:

1. The processes involved in guideline development were reviewed, using the World Health Organization's Handbook for Guideline Development.²
2. The scope of the Guidelines for DR was agreed i.e., they should include prevention of diabetic

- retinopathy (DR) and other eye diseases in people with diabetes as well as the detection and management of diabetic retinopathy and diabetic macular edema.
3. The PICO (Population, Intervention, Comparators and Outcome) questions were agreed, which would determine the recommendations and evidence on which they were based.
 4. Based on the PICO questions, the Information Scientist, Cochrane Eyes and Vision Group, assisted in a thorough literature search with creation of an EndNote database of references. The database was updated as required.
 5. Different components of the Guidelines were allocated to the Technical Experts to write the first draft.
 6. The drafts were reviewed and decisions made for areas of improvement.
 7. The draft, including the recommendations, was completed by a smaller Writing Group who adopted/modified/added to the recommendations for each PICO question. This entailed updating the literature search.
 8. Draft Guidelines were sent to members of the Technical Expert Group and others with expertise in diabetes, and DR and DME management.
 9. A process of anonymous voting was used to reach consensus on each of the recommendations, after amendment following discussion.
 10. A plan for dissemination was developed.
- Suggested date of revision: in three to five years.

References

1. National Health and Medical Research Council, Government of Australia. Guidelines for the Management of Diabetic Retinopathy. 2008.
2. World Health Organization. Handbook for Guideline Development. 2012.

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ABBREVIATIONS

DM	Diabetes mellitus
DME	Diabetic macular edema
DR	Diabetic retinopathy
FFA	Fundus fluorescein angiography
ICO	International Council of Ophthalmology
IOP	Intraocular pressure
IRMA	Intraretinal microvascular abnormalities
IVI	include intravitreal injection
NCD	Non communicable disease
NPCDCS	National Programme for Prevention and Control of Cancers, Diabetes, Cardiovascular Diseases and Stroke
NPDR	Non-proliferative diabetic retinopathy
NVD	neovascularisation on the optic disc
NVE	neovascularisation everywhere
OCT	Optical coherence tomography
PDR	Proliferative diabetic retinopathy
PRP	Panretinal photocoagulation
PwDM	People with diabetes
TRD	tractional retinal detachment
VEGF	Vascular endothelial growth factors
VI	Visual impairment
VTDR	Vision threatening diabetic retinopathy
WHO	World Health Organization

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Executive Summary

- Diabetes is increasing in India and now affects 65 million adults. The number affected is likely to increase to over 130 million by 2045.
- An increasing number of adolescents and young adults are developing diabetes due to changing lifestyles. These individuals are particularly at risk of all the complications of diabetes including vision loss from diabetic retinopathy (DR) and diabetic macular edema (DME).
- Diabetic retinopathy is already an important cause of vision impairment and blindness in South Asia and will increase unless systems and services are put in place to reduce the incidence of DR, and to increase access to diagnosis and effective treatment
- Pregnancy among women with pre-existing diabetes can lead to rapid progression of the more serious, vision threatening form of diabetic retinopathy
- Vision threatening diabetic retinopathy, the severe stages of DR and DME, affects 5–7% of people with diabetes i.e., between 3 and 4.5 million. This will increase as the number of people with diabetes increases and they live longer
- The main risk factors for DR and DME are increasing duration of disease and poor control of high blood glucose and hypertension. Everyone with diabetes will develop DR if they live long enough.
- There is strong evidence that good control of hyperglycaemia and hypertension reduce the incidence of vision threatening DR: interventions which lead to better self-management i.e., a healthier diet, regular exercise are required, as well as taking medication as advised.
- There are highly effective and cost effective treatments for vision threatening DR and up to 98% of blindness can be prevented by timely laser treatment and vitreous surgery.
- There are also effective treatments for DME, including laser and intraocular steroids and AntiVEGF agents, which can prevent further loss of vision and sometimes improve vision
- All people with diabetes need to be examined or screened for DR and DME before vision is lost
- Systems to screen for DR and DME need to be integrated into clinics attended by people with diabetes at all levels of service delivery, with clear referral pathways to eye care centres with the expertise and facilities for diagnosis and treatment if needed.
- Patients known to be diabetic attending eye care services should have a detailed eye examination, including dilated retinal examination to detect DR, with treatment if required
- Close collaboration between physicians and eye care professionals is required.
- Health education and the engagement of people with diabetes about DR; the risk it poses to their vision and the need for annual retinal examination, are essential
- Close collaboration is required between different professional groups, national programmes, and between the different levels of service delivery
- All aspects of the health system need to respond, including governance, health management information systems, developing the capacities of the health workforce, technology and infrastructure and financing.

Introduction and Overview

Diabetes

Types of diabetes

1. Type 1 diabetes usually has an acute onset at an early age, but can also have an onset during adult life.¹ Islet-specific autoimmunity is responsible for a significant majority of people with Type 1 diabetes. Insulin is required to manage the hyperglycaemia. Type 1 accounts for approximately 10% of all diabetes.
2. Type 2 diabetes is the commonest type (>90% of all diabetes) and has a more gradual onset. Risk factors include obesity (defined by a body mass index of greater than 30 kg/m²), lack of physical activity, poor diet, stress, urbanisation and a genetic predisposition. A young age of onset of Type 2 diabetes, which is known as youth-onset Type 2 diabetes, is increasing.²
3. Hyperglycaemia in pregnancy (previously called gestational diabetes) is when women without a history of diabetes develop high blood glucose in the later stages of pregnancy. This usually resolves after delivery. However, women known to have diabetes before pregnancy, or who meet standard diagnostic criteria for DM in the first trimester (who are considered to have pre-existing diabetes) need close observation throughout pregnancy.
4. Diabetes secondary to other conditions, such as chronic pancreatic disease, or secondary to medication such as steroids.

A new classification of diabetes has recently been suggested, which describes five subgroups of diabetes based on six biomedical markers (including beta-cell function and insulin resistance) and the risk of complications.³ Whilst this approach may help to target those most at risk of disease progression and complications, biomedical testing would require considerable resources.

Diagnosis of diabetes

Diabetes is diagnosed on the basis of a fasting blood glucose levels of ≥126 mg/dL (7.0 mmol/L), or HbA1C levels re ≥6.5%, or a random blood glucose level of ≥200 mg/dL (11.1 mmol/L) in the presence of typical symptoms (thirst, weight loss, polyuria) (Table 1.1). In pre-diabetes levels are between the range for normal and diabetes. Individuals with pre-diabetes are at risk of developing diabetes.

Table 1.1 Diagnostic tests for diabetes and pre-diabetes

Category	Fasting plasma glucose		Glucose tolerance test: 2-hour plasma glucose after 75 g glucose load)	
	mmol/l	mg/l	mmol/l	mg/l
Normal	<5.6	<100	<7.8	140 mg/dL
Pre-diabetes	5.6–6.9	100–125 mg//	7.9–11.0	140–199
Diabetes	≥7.0	≥126 mg/l	≥11.1	>200

Pathogenesis of diabetes

Diabetes occurs when the pancreas either does not produce enough insulin (insulin deficiency) (Type 1 diabetes) or when the body cannot effectively use the insulin produced (insulin resistance; Type 2 diabetes). In diabetes low insulin leads to low intracellular glucose and hyperglycaemia, with metabolism of fats and protein.

Risk factors for diabetes

The strongest risk factors for diabetes is excess body fat, from an unhealthy diet and inadequate exercise. Early under-nutrition, smoking and genetic factors also increase the risk.⁴ The control of diabetes is beyond the scope of these guidelines.

Pathogenesis of complications of diabetes

Complications, which are due to changes in the micro-vasculature (diabetic retinopathy (DR), nephropathy and neuropathy) and macro-vascular (cardiovascular disease) are due to complex interactions between a range of mechanisms i.e., glycosylation of proteins secondary to chronic hyperglycaemia, oxidative stress, metabolic and biochemical changes, genetic factors⁵ and inflammation. [Reviewed in the Australian Guidelines.⁶] These are driven by hyperglycaemia.

Diabetic retinopathy and macular edema – an overview

Diabetic retinopathy is a common microvascular complication of diabetes and is an important cause of vision impairment and blindness.

Microvascular changes

Changes in the retina are secondary to occlusion and/or leakage of the microvascular circulation. Features of vascular occlusion are cotton wool spots, closure of retinal capillaries and neovascularisation. Haemorrhage, exudates and edema reflect increased vascular permeability. Intraretinal microvascular abnormalities, e.g., microaneurysms; changes in the caliber of blood vessels; tortuosity of blood vessels, are also frequent findings.

Pathogenesis of diabetic retinopathy and diabetic macular edema

Altered glucose metabolism and hyperglycaemia affect many different metabolic pathways including

vascular endothelial growth factor expression, aldose reductase, protein glycation and epigenetic changes.^{7,8} Understanding these pathways better may lead to new diagnostic tests and interventions.

Diabetic macular edema also has a range of causal pathways, and inflammation plays a key role.⁹

Risk factors for diabetic retinopathy

Everyone with diabetes will develop some degree of DR if they live long enough.

The risk of DR increases with increasing duration of disease, and the risk can be reduced by control of modifiable risk factors, particularly hyperglycaemia and hypertension. Individuals with one microvascular complication, such as nephropathy, are more likely to have another due to their common pathophysiology.

Classification of diabetic retinopathy

Several classification systems have been used for DR. The two well-established classification systems are the Early Treatment of Diabetic Retinopathy Study (ETDRS) classification and the Wisconsin Classification. Both were developed for research and are too complex for clinical management. To address this, the International Clinical Disease Severity Scale for Diabetic Retinopathy (the International Classification) was devised, which was based on these earlier classifications.¹⁰

Classification systems are important for several reasons: defining criteria for referral after screening, documenting change over time, and to allow comparisons between studies and monitoring data from programmes.

Classification of diabetic macular edema

The earlier classification developed in the ETDRS trial has been modified, with characteristic signs being classified as centre-involving and non-centre involving diabetic macular edema (DME). This distinction is important as it guides indications for treatment.

Vision threatening diabetic retinopathy (VTDR)

The following stages of DR are a threat to vision: DME, and severe pre-proliferative and proliferative DR (PDR).

Prevalence and incidence of diabetic retinopathy

Duration of diabetes is the most important risk factor for DR. Approximately 50% of PwDM will

develop some degree of DR after 10 years, and after more than 20 years of diabetes 75% of adults will have some form of DR despite all the advances in diabetes care.¹¹ The prevalence is higher in those with Type 1 and youth-onset DM than Type 2 DM, and those with poor control of glycaemia and hypertension.

Data on the incidence of DR is important for determining how frequently People with Diabetes (PwDM) should be screened. However, incidence studies are difficult to compare as they have studied different groups (Type 1, Type 2 or both), have had varying periods of follow up, and have different outcomes i.e., any DR; vision loss from DR. The majority of studies have been undertaken in high income settings.¹²

Management of diabetic retinopathy and macular edema

Prompt intervention for VTDR is effective at preserving vision, and treatment may stabilise or even improve visual acuity in macula edema.¹³

Screening for diabetic retinopathy

As VTDR can be asymptomatic and not affect the vision, screening is required to detect individuals with VTDR at an earlier enough stage so that treatment can be delivered to preserve or restore vision.

Diabetic eye disease

Diabetes also increases the risk of other eye diseases, such as cataract, glaucoma, retinal vein occlusions, ischaemic optic neuropathy and cranial nerve palsies, as has been reported in India. Cataract surgery can be complicated and have poorer visual outcomes in people with diabetes (PwDM).¹⁴

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1. Epidemiology and impact of diabetes in India and likely trends

1.1 Epidemiology of diabetes globally, in India and Asia, and likely trends

Diabetes – a global epidemic

In 2014 there were estimated to be 422 million adults with diabetes globally, and the prevalence is increasing in most countries because of ageing, life-style changes and interactions between the two.¹ The global prevalence is higher in men (9%) than in women (7.9%). In 2016 diabetes was ranked 8th highest in terms of years lived with disability,² and the years of life lost from diabetes increased 31% between 2006 and 2016 (ranked in 9th place in lower middle income countries).³ The prevalence of diabetes increases with age, affecting 13–20% of those aged 50 years and above. A further 352 million people have impaired glucose tolerance, which increases the risk of diabetes.⁴

The number of adults aged 20–79 years with diabetes is projected to increase to 629 million by 2045.⁴ Three quarters of people with diabetes live in low and middle income countries (LIC, LMIC) and almost half are not diagnosed.⁴

Over 1 million children and adolescents have type 1 diabetes, and 1 in 6 births are to mothers with hyperglycaemia of pregnancy.⁴

Approximately 4 million deaths were attributable to diabetes in 2012⁵ and 12% of global health expenditure is spent on diabetes care (\$727 billion).⁴ The World Health Organization (WHO) projects that diabetes will be the 7th leading cause of death by 2030.

Diabetes in India

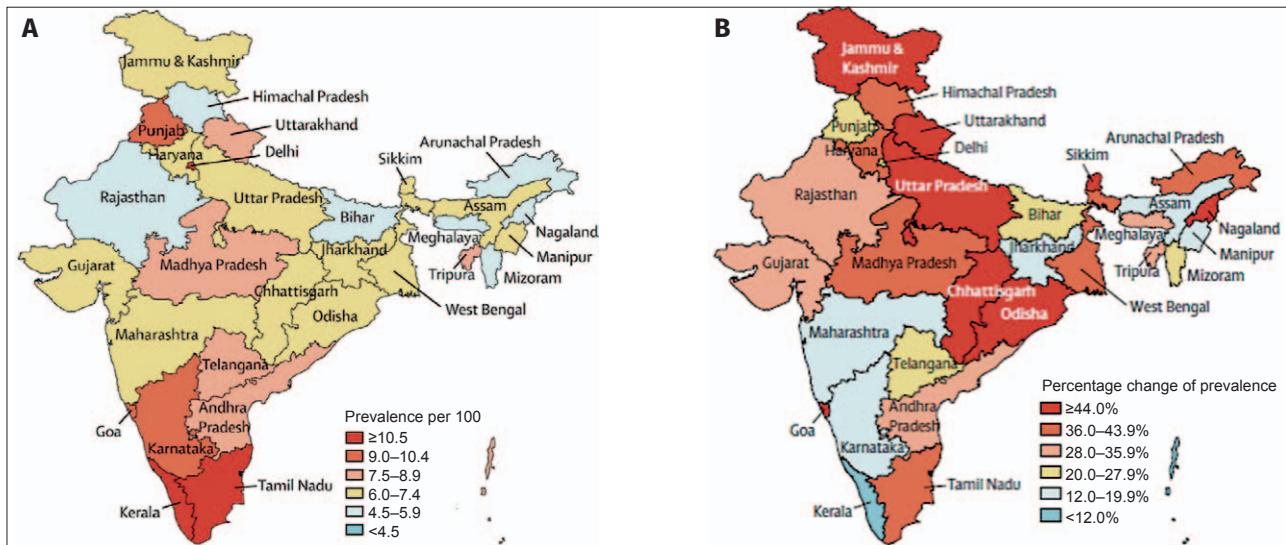
In 2016 there were an estimated 65 million PwDM in India aged ≥20 years, which has increased by 2.5 million since 1990.⁶ In 2016 the prevalence was highest in Tamil Nadu, Kerala and Delhi, and lowest on Rajasthan, Bihar, Himachal Pradesh and North Eastern States (Figure 1.1 A). The prevalence has increased in all states except Kerala, with the greatest increase in States at a lower level of epidemiological transition (Figure 1.1 B).

The overall age-standardised prevalence of DM is 7.9% (95% confidence interval 7.1–8.6%).⁶

The “Indian phenotype”, which comprises several factors, increases the susceptibility of Indians to diabetes.⁷

The overall prevalence of diabetes is higher in males than females, and the prevalence increases with age in men and in women, with a greater increase in men over time (Figure 1.2).

The driver of the increase in diabetes is increasing overweight, which has increased from 9% to 20.4% between 1990 and 2016 (Figure 1.3 A and B). For every 100 overweight Indians aged 20 years or above, 38 have diabetes, which is higher than the global average of 19.⁶



**Figure 1.1 (A) Age standardised prevalence of diabetes in India in 2016 among adults aged ≥ 20 years, by State
(B) Change in age standardised prevalence of diabetes in India in between 1990 and 2016, by State⁶**

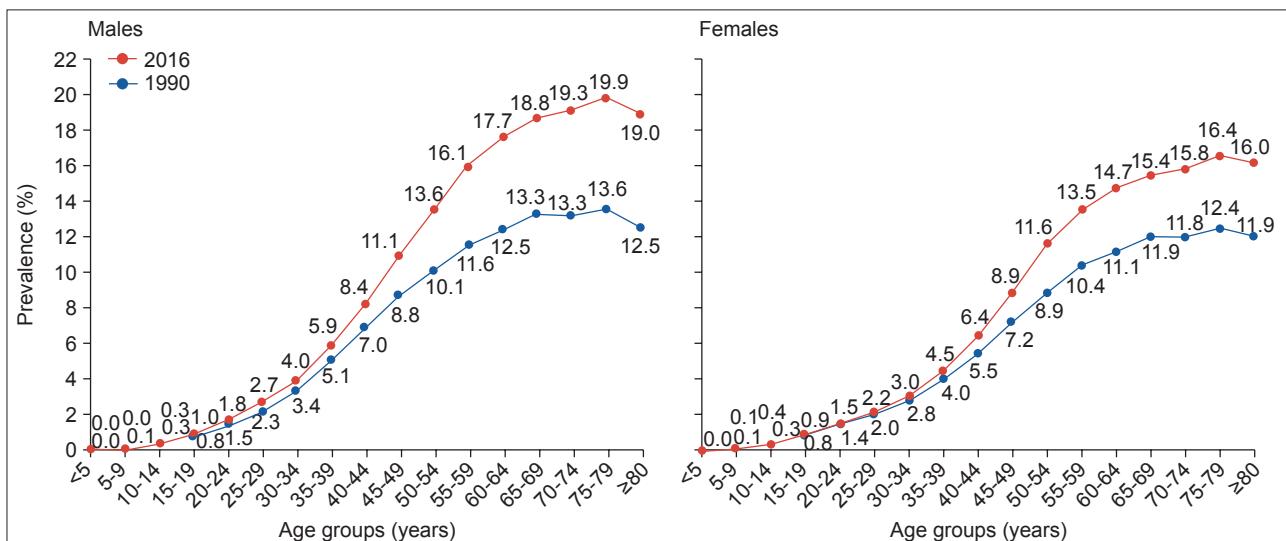


Figure 1.2 Age and sex specific prevalence of diabetes in India, by age group in 1990 and 2016⁶

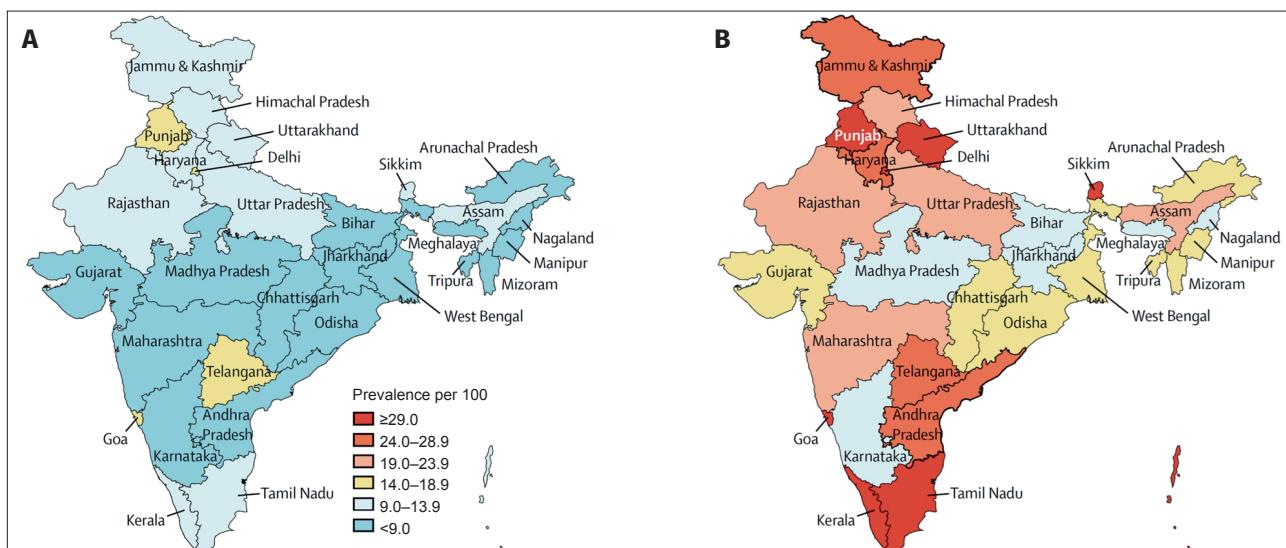


Figure 1.3 Prevalence of overweight adults aged 20 years and above, by State. A in 1990 and B in 2016⁶

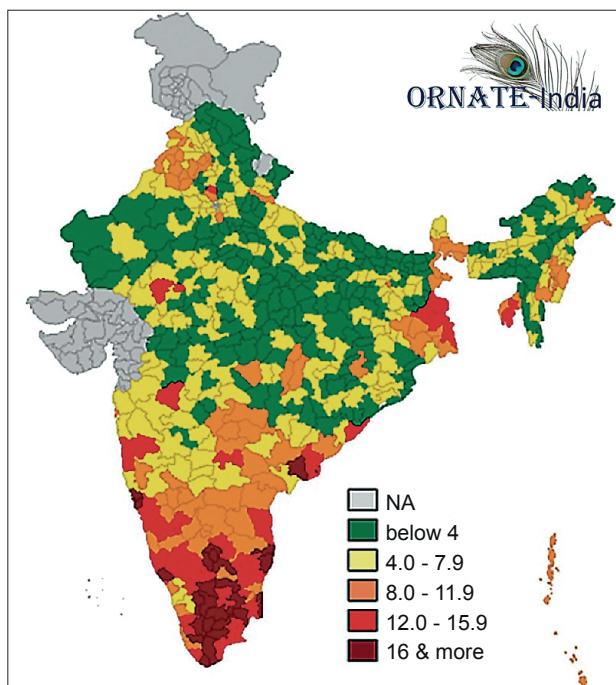


Figure 1.4 Prevalence of known diabetes in India, by District⁸

In another study, which used data from District Health Surveillance, provides district level data on the prevalence of known diabetes. The findings are similar to that at State level (Figure 1.4).⁸

In India almost half of all PwDM (47%) are not diagnosed, as in many other countries,⁹ and are not receiving treatment.

As in other countries, in India the majority of PwDM have type 2 diabetes, and in 2017 there were estimated to be 128,500 young people (<20 years) with Type 1 diabetes.⁴

Pre-diabetes (i.e., raised blood fasting blood glucose of 100 to 125 mg/dL (5.6 to 7.0 mmol/L)

The INDIAB survey of adults aged 20 years and above in 19 States in four zones, and in rural and urban areas, showed that the overall prevalence of diabetes was 7.3% (95% confidence interval (CI) 7.0–7.4%).¹⁰ The prevalence of diabetes and prediabetes were higher than in earlier studies, with variation between States (Figure 1.5 A–C)¹¹ (RM Anjana, personal communication). Rates of prediabetes and rates of undiagnosed diabetes were also relatively high and varied between States, and the prevalence of self-reported DM was higher in urban than in rural and semi-rural populations^{11,12} (RM Anjana, personal communication).

Comorbidities and complications

It is estimated that 10–20% of PwDM have complications, with DR being one of the commonest. Patients with DR are also likely to have other microvascular complications such as nephropathy and peripheral neuropathy, with higher rates amongst those with more severe DR.¹³ Diabetes also greatly increases the risk of macrovascular disease i.e., cardiovascular disease, strokes⁵ and tuberculosis.¹⁴

1.2 Impact of diabetes in India and the response needed

A recent study in India estimated that between 2001 and 2003, 2.1% of all deaths (136,000) among people aged 15–69 years were attributable to renal failure, and that the proportion had increased to 2.9% by 2010–13. Diabetes was the strongest predictor of death from renal failure, with a higher odds in the second time period than the first.¹⁵ Individuals born in the 1970s had a higher risk than those born in the 1950s, suggesting that diabetes is becoming an increasingly important cause of premature mortality in India.

Economic impact of diabetes in India

A World Economic Forum report on the economic implications of non-communicable diseases (NCDs) estimated that India stands to lose \$4.58 trillion before 2030 due to NCDs and mental health conditions with diabetes alone being responsible for US\$0.15 trillion.¹⁶ Health care expenditure for PwDM is 2–3 times higher than people without. The average cost per person is estimated to be INR 3,000–10,000 per annum. The high cost of treatment leads to a high incidence of non-compliance, particularly among the lower socio-economic groups. Diabetes and its complications also imposes an economic burden in terms of lost productivity and opportunity costs which impact on the individual, families and society.

Health interventions

Prevention of diabetes is possible through a mix of individual, population level, whole of government and whole of society level interventions which promote healthier behavior and life-styles.⁵ Many sectors have a role to play in preventing and treating diabetes, including governments, employers, city planners, architects, educators, industry, civil society, private sector, media and individuals.

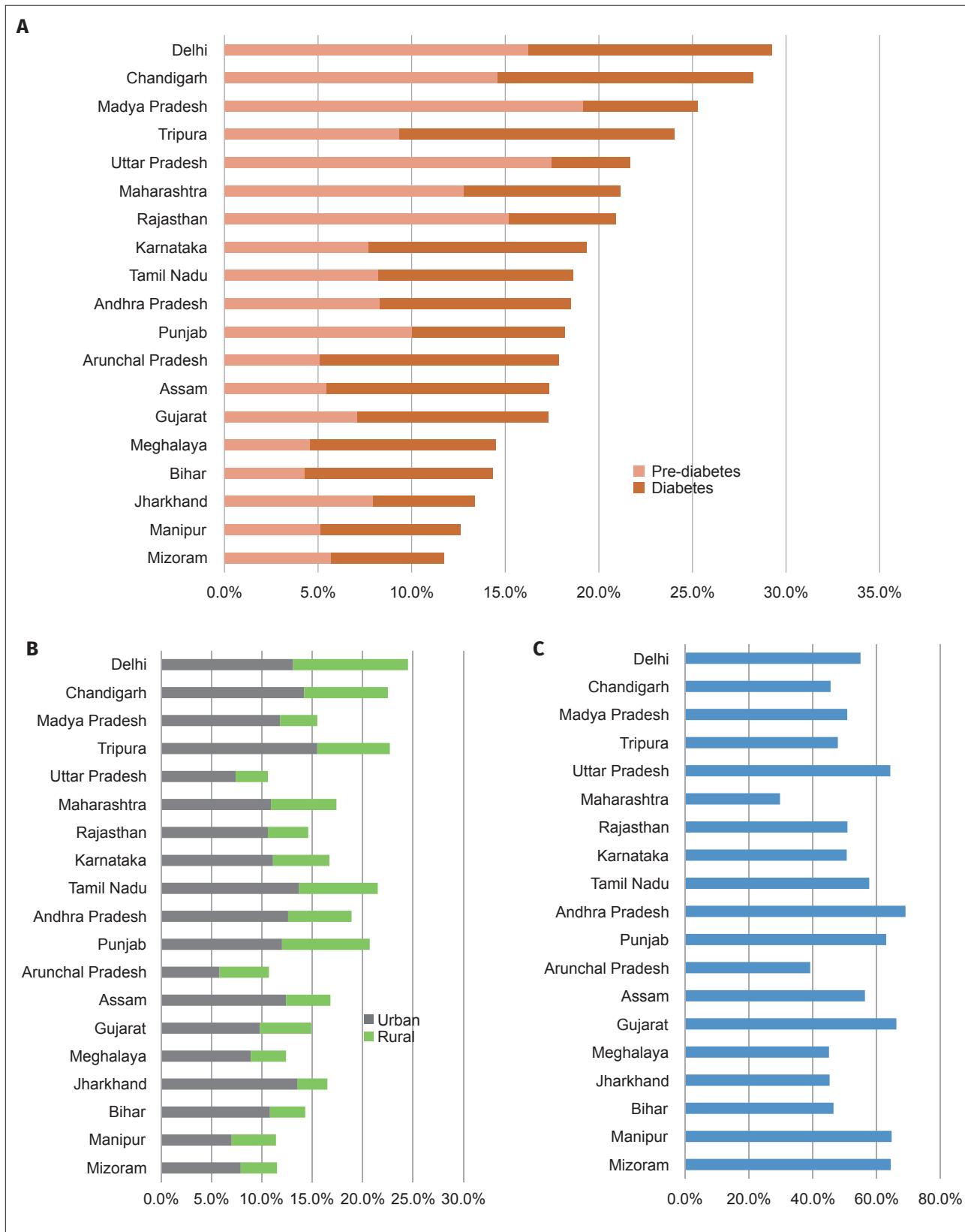


Figure 1.5. Prevalence of pre-diabetes and diabetes (A), in urban and rural areas (B), and the proportion of those with diabetes already diagnosed in India, by State (C) (INDIAB Study) (from^{10, 11})

Cost-effective interventions already exist — these include non-pharmacological and pharmacological approaches which modify NCD risk factors, methods for early detection of NCDs and their diagnoses using inexpensive technologies; and affordable medications for the prevention and treatment of heart attacks and strokes, diabetes, cancer and asthma.

Diabetes and the health system response in India

Multisectoral and intersectoral coordination is essential for diabetes prevention and control. The control of risk factors influencing the occurrence of NCDs, including diabetes, require actions beyond the health sector and hence there is need for multisectoral approach involving other key ministries, the private sector, civil society organisations and the community.

The National Programme for Prevention and Control of Cancers, Diabetes, Cardiovascular Diseases and Stroke (NPCDCS) was launched in 2009.¹⁷ The NPCDCS aims to integrate NCD interventions into the National Health Mission (NHM) framework to optimise scarce resources. NCD cells with additional manpower are recommended at national, state and district level. The 12th Five Year Plan (FYP) highlights the need for NCD clinics in every Community Health Centre (CHC)

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2. Classification of DR and DME

Summary

- Several classifications for DR exist, which are all modifications of the Arlie House (Wisconsin) classification, including the Early Treatment of Diabetic Retinopathy Study Classification (ETDRS), the International Clinical Diabetic Retinopathy and Diabetic Macula Edema Disease Severity Scale¹ (referred to hereafter as The International Classification), and the WHO grading system.²
- The International Classification is widely used in low and middle income countries and is recommended by the International Council of Ophthalmology.

2.1 The International Classification of Diabetic Retinopathy

There are several different classification systems for DR which have different purposes: for research, clinical management or screening. Internationally recognised classifications enable international collaboration and comparison of data.

The International Classification is widely used in low and middle income countries and is recommended by the International Council of Ophthalmology, has five stages, based on the risk of progression of DR, with significant clinical signs being defined by standard retinal photographs.¹ (See Chapter 9 for more details).

1. No apparent retinopathy
2. Mild non-proliferative retinopathy (NPDR) - a few microaneurysms
3. Moderate NPDR - microaneurysms, intraretinal haemorrhages or venous beading that do not reach the severity of the standard photographs
4. Severe NPDR is based on the 4:2:1 rule: 4 quadrants – haemorrhages; 2 quadrants - venous beading; 1 quadrant – intraretinal microvascular abnormalities
5. Proliferative diabetic retinopathy (PDR) – neovascularisation of the optic disc, retina, iris, or angle; vitreous haemorrhage or tractional retinal detachment.

DME is classified as present or absent. If it is present it is classified as centre-involving or non-centre involving. Vision threatening DR (VTDR) includes severe NPDR, PDR and centre-involving DME.

2.2 PICO question: Which classification system should be used for clinical management?

Recommendation for practice

The International Classification can be used in India for clinical examination, to determine the need for treatment following detailed dilated retinal examination using biomicroscopy. This will allow consistency in the indications for follow up and treatment, comparison with other countries using the same classification, and national and international collaborative studies.

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3. Epidemiology of diabetic retinopathy globally and in India

Summary

- DME is a much more common cause of visual impairment than PDR, and causes loss of central vision.
- Visual loss from PDR can be more severe, and can lead to no perception of light in both eyes.
- Risk factors for DR are now fairly well understood, and there is evidence that good control of hyperglycaemia and hypertension reduces the risk.
- Evidence of the efficacy of controlling other factors, such as dyslipidemia and smoking is less compelling.

3.1 Epidemiology of diabetic retinopathy globally and in India

Blindness and visual impairment from diabetic retinopathy

Global data

In 2010 0.8 million adults were blind from DR (2.6% of all blindness) and 3.7 million were visually impaired (1.9%) (Table 3.1).¹ Blindness increased by 27% and vision impairment by 64% between 1990 and 2010. The magnitude is lower in East and south-east Asia and Oceania which have younger populations than North America, West Europe and Australasia which have ageing populations.

In Asia

In 2010, almost 300,000 people were blind from DR and almost 1.5 million were moderate or severely visually impaired in the South Asian region, which includes India.¹ The numbers are likely to increase given the increasing incidence and magnitude of diabetes, and maturing of the “diabetes epidemic”, as years lived with the disease is an important risk factor for DR.^{2,3}

Prevalence of diabetic retinopathy, by type

Global data

In a meta-analysis of 35 high quality surveys which had grading of digital retinal images, the age standardised prevalence of DR of any severity was 35%; 7% had proliferative DR, 6.8% macular edema and 10% had VTDR.¹ South Asian populations had lower rates of DR 19%, PDR 1.3%, DME 4.9% and VTDR 5%, which may reflect the more recent increase in the prevalence of diabetes in Asian than in high income countries.

Prevalence of diabetic retinopathy in India

Several surveys have been undertaken in different States in India, in different age groups and in urban and rural locations (Table 3.2).⁴ Any DR ranged from 9.6% in rural central India to 26.2% in Kerala; VTDR ranged from 0% in central India to 13.5% in Mumbai slums. DME, which was not reported in all studies, ranged from 2.1% to 7.7%. The variability may be because some studies only included known diabetics while others diagnosed PwDM during the survey who were then included. In addition, some surveys were undertaken

Table 3.1 Number of blind and visually impaired persons globally and in South Asia¹

	Blind		Moderate / Severe VI	
	Number (000s)	% of blind	Number (000s)	% of M/SVI
World	834 (703–1102)	2.6%	3,714 (3,128–5,471)	1.9%
South Asia	295 (167–514)	2.8%	1,450 (864–2,873)	2.1%

Table 3.2 Prevalence and types of diabetic retinopathy from population-based surveys in India

State / location	Age (ys)	Sample (total; diagnosis of DM; DR data)	Method of DR assessment	Any DR (%)	Prevalence of different DR types	Author, year
Andhra Pradesh, U	All ages	2522; DM: SR (all ≥30 years): DR status: 124 imaged	Image analysis	1.8%	Mild 0.2% Moderate 0.2% PDR <0.2%. DME ND	Dandona, 1999 ⁵
Kerala	≥50	5212 DM: SR: 260 DR status: 260	Clinical exam (direct/ indirect)	26.2%	Mild 15.4% Moderate 8.1% Severe NPDR 1.2% PDR 1.5%; DME 7.7%	Narendran, 2002 ⁶
Tamil Nadu	≥40	5150; DM: SR/BT DR status: 142 imaged	Clinical exam with 90D lens	17%	NPDR 14.5% Pre-prolif 1.5% PDR 2.2%; DME 2.2%	Nirmalan, 2004 ⁷
Tamil Nadu, Chennai, R	≥30	26,001; DM: SR/RBS DR status: 1715 imaged	Image analysis	17.6%	Mild 9.4% Moderate 6.9% Severe NPDR 0.4% PDR 0.9%. DME ND	Rema, 2005 ⁸
Andhra Pradesh, U and R	≥30	5586 DM: SR DR status: 201 imaged	Clinical exam with 78D lens	19%	Mild 9.7% Mod NPDR 6.8% Severe NPDR 1.5% PDR 0.6%. DME ND	Krishnaiah, 2007 ⁹
Tamil Nadu, Theni, semi-rural	≥30	28,039 DM: FBS DR status: 2448 examined	Clinical exam (direct/indirect)	12.2%	[By eye] Mild/Mod 9.8% Severe NPDR 1.4% PDR 1.1%. DME; ND	Namperm-alsamy, 2009 ¹⁰
Central India, R	≥30	4,711; DM: no data DR status: 262 imaged	Image analysis	9.6%	STDR 0%	Jonas, 2013 ¹¹
Tamil Nadu, Chennai, U	≥40	12,172; DM: SR/FBS/GTT DR status: 1,190 imaged	Image analysis	10.3%	Mild 2.7% Moderate 4.5% Severe NPDR 2.0% PDR 1.0%; DME 2.1%	Raman, 2014 ¹²
Maharashtra, Mumbai slums, U	≥40	6,569; DM: FBS DR status: 592 imaged	Image analysis	15.4%	All NPDR 14.7% PDR 6.7% VTDR 6.6%. DME ND	Sunita, 2017 ¹³

U =urban; R =rural; S/R =semi-rural; SR = self-reported; BT = blood test; RBS = random blood sugar; FBS = fasting blood sugar; GTT = glucose tolerance test; DM = diabetes mellitus; DR = diabetic retinopathy; NPDR = non-proliferative diabetic retinopathy; DME = diabetic macular edema; ND = no data.

more than 15 years ago when the prevalence of DM was lower, and some surveys were under-powered i.e., had small sample sizes.

In the DR programme in India, which was supported by the Queen Elizabeth Diamond Jubilee Trust, UK (2014–2019), 66,455 PwDM were screened for DR in 51 clinics in 10 states across India between 2015 and 2018. 4,020 (6.5%) were treated for VT-DR. This is similar to the 5% reported by Yau.³

Estimate of the number of people with DR in India

Assuming 15–20% of PwDM have any DR, and 5–7% have VTDR, 3.25–4.55 million people are at risk of visual loss, or have already lost vision from DR in India (Table 3.3). The four States with the highest estimates are West Bengal, Maharashtra, Tamil Nadu and Uttar Pradesh as they account for 40% of the number of PwDM.

Global incidence and rates of progression of diabetic retinopathy

The four-year incidence of PDR or severe visual loss from DR is estimated to be 11% and 7.2% respectively.¹⁴ All the studies in this review were

undertaken in high or middle income settings (Mexico) and none were in India. The 10-year incidence (5 studies) of PDR was 17.6%, and 2.5% (6 studies), and 2.5% developed severe visual loss. In these settings the incidence was lower in more recent studies, suggesting improvement in the control of risk factors in these settings. These findings are supported by a more recent review which also did not include any studies from India.¹⁵

Natural history of diabetic retinopathy

The natural history of DR is that it progresses from mild ('background') retinopathy, characterised by a few microaneurysms and haemorrhages, to the more severe, vision threatening stages over time (Table 3.4). An understanding of the natural history is important as it influences the timing of the first examination, and the frequency of subsequent examinations.¹⁶

There are notable exceptions to the data shown below, as DR can develop more rapidly in youth onset (YO) Type 2 DM and during pregnancy (see Chapters 4 and 12).

It is important to note that data in Table 3.4 come from studies in high income settings where

Table 3.3 Estimates of the number of people with diabetes with any DR and VTDR in India and in a typical district of 1 million people

	Number with diabetes*	Any DR (%)		VT DR**	
		%	N	%	N
Nationally	65 million	15-20%	9.8 - 13.0 million	5-7%	3.3 - 4.6 million
District of 1 million, 56% ≥20 yrs	44,800	15-20%	6,720 – 8,960	5-7%	2,240 - 3,136

*Need to be screened/examined; but only approximately 50% are diagnosed; **need treatment.

Table 3.4 Rate of progression of diabetic retinopathy according to stage¹⁶

Stage	Rate of progression			
	To proliferative DR		To high risk proliferative DR	
	1 year	3 years	1 year	3 years
Minimal	No data		No data	
Mild NPDR	5%	14%	1%	15%
Moderate NPDR	12–26%	30–48%	8–18%	25–39%
Severe NPDR	52%	71%	15%	56%
PDR			46%	75%
High risk PDR	Severe visual loss occurs in 25–40% within 2 years			
Macular edema – any severity	Can occur at any stage of DR			

diabetes is usually detected earlier and where management of risk factors is also likely to be better than in India.

In India

A recent study from an urban population in Chennai, India estimated the age-standardised incidence of VT-DR (from no DR or any DR) to be 5% over a four year study,¹⁷ and 22.7% developed VT-DR amongst those with any DR but not VT-DR at baseline. The incidence VT-DR was higher (10.2%) among those who had diabetes for ≥15 years compared with those with 0–4 year's duration (2%). Progression was associated with poor glycaemic control, systolic hypertension and anaemia.

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4. Risk factors for diabetic retinopathy and diabetic edema globally and in India

Summary

- Risk factors for DR and DME are similar.¹
- Risk factors include those that are modifiable and not modifiable.
- Unmodifiable risk factors include duration of disease, type of diabetes, puberty and pregnancy.
 - Duration of disease is a very important risk factor.
 - Data suggest that Youth-onset (YO) Type 2 DM and Type 1 DM have higher rates of DR than Type 2, with (YO) Type 2 DM having the highest risk. After 20 years, the risk of DR is similar in early and late onset Type 1 diabetes.
- Modifiable risk factors are those amenable to interventions, such as hyperglycaemia and hypertension. Poor renal function is often associated with DR, but it is not clear whether the association is causal, or reflects common pathogenic mechanisms.
- Other risk factors with less evidence include dyslipidaemia, smoking, anaemia and some medications.

Risk factors for DR and DME can be grouped as modifiable or not modifiable (Table 4.1).

Table 4.1 Modifiable and unmodifiable risk factors for diabetic retinopathy and diabetic macular edema

Unmodifiable	Modifiable – proven	Modifiable – variable evidence
Duration of disease	Hyperglycaemia	Dyslipidemia
Type of diabetes	Hypertension	Nephropathy
Pregnancy		Anaemia
Puberty (for Type 1 diabetes)		Smoking
		High salt intake
		Glitazone drugs

4.1 Unmodifiable risk factors for diabetic retinopathy and diabetic macular edema

Duration of disease

Global data

Everyone with diabetes will develop DR if they live long enough.

Approximately 50% of PwDM will develop some degree of DR after 10 years, and 80% by 15 years. In the meta-analysis of 35 studies by Yau et al the age standardised prevalence of any DR was 2.6 times higher amongst PwDM who had been diabetic for 10–20 years compared with those diagnosed within 10 years of the study, and was 3.6 times higher among those diagnosed ≥20 years earlier.²

Data from another review indicate a strong association between duration of diabetes and DR for both Type 1 and Type 2 diabetes.³ However, this study does not adjust for the degree of control of diabetes, and does not distinguish between youth-onset and later onset diabetes.

Data from India

In the DiabCare study of 6,168 PwDM, the mean age of onset of diabetes was 45 years ±11 years with a mean duration of 7±6 years.⁴ 95% had Type 2 diabetes. Microvascular complications, which included DR, occurred in 34.4% and nephropathy in 20.4%. The number of complications increased with increasing duration of disease (Table 4.2). Data from this multi-centre, facility-based study showed that 76% of patients who had had DM for >40 years had some degree of DR.⁴

Table 4.2 Relationship between duration of diabetes and the number of complications among people with diabetes attending 330 referral centres in India (from Mohan V et al.⁴)

Number of complications of diabetes	Duration of diabetes (years)	
	Mean ±SD	Range (min–max)
1	6.6 ± 6.2	0.1–40.0
2	8.3 ± 7.0	0.1–41.0
3	8.8 ± 7.3	0.2–60.0
4	8.9 ± 7.0	0.3–40.0
5	9.7 ± 6.0	0.3–27.0

Type of diabetes

Type 1 vs Type 2 diabetes

In the reviews by Yau and Ting, the age standardised prevalence of any DR was 3.1 times higher amongst people with Type 1 DM than with Type 2, and the prevalence of VTDR was 5.6 times higher.^{2,3} However, the definition of Type 1 and 2 DM may have varied between primary studies and the data were not adjusted to address all the known confounders.

In a UK study of approximately 50,000 PwDM, those with Type 2 DM were significantly less likely to develop VTDR than those with Type 1 (adjusted odds ratio 0.35 95% CI 0.31–0.40), but duration of disease and other confounders were not taken into account.⁵

Type 1 diabetes

High income settings

Many of the earlier studies, which were all undertaken in high income settings, report very high rates of NPDR and PDR in people who developed Type 1 diabetes at a young age. After 20 years virtually all developed NPDR, with 70% developing PDR after 30 years.⁶ Another study also reported high rates of NPDR (39% at 10 years and 80% at 15 years) with 20% developing PDR.⁷ More recent studies report lower rates, probably reflecting better management, but a significant proportion progress to PDR.^{8,9}

Evidence suggests that the time interval after puberty is a more important factor than overall duration of diabetes, which has been attributed to changes in growth factors, sex hormones and increasing insulin resistance around the time of puberty, together with greater challenges in controlling hyperglycaemia during adolescence.¹⁰

Ethnic variation

In the UK study outlined above, individuals of Afro-Caribbean descent and South Asians were significantly more likely to have VTDR than white Europeans. However, these data are difficult to compare, as the findings are not adjusted for duration of disease and degree of control of diabetes and other risk factors.⁵

Type 1 early and Type 1 late onset diabetes

A study in Italy compared the prevalence of DR in people with early onset DM (mean age 7.7 years) and a later onset (mean age 19.8 years).¹¹ In the early onset group, the prevalence of moderate to severe DR was 12.7% after a mean of 11.6 years, compared with 21.5% prevalence after a mean of 12.7 Years. By 20 years duration the prevalence of DR was similar between the two groups.

In India

In a study of people with Type 1 diabetes who were aged 10–25 years at diagnosis, 53% had DR after an average of 11–12 years. The age and sex adjusted prevalence of any DR, DME and PDR were 63%, 10% and 7% respectively.¹² Risk factors associated with DR were duration of disease, waist circumference and microalbuminuria.

In this study data on DR (any DR and VTDR) among people with Type 1 DM young-onset were

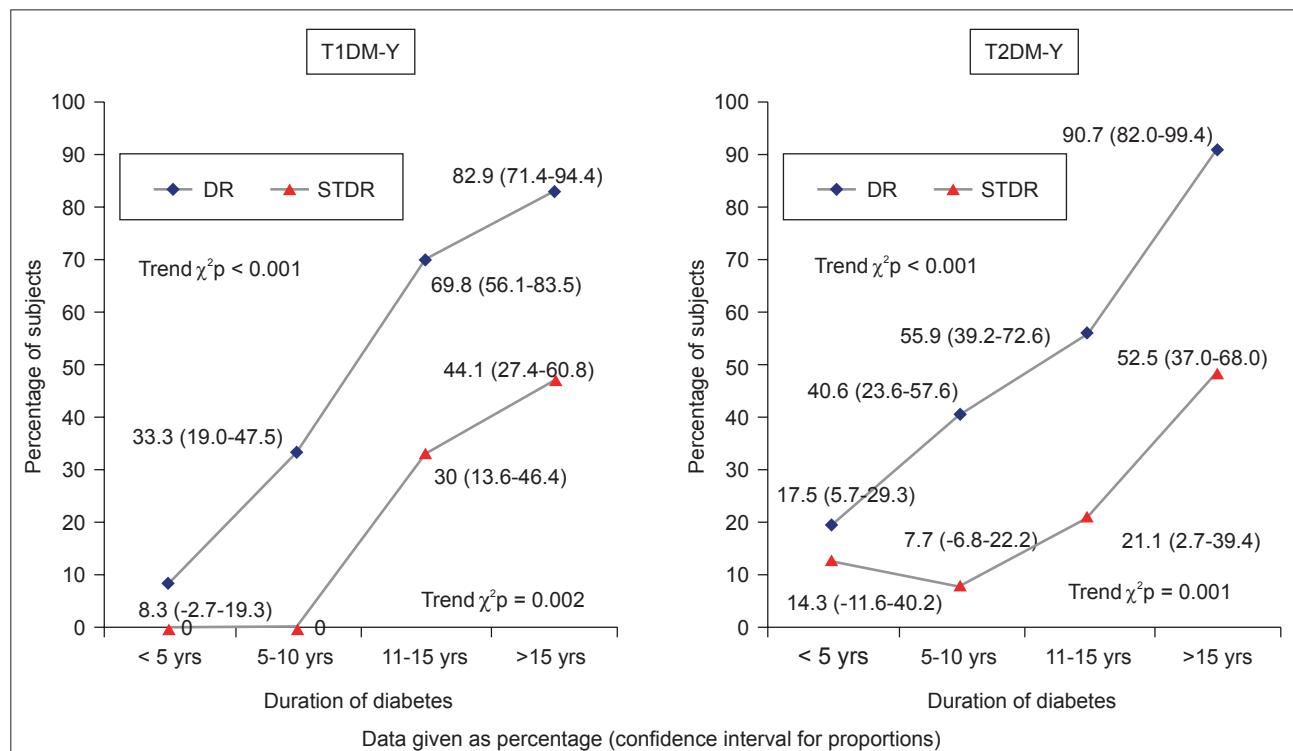


Figure 4.1 Any diabetic retinopathy and sight-threatening retinopathy by duration of disease in people with Type 1 DM of young onset [T1DM-Y] and youth-onset Type 2 diabetes [T2DM-Y]¹²

also analysed by duration of diabetes. None had developed VTDR within 10 years of diagnosis, which increased to 30% by 15 years' duration (Figure 4.1).¹²

Youth-onset Type 2 diabetes

Early onset of Type 2 DM (youth-onset, YO-Type 2) is associated with higher rates of risk factors and complications than Type 1 diabetes.¹²⁻¹⁶ Three studies, one from India,¹⁷ one from Australia,¹⁸ and one from the US¹⁶ compared participants of comparable age with Type 1 and YO-Type 2 DM. Despite those with Type 1 DM having longer duration of diabetes, the YO-Type 2 group had higher rates of complications. In the SEARCH study in the US of 2018 individuals with Type 1 (1746) or YO Type 2 DM (867) both groups had similar duration of disease. The age adjusted prevalence of DR was 2.24 ($p=0.02$) times higher amongst those with YO Type 2 diabetes than those with Type 1.¹⁶ In the Indian study, rates of DR were comparable between the two groups, but DR was more common in Type 1 diabetics in the Australia study.

In the Indian study outlined above, data on DR (any DR and VTDR) among people with YO-Type 2 DM were analysed by duration of diabetes. By 5 years, 14% had developed VTDR which increased to

21% by 15 years. Beyond 15 years' duration, people with YO-T2 DM had a higher prevalence of VTDR (52%) than those with Type 1 DM (44%), but the 95% confidence intervals overlapped (see above, and Figure 4.1).¹²

In a review by Pinhas a high proportion people with YO-Type 2 diabetes had hypertension and signs of nephropathy.¹⁹ Diabetic retinopathy was reported less frequently, but studies from Japan show that 9% of Pw YO-Type 2 DM had DR at presentation, 13% developed proliferative DR by the age of 35 years, 24% of whom became blind before the age of 32 years.

In another study from India of individuals with an onset of DM before the age of 25 years, YO-Type 2 diabetes were also significantly more likely to develop DR than those with Type 1 DM. Ten years after the diagnosis, 41.1% of individuals with YO-Type 2 DM had DR compared with 29.7% of those with Type 1, and the onset occurred earlier in YO-Type 2 than in Type 1 DM. (N Tandon, personal communication).

The higher rate of complications, including DR, amongst people with YO-Type 2 DM may be mediated by late presentation, and poorer control

of glycaemia due to difficulties in accepting the condition which leads to poor clinic attendance, and low adherence to medication and lifestyle changes. People with YO-T2DM are unlikely to develop diabetic ketoacidosis if they fail to take their insulin regularly, thereby increasing the likelihood of their remaining exposed to sustained periods of hyperglycaemia.

4.2 Modifiable risk factors for diabetic retinopathy and diabetic macular edema

Hyperglycaemia

In the Yau review, diabetes control was assessed by HbA1c levels. Analysis showed a clear dose response, as increasing HbA1c was associated with an increasing risk of DR.² Individuals with poor glycemic control (HbA1c >9%) had a 2.8 fold higher age-specific prevalence of DR than those with an HbA1c of ≤7%.

A large number of other studies and systematic reviews have reported similar findings i.e., that poor glycemic control increases the incidence and progression of DR.^{20, 21}

Hypertension

There is also evidence that hypertension is associated with DR in observational studies. A large number of observational studies have reported an association between hypertension and the incidence and progression of DR.²¹ In the meta-analysis by Yau, hypertension was associated with a 22% higher age-specific prevalence of any DR, and those who were hypertensive were 2.3 times more likely to have VTDR.²

Dyslipidemia

The evidence that dyslipidemia is associated with the incidence or progression of DR is mixed, as observational studies give mixed results.

Recent systematic reviews and meta-analyses investigated the evidence for an association between serum lipids and diabetic macula edema (DME).^{22, 23} The observational risk factor studies included cross sectional (5 studies, 3 from India), cohort studies⁵ and case control studies (7, one from India²⁴). Outcomes in the longitudinal studies and trials were the incidence and progression of DME. The meta-analysis of case control studies showed

significant associations with DME for high serum total cholesterol, serum low density lipoproteins and serum triglycerides but not for high density lipoproteins.^{22, 23} Similar findings were reported for the cohort and cross sectional studies.

A recent 30 year follow up study of people with Type 1 diabetes, which was not included in the meta-analysis, showed no evidence of an association between serum lipids and proliferative DR or DME.²⁵ A negative association was also recently reported between any or severe DR and genotypes which increase the risk of hyperlipidaemia.²⁶ The review by Yau et al showed no difference in the age specific prevalence of any DR by level of total cholesterol.²

In a longitudinal study in South India, high serum lipids were an independent risk factor for the incidence and progression of DR in a South Indian population.²⁷

Nephropathy

There is strong evidence from cross sectional studies that individuals with DR are also more likely to have the other microvascular complications of DM (e.g., nephropathy, neuropathy) and macrovascular complications (e.g., cardiovascular and cerebrovascular disease). Due to the lack of data from cohort studies, it is unclear whether nephropathy increases the risk of DR or whether they both reflect common pathogenic pathways.²⁸ Implications for programmes is that individuals with DR, particularly with PDR, need to be assessed for the other complications of DM so they can be managed appropriately.

Anaemia

Multiple studies report that anaemia is more prevalent in people with DR than those without. However, as nephropathy is a cause of anaemia, and nephropathy and DR are highly correlated, there is less evidence that anaemia is an independent risk factor for the onset or severity of DR.¹

However, a cross sectional, facility based study in India showed that anaemia was an independent risk factor for the presence and severity of DR, after adjusting for confounders such as microalbuminuria, a marker of renal disease.²⁹

Smoking

There is no clear association between the incidence and progression of DR with smoking, with some

studies showing the smoking increases the risk of DR, with another showing a protective effect.²¹ As smoking increases the risk of other cardiovascular complications in PwDM, smoking cessation should be recommended on these grounds.

Salt intake

Although reducing dietary salt reduces blood pressure in PwDM,³⁰ evidence of whether a high salt intake is an independent risk factor for DR is very limited.³¹

Retinal complications of drugs used for diabetes

Thiazolidinedione group of drugs

Recent observational studies suggest that the thiazolidinedione group of glucose lowering drugs, particularly the glitazones, may increase the risk of DME in people with Type 2 diabetes.^{32, 33}

Semaglutide and risk of progression of DR

Semaglutide is one of the glucagon-like peptide-1 receptor agonist (GLP-IRA) group of drugs which are widely used in people with Type 2 diabetes as they improve cardiovascular and other outcomes. However, concerns have been raised that semaglutide may be associated with progression of DR, as reported in the SUSTAIN-6 trial.³⁴ Possible explanations include factors associated with the design of the trial, rapid reduction in blood glucose levels which is known to increase the risk of progression of DR, or direct angiogenic or toxic effects.³⁵

A recent meta-analysis showed no increase in DR with this group of drugs.³⁶

A recent review of over 9 million entries in the US Food and Drug Administration Adverse Events Reporting System identified 112,000 events involving GLP-IRAs and almost 700,000 involving other glucose lowering medication.³⁵ Reports of adverse retinal events was significantly lower for GLP-IRAs than other medications (reporting ratio 0.38, 95% CI 0.34–0.43). Patients taking GLP-IRAs had more co-morbid conditions and concomitant medication, and the findings remained significant after adjusting for insulin use and by type of GLP-IRA.

These findings suggest that semaglutide and other GLP-IRA drugs do not increase the progression of DR.

Hydroxychloroquine retinal toxicity

Hydroxychloroquine is sometimes used as a 3rd line medication in the management of diabetes.³⁷ However, retinal toxicity is a recognised complication of long-term use. The toxicity is characterised by damage to different retinal layers in peri- and central macular areas. Early stages do not affect vision and cannot be detected clinically. In late stages there are obvious clinical signs (retinal atrophy) with profound loss of central vision.

There is no known treatment. OCT and visual field tests can be used to diagnose and categorise the severity of the changes, including early, subclinical stages. The changes do not reverse after stopping the medication, and in advanced cases may progress. A pericentral pattern of damage is especially prevalent among Asian patients.³⁸

Recent studies using OCT and visual fields suggest a prevalence of 7.5%.³⁹ At recommended doses the risk of toxicity up to 5 years' use is <1%, 2% by 10 years and almost 20% by 20 years.⁴⁰

Factors which increase the risk of toxicity are duration of treatment, dose and poor renal function. While studies suggest that there is no completely safe dose, in patients with normal renal function the risk is low at 10 years with a dose of ≤5mg/kg *actual* body weight [Note: Dose based on *ideal* body weight was the earlier recommendation.]

Recommendations: See the recent articles from the American Academy of Ophthalmology, one of which takes account of the different pattern of toxicity seen in Asian eyes.^{40, 41}

Risk factors for DR in Indian studies

Similar risk factors have been reported from observational studies in India (Table 4.3) which confirms the importance of duration of diabetes, poor glycaemic control and, in some studies, hypertension as risk factors for DR. Most studies did not investigate associations with serum lipids.

Table 4.3 Risk factors for diabetic retinopathy in population based studies in India

Location	Tamil Nadu, Chennai	Tamil Nadu, Chennai#	Tamil Nadu, Chennai	Andhra Pradesh, Urban/rural	Tamil Nadu	Maharashtra, Mumbai	Central
Reference	Rema, 2005 ⁴²	Raman, 2014 ⁴³	Pradeepa, 2010 ⁴⁴	Krishnaiah, 2007 ⁴⁵	Nampul.. 2009 ⁴⁶	Sunita, 2017 ⁴⁷	Jonas, 2013 ⁴⁸
Not modifiable							
Duration	++++	+++	+++	++++	+++	+++	No data
Type of DM	No data	No data	No data	No data	No data	No data	No data
Increasing age	NS	No data	No data	++	++	NS	+++
Sex	Female	Male	Male	Male	NS	Male	No data
Modifiable							
Hyperglycaemia	+++	++++	+++	No data	++	-	++++
HT – history	No data	No data	No data	No data	No data	NS	No data
HT – systolic	NS	+++	NS	+++	++	No data	NS
HT – diastolic	NS	NS	NS		No data	No data	
High lipids	No data	NS	NS	No data	No data	No data	NS
Poor renal function	No data	NS	++	ND	No data	No data	NS
Smoking	NS	No data	No data	NS	NS	No data	No data

risk factors for the incidence of diabetic retinopathy. NS = not statistically significant; HT = hypertension;

Nampul. = Namperumalsamy.

+ weak evidence of association; ++++ strong evidence of association.

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5. Efficacy of interventions to reduce the risk of DR

Summary

- There is good evidence from systematic reviews of randomised clinical trials that controlling hyperglycaemia and hypertension lower the incidence of DR.¹
- There is also good evidence that controlling hyperglycaemia reduces the progression of DR.
- Despite observation studies suggesting an association between dyslipidemia and DR and DME, there is less good evidence on the impact of controlling dyslipidemia. More studies are needed, particularly in India.
- There is less, or no evidence on the impact of improving renal function and anaemia, and smoking cessation and salt restriction on DR or DME.

5.1 Efficacy of interventions to reduce the risk of DR, by type of diabetes

Glycaemic control

In Type 1 diabetes

There is strong evidence from a meta-analysis of randomised clinical trials and a Cochrane systematic review that interventions to improve glycaemic control in people with Type 1 diabetes reduces the incidence and progression of DR (3 trials in the UK, Norway and Sweden; a meta-analysis² and a multi-centre study).

In the Diabetes Control and Complications Trial (DCCT) every 10% decline in HbA1c reduced the risk of DR by 39%.^{3,4} The benefits were maintained 10 years later, with hazard reductions of 53%–56% for progression of DR, and to proliferative DR or worse.⁵

A recent systematic review of 18 trials on tight glycaemic control in Type 1 diabetes, had inconsistent findings for DR but showed reductions in nephropathy and macrovascular disease.⁶

In Type 2 diabetes

A recent Cochrane review included 28 randomised trials of tight glycaemic control vs conventional glycaemic control which enrolled 35,000 PwDM with follow up which ranged from 3 days to 12.5 years.⁷ The meta-analysis showed a reduction in the incidence of DR of approximately 20% (RR 0.79, 95% CI 0.68 to 0.92). However, trial sequential analysis, which gives better control of type I and type II errors, could not confirm a relative risk reduction of 10%.

Another systematic review for Type 2 DM showed that tight control reduced the progression of DR but not the incidence.⁸

The more recent ADVANCE trial explored whether improved glycaemic control improved a range of outcomes among different ethnic groups in three regions.⁹ The trial involved over 11,000 PwDM in 215 centres in 20 countries, including two centres in India. The authors concluded that improved glycaemic control, to a

target HbA1C of 6.5–7.0%, improves cardiovascular outcomes despite the use of different combinations of medication. The trial also had a modest impact on the incidence and progression of DR.

There is no threshold level of blood glucose in PwDM below which the risk of DR is negligible.

Complications of tight glycaemic control

However, tight control can increase the risk of episodes of hypoglycaemia,^{6,7} and the risk of DR worsening is more likely if DR is already present. Gradual reduction of glucose levels is recommended for those with very high glucose levels who have DR.¹⁰

Hypertension control

Hypertension (defined as a blood pressure $\geq 140/90$ mmHg) is a common condition in diabetes, affecting 20–60% of patients with diabetes, depending on obesity, ethnicity, and age.¹¹

The United Kingdom Prospective Diabetes Study (UKPDS) showed that a reduction of mean systolic blood pressure from 154 to 144 mmHg reduced the number of microaneurysms at 4.5 years, reduced hard exudates and cotton-wool spots at 7.5 years, and was associated with less need for photocoagulation and less deterioration of 2-step or more on the ETDRS retinopathy scale.¹² In the ACCORD trial progression of retinopathy was compared between intensive control (systolic blood pressure <120 mmHg) and standard control (<140 mmHg) in the presence good glycaemic control. In this trial there were no significant differences in the progression of retinopathy in the two arms of the trial, possibly because the standard control arm had lower blood pressures than anticipated (median 133 mmHg).¹³

A recent Cochrane systematic review included 15 trials: 5 trials for Type 1 diabetes and 10 for Type 2.¹⁴ The trials differed with respect to target levels of blood pressure, and adverse events were not reported systematically. Most trials used the ETDRS classification, or modifications to assess DR outcomes, although the degree of change considered significant differed between trials. Trial outcomes included the incidence and/or progression of DR. Most trials were classified as having a low risk of bias.

None of the trials were undertaken in India but the authors conclude that “none of the trials provided

data to suggest that diabetic individuals from different racial or ethnic groups differed in their response to blood pressure control”¹⁴

In Type 1 diabetes

In the Cochrane review five trials have been undertaken involving 4036 people with Type 1 diabetes (Chase, Direct Prevent 1; DIRECT Protect 1; EUCLID and RASS, all in high income countries).¹⁴ Participants had an average age of around 30 years, all were normotensive and the majority had no DR at baseline.

One trial reported a lower incidence of DR with intensive blood pressure control.¹⁴

In Type 2 diabetes

In the Cochrane review ten trials have reported data on 8251 patients with Type 2 diabetes.¹⁴ The average age was 51–66 years. Four trials recruited individuals without or with well controlled hypertension (ABCD 1; ACCORD EYE; DIRECT Protect 2). In six trials, participants were hypertensive at baseline (ABCD 2; ADVANCE/AdRem; BENEDICT; DEMAND; Steno-2; UKPDS/HDS). Trial designs varied, with some having a placebo or no treatment arm; different medications were used; some were factorial in design and also included interventions to control glucose levels. Two centres in India took part in the ADVANCE trial.

Five trials reported a lower incidence of DR with intensive blood pressure control, but the impact was modest (approximately 20%). In the four trials which reported progression of DR, the evidence overall indicated no benefit. In the four trials which assessed incidence and progression there was also only a modest effect (approximately 20% lower risk).

There is some evidence that drugs which act on the renin-angiotensin system may have additional benefits on DR over and above their hypotensive properties, but the evidence is inconclusive.¹⁵

Targets for lowering blood pressure need to bear in mind that a blood pressure that is too low can have adverse effects among PwDM.

Summary of the role of lowering blood pressure

Evidence of lowering blood pressure to control DR shows a modest benefit on DR. However, as control of hypertension in PwDM has substantial other benefits e.g., on survival and other complications

such as nephropathy (particularly drugs which act on the renin-angiotensin system), hypertension should be controlled in PwDM for these reasons.¹⁶ Close monitoring is required to prevent adverse events.¹¹

Dyslipidemia and DME

The meta-analysis by Das (above) included four randomised controlled trials one of which was undertaken in India.^{17,18} Outcomes in the trials were the incidence and progression of DME. All the RCTs were placebo controlled, and used fenofibrate, fenofibric acid or atorvastatin as the lipid lowering agents. The meta-analysis showed no effect on clinically relevant outcomes.

The summary odds ratio for the progression of hard exudates was 1.00 (95% CI, 0.47–2.11), and 1.18 (95% CI 0.75–1.86) for severity of DME.¹⁷ In the ACCORD trial, a subset of patients who had marked lowering of lipid levels showed some benefit in two thirds.¹³ Some of the studies had a very small sample sizes, or were underpowered to detect differences due to the small number of new cases.

The trial in India by Gupta showed a protective effect but the findings were not statistically significant due to the small sample size (RR 0.17; 95% CI 0.02–1.22).¹⁸ Another small randomised trial of simvastatin vs conventional care in India also was of benefit in terms of reducing hard exudates in patients treated with laser for DME.¹⁹

Summary of impact of lipid lowering and DR

Despite some observational studies showing an association between hyperlipidemia and DR, there is less evidence of benefit from clinical trials of lipid lowering medication. These medications cannot be recommended currently as a therapy to reduce the risk of DR. More RCTs are warranted, particularly in India given the postulated origins and characteristics of diabetes in India i.e., higher central obesity, higher rates of dyslipidemia, increased inflammatory markers (e.g., C-reactive protein), greater insulin resistance, early loss of beta cell function, and a higher risk of coronary artery disease.²⁰

However, lipid control is recommended because of beneficial effects on the risk of cardiovascular disease.^{21,22}

Metabolic memory

There is evidence from some of the earlier clinical trials that good control of hyperglycaemia, hypertension and lipids lead to long term benefits on a range of outcomes, including (in some trials) the need for retinal photocoagulation.^{23–25} This has led to the concept of 'metabolic memory', or 'legacy effects', but the mechanisms are not fully understood. These findings support the need for good control of risk factors from as soon as possible after the diagnosis of diabetes has been made.

Complications of drugs used for diabetes

Stopping glitazone medication can reduce the severity of DME.²⁶

5.2 Other medical treatments to reduce the incidence or progression of DR

Probiotics

Probiotics, such as fermented milk and yoghurt, are receiving attention because of their beneficial effects on the immune system, lipid metabolism and anti-oxidant properties. A recent systematic review of 10 small trials indicate that they may reduce hyperlipidemia, hypertension and fasting blood glucose in people with Type 2 diabetes.²⁷ No data were reported on DR.

Others

A range of compounds implicated in the causal pathways for DR have, or are being investigated, including antiplatelet agents and inhibitors of angiotensin converting enzymes, advanced glycation end products and aldose reductase. [Reviewed in the Australian Guidelines.²⁸] There is currently no conclusive evidence of the effectiveness of these agents and trials are ongoing for those which appear promising, including fenofibrate,²⁹ a lipid lowering medication, and agents which block PKC-beta.^{30,31}

5.3 PICO question: Which interventions reduce the risk of DR, by type of DM if different?

Recommendations to reduce the risk of DR and DME

► General recommendation for practice

- All people with diabetes should be managed by a physician or diabetologist, to control blood glucose, hypertension and lipids, and to support life style modification, including smoking cessation and reduction in dietary salt intake.

► Recommendations for treatment

Blood glucose levels targets for Type 1 and Type 2 diabetes

- Target HbA1C of 7% (53 mm/l), adjusted for the individual within the range 6.5–7.5% (48–58 mm/l) (Level I).

Blood pressure targets for Type 1 and Type 2 diabetes

- Systolic of ≤130 mmHg for those with DR. Close monitoring is required to prevent adverse events¹¹ (Level I).
- Systolic of <140 mmHg for those without DR or cardio-renal complications of diabetes (Level I).

Lipids

- Consider lowering lipids to reduce diabetic macrovascular complications and the progression of DME (Level I).

► Recommendations for practice

- Consider replacing glitazone if there is evidence that DME developed on treatment (Level IV).
- Regular HbA1c levels and regular blood pressure measurement are required i.e., every three to six months for stable diabetes, more frequently if unstable.
- Patients need to be counseled to follow advice of clinicians regarding medication.

► Recommendation for research

- More evidence is needed on the impact of lipid lowering agents on the incidence and progression of DR in India.

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6. Effectiveness of interventions to reduce DR in real-world settings

Summary

- Despite evidence of the efficacy of interventions which can prevent DR amongst PwDM there is limited evidence of the effectiveness of these interventions on the incidence or progression of DR in the real world.
- Supporting PwDM to improve the management of their disease requires a multi-faceted approach, with advice tailored to the individual patient and shared decision making.

6.1 Evidence of effectiveness of complex interventions on the risk of DR

Physical activity

There is evidence from two systematic reviews that moderately strenuous exercise such as aerobic exercise and resistance training by PwDM Type 2 improves glycaemic control.^{1,2} In the earlier of the two reviews, HbA1c levels were lower in the exercise than control groups (7.54% vs 8.31% respectively, difference -0.66%, p=<0.001).¹ Differences were very similar in the more recent meta-analysis of 47 trials.² Regular exercise also reduces blood pressure in hypertension.³

Nutrition advice and healthy diet

Nutrition advice can lead to PwDM having better control, as long as the advice is tailored to the individual patient.^{4, 5}

A recent systematic review that a healthy diet, i.e., reduced calorie intake, high fibre intake, oily fish and the “Mediterranean diet” reduce the risk of DR.⁶

Self management of diabetes

As with all chronic conditions, self-management is of vital importance in diabetes,⁷ entailing daily decision making in relation to adherence to medication and dietary intake (which need to be tailored to the individual), increasing physical activity and attendance at clinical appointments. All these factors are influenced by personal health beliefs, social support, and environmental factors (i.e., access to health services and technology for self-monitoring, the availability of community programmes), and cultural factors.⁸

While traditional programmes have tended to be didactic, focusing on improving patients' knowledge of their disease, current approaches aim to provide patients with skills and strategies to promote and change their behaviour, which can be effective. There is potential for technology to assist people with diabetes to improve self-management, through internet based behaviour change programmes,⁹ and mobile phone applications, although many apps for diabetes management have not yet been validated.

Despite good evidence from clinical trials, there is less evidence of the effectiveness of delivering control strategies in the real world.¹⁰ For example, there is some evidence of effectiveness of interventions which

promote self-management which target service providers, patients with DM, or both groups, particularly if there are computerised tracking systems or nurses who regularly contact patients.¹¹ Another review of shared decision making, highlighted the importance of interventions which include both patients and service providers.¹² Trials which focused narrowly on one strategy or intervention had weaker evidence of effectiveness (e.g. intensive health education,^{12,13} or specialist nurse practitioners¹³) whereas dietary advice was more effective in conjunction with advice on physical activity.¹⁴

A review of studies designed to modify overall food intake showed that smaller portion sizes, food packaging and tableware reduced food intake, but none of the studies included people with diabetes.¹⁵

Peer support groups

Systematic reviews of randomised trials of peer support groups shows that they can have a significant albeit minor impact on glycaemic control,¹⁶ and hypertension.¹⁷ A recent trial of women with diabetes in India compared three interventions: usual care, biweekly yoga and peer support groups. Short-term outcomes at three months were promising: fasting glucose was lower in both intervention arms, and diastolic blood pressure was lower in the yoga arm.¹⁸

AYUSH treatments

Facilities to deliver the Indian system of medicine, AYUSH (Ayurveda, Yoga, Unani, Siddha and Homeopathy) are being set up by the National Rural Health Mission in Primary Health Centres (PHCs), Community Health Centres (CHCs) and district hospitals, headed by qualified AYUSH practitioners.¹⁹ These facilities tend to be accessed by the poor, and those with chronic conditions.²⁰ People with diabetes often frequent AYUSH practitioners and use Ayurvedic herbs. However, there are challenges in accurate plant recognition and standardisation of preparation for the large number of plants which show anti-diabetic activity, several of which are undergoing clinical trials.²¹

A review of a range of studies in 2005 suggested that several herbs may have glucose lowering effects.^{22,23}

A recent systematic review indicates that yoga may be beneficial as it reduces glucose and blood

pressure and improves body composition.²⁴ Among PwDM yoga can lead to reduction in HbA1C levels, blood pressure and body mass index.²⁵

Summary of evidence of AYUSH treatments

There is some evidence that yoga may be of benefit in controlling risk factors for DM and DR.

There is no robust evidence of the effectiveness of other AYUSH practices on DR.

6.2 Achieving targets for control of risk factors

Global data

A recent review and meta-analysis, which used routinely collected data from 24 studies in 20 countries involving 369,251 PwDM, assessed the extent to which patients achieved internationally recommended targets for control of risk factors for the complications of diabetes.²⁶ Most studies were from high income countries, with nine from Asia or the Middle East. No data were available for India. The proportion of patients achieving targets were as follows: 43% for hyperglycaemia (HbA1C), 29% for hypertension; 49% for LDL-C control and 62% for triglycerides. Values were lower for studies in LICs and LMICs, suggesting that much more needs to be done.

In India

Similar findings have been reported in the DiabCare study in India, which was undertaken in 330 referral diabetes care centres across India, and in a recent study of primary care centres in Delhi.

In the DiabCare study of 6168 PwDM, the mean age of onset of diabetes was 45 years ± 11 years with a mean duration of 7 \pm 6 years.²⁷ Up to 95% patients had Type 2 diabetes and 42% reported taking regular exercise. HbA1C had been measured in 28% at least once in the previous year and the mean HbA1C was 8.9% \pm 2.1%.

A study of PwDM, physicians and chart review in primary care clinics in Delhi indicated that 88% had undergone blood pressure measurement and 52% had at least one measure of HbA1C in the preceding year.²⁸ Only 7.4% had undergone dilated retinal examination. Up to 27% had a microvascular complication, including DR (9%), and 34% had a macrovascular complication.

6.3 PICO Question: How should interventions which reduce the risk of DR be delivered?

Recommendations for practice

- To achieve better control of diabetes, promote self-management of diabetes tailored to the individual.
- Promote regular, moderately strenuous exercise and yoga if not contraindicated.
- Establish self-help / peer support groups to improve and sustain control of diabetes and its risk factors.

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7. Level of awareness about DR among patients and providers, and barriers to care in India

Summary

- There is limited evidence of the availability of services for patients with DR.
- In India, levels of awareness about DR amongst PwDM in terms of their knowledge and the importance of annual eye examinations is low.
- Awareness amongst health care professionals is also not as good as it should be.

7.1 Services for diabetes and diabetic retinopathy in India

In India, services for PwDM and eye care are provided by the public health system, private practitioners and the not for profit sector. The Ministry of Health and Family Welfare (MoHFW) has a programme for control of NCDs (the National Programme for Prevention and Control of Cardiovascular Disease, Diabetes and Stroke) and for blindness (the National Programme for the Control of Blindness and Visual Impairment).¹ Little information is currently available concerning the services being provided and whether there are major gaps in relation to the prevention of DR or treatment of people identified with VTDR.

A range of different approaches are being used by the government and not-for-profit sector in India to detect and treat DR. However, it is not known which of these approaches is the most effective, sustainable and efficient, nor which approach could readily be taken to scale to meet the emerging challenge of blindness from DR.

7.2 Awareness about DR amongst patients

Several studies in India have addressed the level of knowledge about DR among PwDM.

Facility-based studies

In the recent “11-city study”, 376 adults with DM attending eye clinics in India were interviewed: 62.8% knew that DR could lead to blindness, and 58% reported that good control of diabetes meant having blood glucose/HbA1C levels within normal limits.² Duration of diabetes (41%), poor glycaemic control (39.4%) and age (20.7%) were considered the most important risk factors for DR, and 14.6% did not know of any. The main challenges they faced in managing their diabetes were modifying their diet and taking exercise. A third had not received any information on DR. Almost half (45%) had lost vision before the condition was diagnosed. The better educated and those attending private clinics had better levels of knowledge.

In another study of 6,000 people with type 2 diabetes (the DIAMOND study), 63% did not know that diabetes can affect the retina, and 68% did not know that DR can be prevented and treated.³ Most would only have an eye examination if they lost vision. These findings were similar to other facility-based studies.^{4,5} In another study many patients did not understand that HbA1c tests are to assess glycaemic control.⁶

Population-based surveys

In Tamil Nadu almost 90% of PwDM reported that they test their blood glucose every three months. Although three quarters knew that DM could affect the eyes, the majority did not know what these effects were. In all

studies, levels of awareness about DR, what the risk factors are were low, and less than half of the PwDM interviewed had had an eye examination.⁷⁻⁹

7.3 Awareness about DR amongst service providers

Fewer studies have addressed providers' perspectives on DR awareness.

In the 11 city study mentioned above, 59 senior physicians and endocrinologists were interviewed about the challenges they faced in providing care for PwDM and its complications.¹⁰ The main themes that emerged were lack of awareness amongst patients, poor compliance with life-style changes, a reliance on medication to control diabetes and inadequately staffed, over-crowded clinics. Self-monitoring of blood glucose levels had improved.

Awareness amongst staff about DR was generally low, and practices varied in relation to how and whether patients underwent screening for DR.

In the same study as above, 86 eye care providers were visited across all sectors. Only 14 hospitals were providing screening for DR, two of which were in the not-for-profit sector.¹¹

A community sample of 199 non-medical para-medical staff would give the following advice to people with diabetes: diet (70%), exercise (48%), medical treatment (82%) or they would refer to a doctor (85%).⁹ A high proportion (89%) knew that diabetes could affect the eyes, but almost half (45%) were not aware of any of the risk factors for DR. A high proportion (59%) considered complications would not be a problem if the diabetes was well controlled, but the majority (86%) would recommend an eye examination.

7.4 PICO Question: What can be done to increase awareness about DR?

Recommendations for practice

- More needs to be done to increase awareness among people with diabetes about the complications of diabetes, including DR and the need for annual eye examination through information, education and communication at every level of service delivery.
- More needs to be done to increase awareness among health professionals providing services for people with diabetes at every level of service delivery about the complications of diabetes, including DR and the need for annual retina examination.

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8. Classification and diagnosis of diabetic retinopathy and diabetic macular edema

Summary

- The International Classification of Diabetic Retinopathy is widely used in clinical practice, for diagnosis and to indicate the frequency of follow up and research, and provides the basis for the criteria for referral after screening.
- The diagnosis of DR and DME requires a detailed clinical examination, with additional investigations to assess the severity of DR, and type and severity of DME, which guide management decisions.

8.1 The International Classification of Diabetic Retinopathy

This classification system, which is based on clinical signs, is useful as it provides a guide to the indications for treatment of DR and DME (Table 8.1).

Table 8.1 International Classification of Diabetic Retinopathy and Diabetic Macular Edema¹

Diabetic retinopathy	Findings by clinical examination
No apparent DR	No abnormalities.
Mild non-proliferative DR	Microaneurysms only.
Moderate non-proliferative DR	Microaneurysms with other signs (e.g., dot and blot haemorrhages, hard exudates, cotton wool spots), but less severe than non-proliferative DR.
Severe (high-risk) non-proliferative DR*	Moderate non-proliferative DR with any of the following: <ul style="list-style-type: none">intraretinal haemorrhages (20 in each quadrant).definite venous beading (in 2 quadrants).intraretinal microvascular abnormalities (IRMA)(in one quadrant).no signs of proliferative retinopathy.
Proliferative DR ¹	Signs of severe non-proliferative DR, with one or more of the following: <ul style="list-style-type: none">neovascularisation on the optic disc (NVD) and/or elsewhere (NVE).vitreous/preretinal haemorrhage.
Diabetic macular edema	Findings by clinical examination
No DME apparent	No retinal thickening or hard exudates in the macula.
Non-central involving DME	Retinal thickening in the macula that does not involve the central subfield zone that is 1mm in diameter.
Central involving DME	Retinal thickening in the macula that does involve the central subfield zone that is 1 mm in diameter.

1 See 'Wilkinson CP et al.', in the references list.

High-risk characteristics of DR

The DRS trial identified a subgroup of people with PDR who had a poor prognosis, with “high-risk PDR” characterised by one of the following:

- disc new vessels greater than or equal to one-third of the disc area in extent,
- any disc new vessels with vitreous or pre-retinal haemorrhage,
- new vessels elsewhere greater than or equal to half of the disc area in extent associated with vitreous or pre-retinal haemorrhage.^{2,3}

The presence of three or more of the following high-risk characteristics also defines high-risk PDR:²

1. Vitreous haemorrhage or pre-retinal haemorrhage,
2. Any active neovascularisation,
3. Location of neovascularisation on or within one disc diameter of the optic disc,
4. NVD greater than one-third of the disc area or NVE greater than half of the disc area.

Diabetic macular edema and ischemic maculopathy

DME is defined as retinal thickening, and this requires a three-dimensional assessment that is best performed by a dilated examination using slit-lamp bimicroscopy and/or stereo fundus photography.¹

The ETDRS guidelines for clinically significant macular edema (CSME) included the following clinical criteria based on evaluation of stereoscopic colour photos:

- any retinal thickening within 500 microns of the centre of the macula,
- hard exudates within 500 microns of the centre of the macula with adjacent retinal thickening,
- retinal thickening at least 1 disc area in size, any part of which is within 1 disc diameter of the centre of the macula.

Another category of retinopathy involving the macula is ischaemic maculopathy, characterised by capillary dropout at the fovea, with enlargement of the foveal avascular zone.⁴ Ischaemic maculopathy cannot be treated, and leads to pronounced loss of visual acuity. When considering treatment for DME it is important to rule out ischaemic maculopathy,

as inappropriate treatment can exacerbate loss of vision (see Chapter 11). Ischemic maculopathy has been shown to be strongly associated with nephropathy, and affected patients should be referred for investigation, if required.⁵

8.2 Follow up of people with diabetes to detect or monitor DR

Patients with or without DR need to be followed up, to detect progression or new disease. Ideally local incidence and progression estimates be used but these data are limited in India. The recommendations in Table 8.2 below, are derived from other guidelines, and have been modified using data from India.⁶⁻⁸

8.3 PICO Question: How frequently should people with diabetes, with or without DR, be followed up?

Recommendations for practice

The frequency of follow up of people with diabetes according to their DR status is shown in Table 8.2.

Table 8.2 Follow-up recommendations for diabetic retinopathy in the absence of DME.⁶⁻⁸

Type of diabetic retinopathy	Frequency
None	Annual
Mild	6–12 months*
Mod	4–6 months*
Severe	2–4 months*
PDR	Treat within 4 weeks

*more frequently for those with poor glycaemic control or other risk factors.

8.4 Diagnosis of diabetic retinopathy and DME

Clinical examination

A detailed retinal examination is the mainstay in the diagnosis of DR. Examination must entail the following: history, visual acuity measurement, undilated anterior segment slit lamp examination to examine the iris and angle for rubeosis, and dilated retinal examination using slit lamp biomicroscopy with a 78D or 90D lens for the macular, and/or indirect ophthalmoscopy with a 20D lens.

Investigations

Imaging in DR is essential to document findings and to establish correlations between structure and function. Serial imaging is very useful in detecting change over time and assessing response to treatment. The following investigations, with the exception of colour fundus photography, are adjuncts to clinical examination and do not have a role in screening for DR.

Colour fundus photography has been established as a standard in screening and as adjunct to clinical examination, to document findings to assess changes at follow-up. Ultra-wide field colour fundus photography has further enhanced detection and identification of prognostic factors for the progression of DR.^{6,9}

Red-free imaging allows better visualisation of subtle abnormalities, such as IRMAs and neovascularisation elsewhere, making it a valuable tool in the clinic.

Ultrasound is useful to assess the configuration of the vitreous and retina, particularly if the media are not clear i.e., in the presence of cataract or vitreous haemorrhage. The decision to operate is often made based on ultrasonography according to the status of the retina and the location of haemorrhage in relation to the vitreous.¹⁰

Optical coherence tomography (OCT)

OCT, which is a non-invasive, quick, cross-sectional imaging tool, has almost replaced fundus fluorescein angiography as the standard of care in DR, especially for DME. OCT facilitates visualisation of the nature, location and extent of changes in the retina along with quantification of changes in the retina and choroid (see Table 8.3 for indications).

OCT has revolutionised our understanding of changes at the macula in diabetes, and guides

detection, prognostication and the treatment of choice. OCT is also used to assess responses to treatment for DME. OCT is now the reference standard for the assessment of DME.^{11,12}

The evolution of OCT from time-domain to spectral domain and swept-source has brought about a sea-change in the interpretation of OCT in DR and DME. OCT biomarkers such as the presence or absence of sub-retinal fluid, hyper-reflective foci, disorganised retinal inner layers, and the integrity of the external limiting membrane and ellipsoid zone, are used to predict the outcome of treatment.^{13,14} Most of the landmark trials have used OCT as a key tool in assessing anatomical changes in response to a range of treatment modalities.¹⁵

OCT classifies macular edema as centre involving and non-centre involving. OCT can also detect a range of clinical findings such as intraretinal cystoid spaces, spongy retinal edema, neurosensory detachment and tractional edema due to thickened posterior hyaloid or epiretinal membrane. These findings along with the biomarkers mentioned above and quantification of edema in response to therapeutics makes OCT the go-to test in DR and DME.¹⁶

The earlier definition of DME used in ETDRS has been modified and DME is now classified as “centre-involving” i.e., involving the centre of the macular including the fovea and “non-centre-involving”¹⁷

Fundus fluorescein angiography (FFA)

Fundus fluorescein angiography (FFA) provides information on the vascular competency of retinal and choroidal vessels, including at the macula. FA classifies DME as focal or diffuse based on the source of leakage – microaneurysm predominated leakage is defined as focal while outer blood-

Table 8.3 Indications for OCT (from AAO Guidelines¹⁸)

Situation	Usually	Occasionally	Never
To investigate unexplained loss of visual acuity	•		
To identify areas of vitreo-macular traction	•		
To evaluate patients who are difficult to examine clinically	•		
To monitor response to treatment	•		
To investigate other possible causes of macular swelling		•	
To screen patients with no or minimal DR			•

retinal barrier mediated leakage is defined as diffuse. Altered foveal avascular zone (FAZ) shape, a crenelated FAZ and an enlarged FAZ on FFA are features of ischemic maculopathy.^{19,20} (See Table 8.4 for indications for FFA.)

In DR grading, FFA has been the gold standard in the diagnosis of PDR as the presence of neovascularisation is unambiguous on FA. Pre-proliferative lesions, such as IRMA, are also well defined. Wide-field FFA allows detection of ischemic peripheral retina, which is not detected on conventional FFA, which has been implicated in recurrent vitreous haemorrhage and the development and persistence of DME.⁹

As severe reactions can occur following intravenous injection of fluorescein, the indications for FFA in clinical practice have declined, and many of the previous indications have been replaced by OCT. The main use of FFA is to assess retinal, and in particular, macular ischaemia. Resuscitation equipment and medications should be readily available whenever FA is performed, as recommended in other national guidelines.^{21,22} Fluorescein sodium dye is metabolised by the kidneys, and there is some evidence that FFA may have a harmful effect on renal function in some PwDM.²³

Both OCT, and standard and wide-field FFA are used in India. Studies highlight the use of FFA in detecting new vessels not seen clinically, for

delineating the different features of DME, assessing response to treatment and for the other indicators listed above.²⁴⁻²⁶

New technologies

OCT combined with FFA is called OCT angiography (OCTA). OCTA allows simultaneous imaging of the micro-anatomy of the retina and choroid, including blood vessels,²⁷ and is proving extremely useful in delineating pathology and guiding the most appropriate interventions. En-face imaging of different vascular levels within tissues, the non-invasive nature and quick acquisition time make OCTA a very useful adjunct to routine angiography. OCTA can assess most of the changes seen in DR/DME both quantitatively and qualitatively, and can quantify the foveal avascular zone at different levels and vessel rarefaction, allowing good correlation between structure and function.

Although not yet widely available, OCTA is better than FFA in assessing macular circulation²⁵ and is likely to become the gold standard in subsequent clinical trials of DME. OCTA has also been reported in a few studies in India.²⁷⁻²⁹

OCTA, retinal thickness analysis, ultra-wide field imaging, retinal oximetry and adaptive optics are some of the newer technologies which may emerge as useful tools in the assessment of DR and DME in the future.

Table 8.4 Indications for the use of fluorescein angiography (From American Academy of Ophthalmology Guidelines)¹⁸

Situation	Usually	Sometimes	Never
To investigate unexplained loss of visual acuity	•		
To guide laser treatment for DME	•		
To identify suspected but clinically obscure neovascularisation	•		
To identify areas of vitreo-macular traction		•	
To identify large areas of capillary non-perfusion		•	
To rule out other possible causes of macular swelling		•	
To evaluate patients who are difficult to examine for DME		•	
To screen patients with no or minimal DR			•

8.5 PICO question: What diagnostic tests should be used for DR and DME?

Recommendations for practice

- Visual acuity measurement and detailed, dilated fundus examination (preferably by slit lamp biomicroscopy and/or indirect ophthalmoscopy) are essential in the assessment of DR and DME.
- OCT should be used when DME is diagnosed or suspected clinically, to quantify and characterise macular changes. OCT should also be used when the clinical picture and visual acuity do not correlate.
- FFA is indicated when severe NPDR or PDR is suspected, to identify neovascularisation and to assess peripheral and macular vascular competency. Being invasive, FFA can be used when clinical examination and OCT cannot adequately characterise the status of DR and DME.
- Resuscitation equipment/consumables with instructions, must always be available when FFA is being undertaken.
- Ultrasound is an important pre-operative tool for surgical planning.
- Newer investigations such as OCTA and ultra-wide field imaging are useful adjuncts and can be used for better disease characterisation.

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9. Screening for/detecting diabetic retinopathy

Summary

- Screening for DR fulfils the majority of the criteria for a screening programme.
- Screening should be of people known to be diabetic.
- When screening should start is different for different types of diabetes.
- Screening for DR and DME can readily be integrated into the health system at different levels, at locations where people with diabetes access services.
- Retinal imaging, including non-mydriatic imaging systems, has high levels of validity in DR screening.
- The International Council of Ophthalmology criteria for referral at the time of screening are widely used in low and middle income countries.
- Reliable systems need to be in place to ensure the results of screening are communicated to patients in a timely fashion.
- Expertise for the diagnosis and management of DR and DME must be in place before screening is initiated.

In this section screening / early detection of DR and DME is discussed, considering the frequency of screening for different groups of PwDM, how and where this should be done and by whom, who should be referred and the need for documentation, communication and collaboration.

Screening / early detection of DR and DME efforts should focus on people known to be diabetic whether they are attending services in the government, private for profit, or not-for-profit sector, and whether they are attending physicians' or NCD clinics, or eye departments.

Principles of screening

Screening for diabetic retinopathy fulfils the majority of the criteria for a screening programme:¹

1. The condition should be an important health problem.
2. There should be a treatment for the condition.
3. Facilities for diagnosis and treatment should be available.
4. There should be a latent stage of the disease.
5. There should be a test or examination for the condition.
6. The test should be acceptable to the population.
7. The natural history of the disease should be adequately understood.
8. There should be an agreed policy on whom to treat.
9. The total cost of finding a case should be economically balanced in relation to medical expenditure as a whole.
10. Case-finding should be a continuous process, not just a "once and for all" project.

9.1 Timing and frequency of screening for different groups of PwDM

Given the limited data on the incidence and progression of DR in India, the following recommendations have been drawn from guidelines from other countries, most of which are for high income countries, and from ICMR (2018),² the International Council of Ophthalmology (2017),³ VISION2020 India (2015)⁴ and a review of guidelines in Asia.⁵ Other factors to consider are that diabetes is likely to be diagnosed later in India, particularly amongst the poorer sectors and in rural areas, and control of risk factors is also likely to be poorer. The recommendations, are therefore, conservative.

9.2 PICO Question: Who should be screened for DR and when should this start?

Recommendations for practice

- ▶ Type 1 diabetes with an onset before puberty
 - Start screening at 10 years of age.
 - Annual screening thereafter if no or mild NPDR (see 9.4 and 9.5 for indications for referral).
- ▶ Type 1 diabetes with an onset after puberty
 - Detailed eye examination at diagnosis.
 - If no DR, start screening 5 years after diagnosis.
 - Annual screening thereafter if no or mild NPDR (see 9.4 and 9.5 for indications for referral).
- ▶ Type 2 diabetes, including Youth-onset diabetes
 - Start screening at diagnosis.
 - Annual screening thereafter if no or mild NPDR (see 9.4 and 9.5 for indications for referral).

9.3 Imaging grading systems for screening

During screening it is not necessary to make a complete diagnosis, as the purpose of screening is to identify individuals in the “latent stage” of disease i.e., before visual acuity has been lost but where there is a risk of vision loss. This means that simpler grading systems can be used to screen for “referable DR or DME” than are needed during a diagnostic examination by an expert.

How the criteria for referral recommended by the International Council of Ophthalmology relate to the International Classification of Diabetic Retinopathy is shown in Table 9.1.⁶

However, other there are other considerations which influence the referral decision, including whether there is loss of visual acuity (<6/12 in one or both eyes),⁶ and whether other retinal abnormalities are detected. In addition, images may not be gradable despite pupil dilation. The retinal findings in relation to DR and/or DME in combination with these other factors influence the final decision (Figure 9.1).

9.4 PICO Question: Which grading system should be used during screening?

Recommendation for practice

- The grading system developed by the International Council of Ophthalmology be used to grade retinal images obtained during screening.

9.5 PICO Question: What are the indications for referral during screening?

Recommendation for practice

- The indications recommended by the International Council of Ophthalmology be used for referral to an ophthalmologist.
- Referral to an ophthalmologist should also take place for those with reduced visual acuity (<6/12) on one or both eyes, or if other retinal pathology is detected, or if images are not gradable.

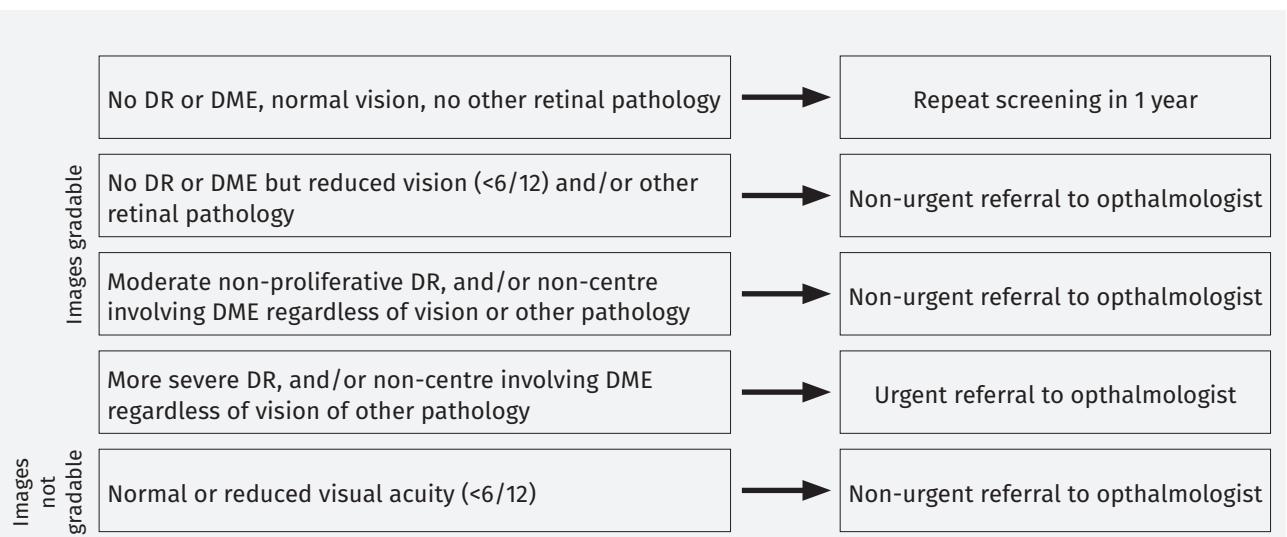
9.6 Validity and diagnostic accuracy of different screening methods

In any screening programme it is important that a high proportion of those with the condition of interest are detected (i.e., high sensitivity) and referred for confirmatory diagnosis, and that a high proportion of those without the condition are classified as being disease free (i.e., high specificity; a low proportion of false positives). The UK National Institute for Clinical Excellence (NICE) guidelines states that a DR screening test should have sensitivity and specificity of at least 80% and

Table 9.1 Relationship between referral criteria recommended by the International Council of Ophthalmology and the International Classification of Diabetic Retinopathy⁶

Diabetic retinopathy	Findings on dilated retinal examination (from the International Classification of DR) ⁷	Referral
No apparent DR	No abnormalities seen	Screen again in 12 months
Mild non proliferative DR	Micro aneurysms only	Screen again in 12 months
Moderate non proliferative DR	More than just micro aneurysms, but less than severe non proliferative DR	Screen again in 6–12 months or refer to an ophthalmologist
Severe non proliferative DR	Any of the following:	Refer to ophthalmologist
	1. Intra-retinal haemorrhages (≥ 20 in each quadrant)	
	2. Definite venous beading (in 2 quadrants)	
	3. Intra-retinal micro vascular abnormalities (in 1 quadrant)	
Proliferative DR	4. No signs of proliferative retinopathy	Urgent referral to ophthalmologist
	Severe non proliferative DR and 1 or more of the following:	
	1. Neovascularisation	
	2. Vitreous / pre retinal haemorrhage	
Diabetic Macular Edema	Findings on dilated retinal examination	Referral
No apparent DME	No retinal thickening or hard exudates in posterior pole	Screen again in 12 months
DME that does not involve the centre of the macula	Retinal thickening or hard exudates in the posterior pole but not involving the centre of the macula	Refer to ophthalmologist, to be seen within 2-3 months
DME that does involve the centre of the macula	Retinal thickening or hard exudates involving the centre of the macula	Urgent referral to ophthalmologist, to be seen as soon as possible

Figure 9.1 Summary of referral criteria taking account of other factors



95% respectively, with a technical failure rate of less than 5%.⁸ The validity of different screening methods has recently been reviewed (Table 9.2).⁹

These studies show direct ophthalmoscopy has low levels of sensitivity and specificity, particularly when not performed by eye care professionals. The studies also show that retinal imaging can give high levels of sensitivity when two or more images are used, and this also applies to image interpretation by non-ophthalmic professionals.

Another, more recent systematic review of 26 clinic-based screening studies, 21 of which were included in a meta-analysis, determined the diagnostic accuracy of detecting any degree of DR using imaging.¹⁰ The highest sensitivity was attained with mydriatic imaging using more than two fields of view (94%; 95% CI 93–96). There was no difference between mydriatic and non-mydriatic imaging after excluding ungradable images (86%; 95% CI 85–87). In these studies the mean proportion of ungradable images in studies using non-mydriatic methods was 18.4% (SE ± 2.2, 95% CI 13.6–23.3%).

The authors conclude that a non-mydriatic, two-field strategy could be a pragmatic approach for facility-based screening in low-income settings, with dilatation of the pupils of those who have ungradable images.¹⁰

There is evidence from other areas of eye care, such as screening for retinopathy of prematurity, that image grading by non-medical personnel can have high levels of diagnostic accuracy.¹¹ This requires competency-based training. Indeed, in the NHS England diabetic retinopathy screening service, all images are graded by non-clinical technicians.¹² A recent study from China shows that non-medical personnel can also accurately detect DR from images.¹³

A recent proof of concept study in India, which used a smartphone retinal imaging system (“Fundus on phone” (FOP) Remidio Innovative Solutions Pvt Ltd, Bangalore) had the following sensitivities and specificities when the images where read by ophthalmologists: any DR, sensitivity 93% (88–96) and specificity 98% (94–100), and for VTDR,

Table 9.2. Screening methods, and validity of screening by different practitioners⁹

Screening method	Practitioners	Outcome measure	Sensitivity (95% CI)	Specificity (95% CI)
Clinical examination				
Direct ophthalmoscopy	General doctor	Any DR	63 (56–69)	75 (70–80)
	Optometrist	Any DR	74 (967–81)	80 (75–85)
	General doctor	Referable DR	66 (54–77)	94 (91–96)
	Optometrist	Referable DR	82 (68–92)	90 (87–93)
Dilated slit lamp examination	Ophthalmologist	Referable DR	87 (84–92)	95 (92–98)
	Optometrist	Referable DR	73 (52–88)	90 (87–93)
Retinal imaging – mydriatic				
1 field 35° – colour	General doctor	Any DR	79 (74–85)	73 (68–79)
	Optometrist	Any DR	88 (83–93)	68 (62–74)
	Diabetologist	Any DR	73 (67–79)	93 (90–96)
2 fields 50° – colour	Retinal photographer	Referable DR	96 (87–100)	89 (86–91)
2 fields 50° – red-free	Retinal photographer	Referable DR	93 (82–98)	87 (84–90)
3 fields 30° – colour	Ophthalmologist	Any DR	95 (87–98)	99 (95–99)
	Medical Officer	Any DR	92 (83–96)	96 (92–98)
Retinal imaging – non mydriatic				
1 field 35° – colour	Trained grader 1	Any DR	72 (66–79)	96 (92–99)
	Trained grader 2	Any DR	64 (57–71)	99 (95–100)
1 field 35° – red free	Trained grader	Referable DR	78	86
Retinal video – colour				
Posterior pole and periphery	Ophthalmologist 1	Any DR	94 (84–98)	99 (95–99)
	Ophthalmologist 2	Any DR	93 (83–98)	95 (89–98)

sensitivity 88% (83–93) and specificity 95% (90–98). However, without further validation this system cannot yet be recommended, but holds promise.¹⁴

Detection of DME during imaging to screen for DR

A recent study showed that visual interpretation of retinal images using three different grading classification systems had positive predictive values of 90.7–91.7% and negative predictive values around 31.9–33.3%, using OCT as the reference standard. This suggests that digital imaging is a reliable, but not very specific means of detecting DME during screening.¹⁵

Tele-ophthalmology

Telemedicine screening for DR is one of the most common uses of this approach.¹⁶ Many programmes for DR screening rely on the remote interpretation of images either by trained non-physician graders, or by eye care professionals. Whilst this approach has the potential to increase the coverage of screening, it is imperative that systems are put in place to manage individuals with ungradable images, that findings are communicated back to the patient who is then counseled about the management decision, and there is close collaboration between relevant sectors of the health system¹⁷ (Figure 9.2). Training of graders

needs to ensure that they achieve high levels of competency, and quality assurance systems must be in place.

New developments in screening

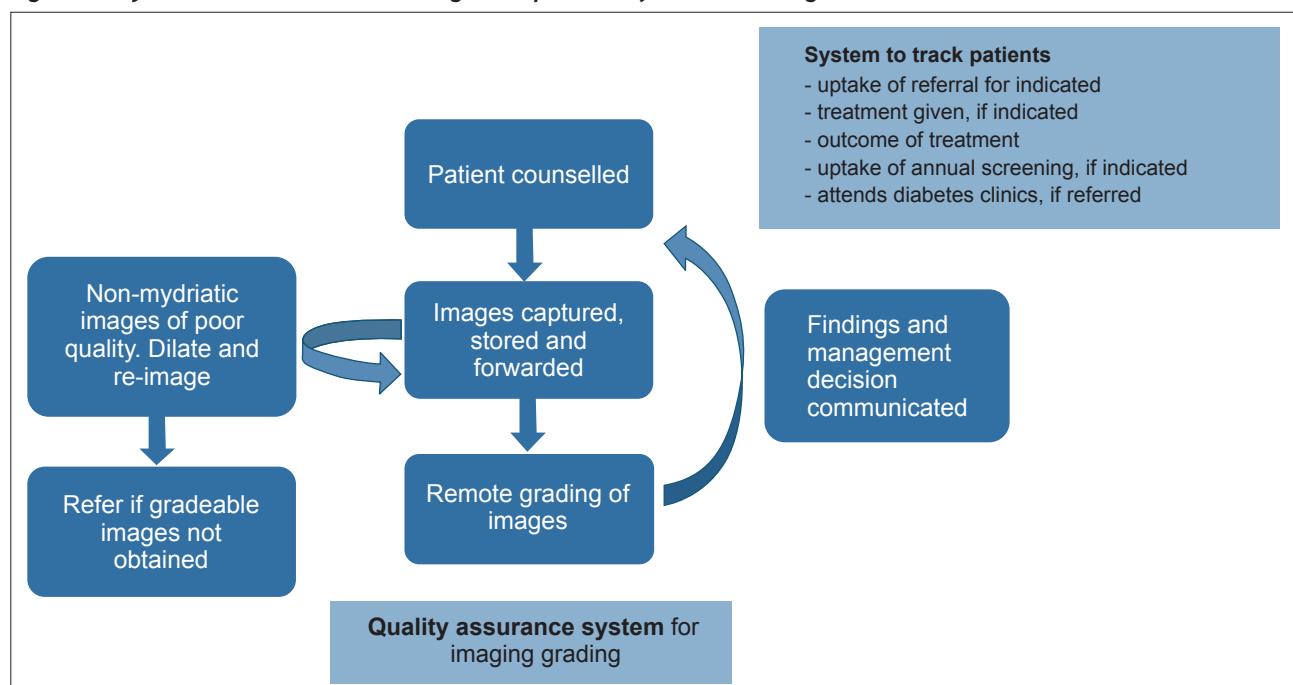
An exciting recent development is the potential for automated image analysis.

Automated image analysis is a very active area of research, and holds promise for the future as it has the potential to improve the effectiveness and efficiency of DR screening,^{18–21} as it has high levels of sensitivity and specificity.²² Several studies have been reported from India.^{23–26}

Many of the current automated imaging systems are imaging-device specific, which limits their usefulness. DeepMind Health is currently pilot testing artificial intelligence systems which could be used to detect DR from images captured from any imaging device.²⁷ This approach has also been used using real-world settings to assess OCT images.²⁸

Automated image analysis has the potential to greatly increase access to screening, as images can be captured by anyone with high enough levels of competency, with almost real-time, valid interpretation of the images, be they photographs of the retina or OCT images of the macula.

Figure 9.2 Systems needed in remote image interpretation for DR screening



9.7 PICO Question: What approaches can be used in India to screen/detect DR: where, by whom and how; which grading systems should be used, and what are the indications for referral for diagnostic examination?

Recommendations for practice for DR screening/detection

- Screening for DR and DME should be of known diabetics.
- Screening should be integrated into services attended by people with diabetes for their diabetes care or eye care.
- Several approaches to detecting DR are recommended for India, as there is not one size which fits all.
- Retinal digital photography (imaging) using validated imaging systems is recommended for screening as it has high levels of sensitivity and specificity and provides documentary evidence.
- Image grading to be undertaken by health personnel trained in grading at the time of imaging, or remotely as soon as possible, and the findings communicated to patients.

Table 9.3 Locations within the health system where screening can take place

	Services for PwDM	Imaging	Pupil dilation	Image grading
Primary care services				
In NCD clinics without eye care services e.g., in PHCs	Yes	Yes	No ^a	Remote grader
In NCD clinics with refraction / primary eye care without a Medical Officer	Yes	Yes	No ^a	Imager /remote grader
In NCD clinics with refraction / primary eye care with a Medical Officer	Yes	Yes	Yes ^b	Imager /remote grader
Secondary /tertiary services				
In NCD /physicians' clinics	Yes	Yes	Yes ^b	Imager /remote grader
In eye departments /hospitals ^d	No	Yes	Yes ^c	Ophthalmologist

a. Not possible as a medically qualified person needs to be present to sanction pupil dilation.
b. If needed, to obtain a good image of the retina.
c. Pupils should be dilated routinely in eye departments / hospitals.
d. Opportunistic screening by an ophthalmologist of all patients known to be diabetic (dilated retinal examination with slitlamp biomicroscopy), regardless of them visiting an eye department with a complaint; to be followed by further investigations as required.

9.8 PICO Question: How many retinal images should be taken when screening using retinal imaging?

Recommendations for practice – see table below

Table 9.4 Assessments to be undertaken during screening

Location	Methods	Field size and number of images	Grading system	Referral
Screening in all non-ophthalmic settings (NCD/ physician's clinics)	Visual acuity measurement Non-mydriatic retina imaging	45° 2 images: centred on macula and optic disc Pupil dilation if required	ICO guidelines	Visual acuity <6/12 in one or both eyes and/ or moderate NPDR or worse, and/or other retinal pathology
Opportunistic screening in eye departments/ clinics	Visual acuity measurement Dilated fundus photography: colour and red-free	30 or 45° 4 images: centred on macula and optic disc, and upper and lower fields	International Classification	Referral may be required to better resourced facilities for investigations/ management

9.9 PICO Question: How should diabetics be counselled before screening?

Recommendations for practice

- The procedures should be fully explained, including that pupil dilation may be required
- Patients should be told how and when they will know about the outcome of screening, and the importance of following the advice they will be given

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10. Management of diabetic retinopathy

10.1 Overview of impact of management of DR and DME

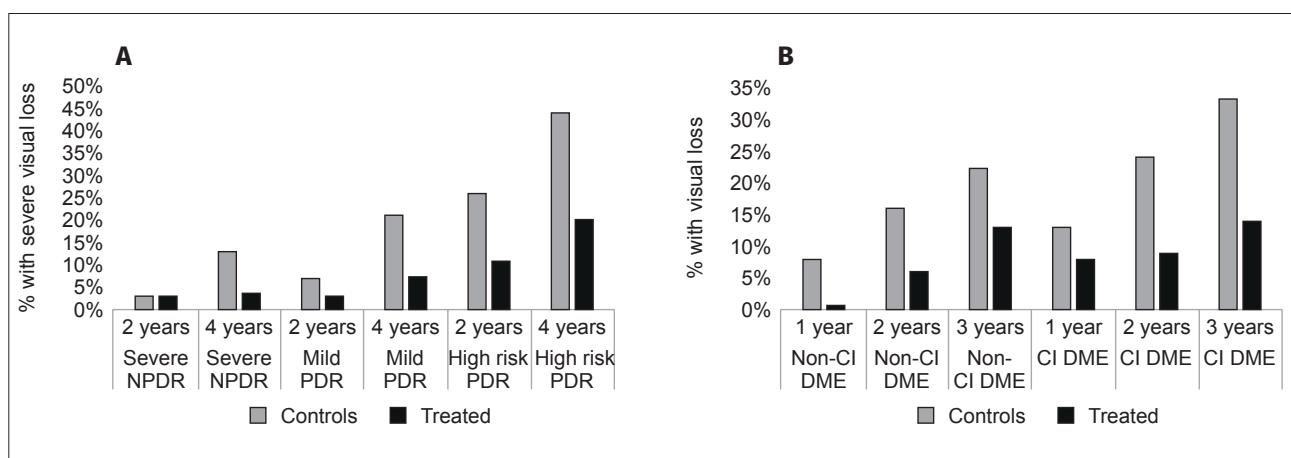
Early treatment of DME and PDR is important as it can prevent severe vision loss or stabilise or improve visual acuity. Findings from two of the important early trials which compared laser treatment with no treatment are summarised in Figures 10.1 A&B)¹⁻⁴

For PDR and severe NPDR peripheral retinal photocoagulation with laser remains the standard treatment. AntiVEGF agents may play a role under some circumstances.

The management of DME, has, however, changed considerably over the last two decades: focal or grid laser photocoagulation was the only treatment available, but now there are a wider range of management options, including intravitreal steroids and AntiVEGF agents. Which option is adopted needs to be based on OCT findings and whether patients are likely to comply with frequent and long-term follow up, as well as the effectiveness of the different agents and the availability of resources to deliver them. The recommendations in these guidelines take all these parameters into account.

There is also evidence that screening and treatment can lead to a reduction in visual impairment. In the UK's English NHS Diabetic Eye Screening Programme, between 2015 and 2016 82.8% of people known to be diabetic and registered with a general practitioner were screened (2.14 million). In England, DR/DME are no longer the leading causes of certifiable blindness among working age adults.⁵

Figure 10.1 Outcome of treatment of A. pre- and proliferative DR (from DRS), B. Centre and non-centre involving diabetic macular edema (from ETDRS)



Management of diabetic retinopathy

Summary

- There is high level evidence that laser panretinal photocoagulation for PDR and severe NPDR preserves vision. The complications are well described.
- Repeated injections of AntiVEGF agents can also be effective for PDR. The complications are well described.
- Which treatment is recommended for an individual patient is influenced by several factors, but principally their ability to comply with the frequent and longterm follow up required for AntiVEGF agents.
- There is good evidence that vitrectomy is of benefit for vitreous haemorrhage but less clear for the other forms of advanced DR.

10.2 Efficacy of laser treatment

There have been a number of landmark randomised clinical trials for the treatment of DR using pan-retinal photocoagulation (PRP). The Diabetic Retinopathy Study (DRS) randomised individuals between 1972 and 1975 with PDR to PRP using xenon arc or argon laser treatment, or no treatment.⁴ In this trial, treatment reduced severe visual acuity loss (defined as visual acuity 5/200 or worse) by approximately 50% compared to no treatment over five years of follow-up. In the Early Treatment of Diabetic Retinopathy Study (ETDRS), individuals with mild-to-severe non-proliferative or early PDR were randomised to immediate or deferred treatment.^{1,2} In this trial, earlier treatment was associated with a 20% lower risk of loss of vision.

Evidence from these and later trials are summarised in a recent Cochrane review and meta-analysis.⁶ Five trials were included, three were conducted in the USA (DRS, 1978; ETDRS, 1991, Yassur, 1980), one in the UK (Hercules, 1977) and one in Japan (Sato, 2012).

The trials recruited patients with varying degrees of DR: PDR alone, PDR and severe NPDR, or severe NPDR only. The DRS trial compared laser treatment for PDR with placebo; ETDRS compared early treatment (i.e., for severe NPDR or early PDR) with treatment of high risk PDR. Most trials used argon laser PRP, whereas in one trial, only ischemic areas of peripheral retina were treated. All had some degree of bias, particularly in relation to masking of the assessment of outcomes and attrition.

Using data from four of the trials (99% of participants), treatment reduced severe vision loss (best corrected acuity of <6/60) by over 50% at 12 months (RR 0.46, 95% CI 0.24–0.86)(moderate quality evi-

dence). There was a significant reduction in the progression of DR (RR 0.49, 95% CI 0.37–0.64) and the occurrence of vitreous haemorrhage (RR 0.56, 95% CI 0.37–0.85)(low quality evidence).⁶

Long-term follow up of subset of the EDTRS trial (13–19.5 years) showed good preservation of vision with 42% having normal vision (6/6) and 84% having a visual acuity of 6/12 or better.⁷

A study (non-randomised) of laser PRP for severe NPDR or early PDR but without DME compared laser treatment at one session with four sessions in 155 eyes. There was no appreciable clinical difference in visual acuity or central foveal thickness at 34 weeks.⁸

Different types of lasers

A range of different lasers are available to treat retinal conditions, including DR, such as argon, krypton, dye, diode lasers, ruby and Nd:YAG. (Reviewed in NHMRCGA⁹) The lasers vary in a number of ways i.e., wavelength and tissues which absorb the laser energy, mode of delivery, spot size, degree of pain etc.

Recent developments in laser technology

Lasers are able to deliver several laser spots simultaneously (e.g., PASCAL, Pattern Scan Laser), there are navigated laser delivery systems (e.g., Navilas) and subthreshold micropulse lasers are now available¹⁰ (Table 10.1).

The PASCAL laser uses shorter duration laser pulses (10-30 ms) than conventional laser, and delivers laser spots in patterns delivered with one foot pedal-push. PASCAL PRP has better precision and less pain.¹¹ The Manchester PASCAL randomised control trial reported favourable

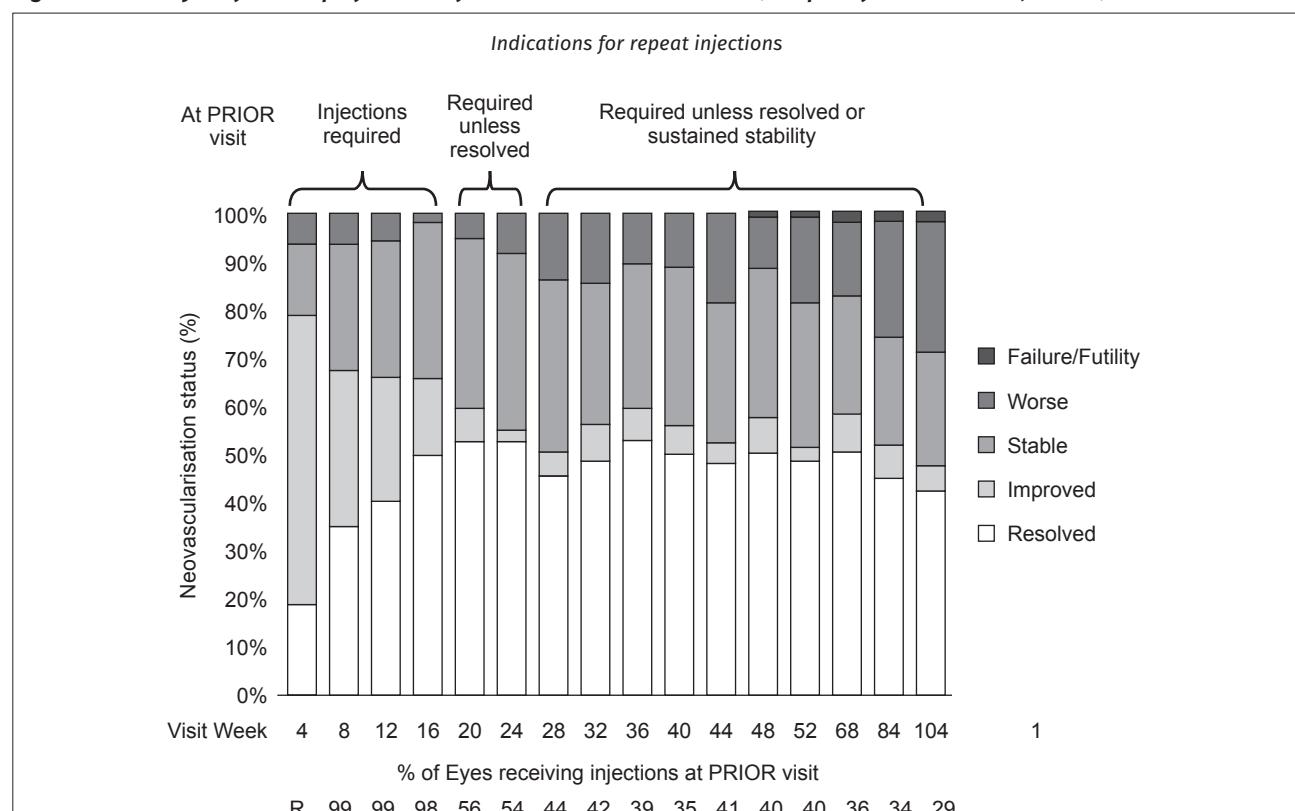
clinical, anatomical and functional outcomes with a single session of short pulse (20ms) multispot PRP compared with single spot higher pulse (100ms), multiple session PRP. The efficacy and safety of PASCAL laser for treating PDR has been established in multiple studies.¹¹⁻¹⁴ PASCAL using wide-field imaging delivered to selected areas of peripheral

retinal ischemia has shown good clinical efficacy with less increase in central macular thickness.¹⁵ Navigated laser systems, such as NAVILAS-OD-OS, deliver targeted photocoagulation using wide-field imaging, and sub-threshold diode microsecond laser for PRP.¹⁶ NAVILAS provides multi-modal imaging integration along with eye tracking, the

Table 10.1 Comparison of newer forms of laser treatment compared with conventional laser^{12, 13, 16-18}

Parameter	Conventional laser	PASCAL	NAVILAS
Efficacy	Proven	Proven	Not reported
Impact on DME	Worsening documented	No change noted	Not reported
Advantages	Economical Accessible	Less painful Cost-effective as single sitting treatments Efficacy well established in advanced PDR	Least painful Safe as no image inversion Integrated multimodal imaging Documented treatment sittings
Disadvantages	Painful Adverse effects like exudate and choroidal detachments Low accuracy	Cost Image inversion Lack of eye tracking Documentation variable	Cost
Time to treat each eye	59.3 minutes/session 3 sittings needed	15 minutes/session: 2-3 sittings needed	8.5 minutes/session: 2-3 sittings needed

Figure 10.2 Five year follow up of status of PDR in the Protocol S trial (adapted from Sun et al., 2019²⁶)



option of microsecond laser, better accuracy and shorter treatment. NAVILAS is associated with even less pain than PASCAL.^{17,18}

Sub-threshold diode microsecond laser, which does not damage the retinal pigment epithelium, has yielded promising results in the management of PDR¹⁹⁻²¹ and DME.^{20,22,23} This form of laser can safely retreat areas of the retina and as there is less inflammation, pre-retinal fibrosis and contraction.

10.3 Efficacy of AntiVEGF agents for PDR

The treatment of PDR with AntiVEGF agents requires multiple injections, often monthly for a year or longer.

A Cochrane review (2014) included eight trials which recruited individuals eligible for PRP.²⁴ The trials compared AntiVEGF agents with or without PRP with PRP alone (PRP was given, if required in the AntiVEGF only arms). The review showed low quality evidence in favour of AntiVEGF agents in terms of disease regression, and there was no difference in complication rates.

Further trials have since been reported, which used AntiVEGF agents (CLARITY and DRCR Protocol S). The CLARITY trial reported that repeated injections of Aflibercept gave better outcomes in terms of visual acuity, regression of neovascularisation, development of DME, vitreous haemorrhage and need for vitrectomy.²⁵ Results from the DRCR Protocol S trial at 5 years showed regression in of PDR in 43% at 2 years (Figure 10.1).²⁶

Four of the trials designed to investigate AntiVEGF agents for the treatment DME also reported regression and slowing of the progression of DR in treated eyes with Ranibizumab (RISE and RIDE trials); Aflibercept (VIVID and VISTA) and all three agents (Protocol T).²⁷ However, these findings need to be interpreted with caution as in these trials these eyes were not randomised on the basis of their DME status.

However, despite these promising results, PDR can progress once AntiVEGF agents are discontinued whereas the effects of laser are longer lasting. Importantly, repeat AntiVEGF agents was not associated with better visual acuity outcomes.²⁶

The need for prolonged, frequent follow-up with AntiVEGF agents, particularly in the first year, the lack of a defined end point for treatment or follow-up, a 30% worsening of retinopathy despite treatment, and the contraindication in the presence of pre-existing traction are factors which need to be taken into account when considering AntiVEGF injections for PDR, in addition to the cost implications.

The advantages and disadvantages of laser and AntiVEGF agents are shown in Table 10.2.

Combined laser and AntiVEGF agents

Laser PRP for severe NPDR can lead to DME and several trials have explored the impact of intravitreal injection of AntiVEGF agents one week or immediately before laser PRP.²⁸⁻³¹ The trials report positive benefits in terms of greater resolution of new vessels and/or less DME, but all trials were small with limited follow up.

Table 10.2 Advantages and disadvantages of AntiVEGF agents and laser PRP

	AntiVEGF agents	Laser
Number of procedures	Repeated injections in year one, declining thereafter.	Can be performed in 1-2 visits. Retreatment required if incomplete regression.
DME	Less DME than with laser.	More DME than AntiVEGF agents.
Follow up	Multiple visits (monthly) in first year.	First follow up at 3-4 months or earlier.
Visual acuity	Better visual outcomes.	Poorer visual outcomes.
Other procedures	Less PRP and fewer vitrectomies.	May need Anti-VEGF injections for DME.
Adverse events	Invasive, with risk of complications such as cataract and endophthalmitis.	Non-invasive. Low risk of serious adverse events.
Cost effectiveness	Ranibizumab is cost-effective vs laser PRP if DME is also present.	PRP is more cost-effective if no central-involving DME.

10.4 Efficacy of vitrectomy for advanced DR

Indications for vitreous surgery include eyes with PDR which does not respond to aggressive laser PRP, non-resolving retinal haemorrhage, recent (less than six months) tractional retinal detachment (TRD) involving the macula, progressive TRD which threatens the macula, and tractional rheumatogenous detachment.^{32,33} Early vitrectomy may have a role in severe PDR, and should be undertaken in people with Type 1 DM who have severe vitreous haemorrhage within one month to enable endo-photocoagulation if required.^{34,35}

A systematic review and other studies show that pre- or perioperative AntiVEGF agents may reduce post-operative haemorrhage and are safe.^{36,37} It is important to note that the interval between anti-VEGF injections and surgery should be kept at bare minimum (around one week) to avoid worsening of traction.³⁸

New surgical techniques and instrumentation for vitreoretinal surgery are making the procedure safer, with fewer complications.

Only Bevacizumab is on WHO'S 2017 Essentials Drugs List.³⁹

10.5 Side effects and complications of treating DR

Table 10.3. Side effects and complications of treatment of DR (From AAO Guidelines⁴⁰)

Treatment	Side effect/complication
Panretinal photocoagulation (scatter) for NPDR or PDR ⁴¹	<ul style="list-style-type: none"> Transient central vision loss from macular edema Peripheral visual field constriction with delayed dark adaptation Vitreous haemorrhage if neovascularisation is present Reduced or compromised accommodation Pupillary dilation (mydriasis)
Vitrectomy for PDR ⁴²	<ul style="list-style-type: none"> Recurrent vitreous haemorrhage Retinal tear or detachment Vision loss Infectious endophthalmitis Cataract
Anti-VEGF agents ²⁶	<ul style="list-style-type: none"> Cataract, retinal tear and endophthalmitis Worsening of traction Thrombo-embolic events** Intraocular inflammation

**The network analysis outlined above reviewed three systemic adverse events following use of three different AntiVEGF agents in comparison to laser treatment.⁴³ No increase in risk was identified.

10.6 PICO Question: What are the indications for and optimal treatment modality for PDR?

Table 10.4 Recommendations for treatment of PDR and severe NPDR by level of patient compliance and DME status. From the Guidelines for the Prevention and Management of Diabetic Retinopathy and Diabetic Eye Disease in India, June 2019 (www.iapb.org)

Type of DR	DME status	Patient likely to comply with follow up	Patient not likely to comply with follow up
PDR	No DME	<ul style="list-style-type: none"> Laser PRP^a or AntiVEGF monotherapy within four weeks.^a Consider AntiVEGF injection one week before laser PRP to prevent DME.^b 	<ul style="list-style-type: none"> Laser PRP a within four weeks. Consider AntiVEGF injection one week before laser PRP to prevent DME.^b
	DME present*	<ul style="list-style-type: none"> AntiVEGF injection before panretinal photocoagulation.^b 	<ul style="list-style-type: none"> Laser PRP and focal/grid laser to the macula.^a
Severe NPDR**	No DME	<ul style="list-style-type: none"> Regular follow up. 	<ul style="list-style-type: none"> Laser PRP.^a
	DME present*	<ul style="list-style-type: none"> AntiVEGF or steroid injections.^a 	<ul style="list-style-type: none"> Scatter laser PRP and focal/grid laser to macula.^a

*See Chapter 11. **See next page (a) Level I evidence, (b) Level II evidence.

10.6 PICO Question: What are the indications for and optimal treatment modality for PDR?

► 1. Severe pre-proliferative DR

Recommendations for treatment

- Consider laser PRP for severe NPDR for individuals who are not likely to comply with regular follow up (every three months) and/or if the other eye has poor vision (Level I).

► 2. Severe pre-proliferative DR and PDR

Recommendations for practice following laser PRP

- First follow up should be at three to four months – ideally at two months, as the four months recommended in Protocol S may not apply in India.
- PDR: Retreatment is required if vessels have not regressed, or further new vessels develop.

Recommendations for practice following AntiVEGF monotherapy for PDR

- Frequent, regular, follow up i.e., every two to three months for at least a year is an essential prerequisite for the treatment of PDR with AntiVEGF agents.
- Repeat injections, if required.

► 3. Vitrectomy

Recommendations for treatment

- Early vitrectomy (within three months) is indicated for people with Type 1 DM who develop severe vitreous haemorrhage in whom severe PDR is suspected (Level I).
- Consider early vitrectomy in eyes where PDR does not respond to extensive and aggressive laser PRP (Level II).
- Consider vitreoretinal surgery to relieve vitreoretinal traction if the macular is detached or threatening to detach, to salvage some vision (Level IV).
- Consider an intravitreal injection of an AntiVEGF agent within a week of vitrectomy to reduce the risk of intraoperative complications (Level I).
- Consider combined cataract surgery / vitrectomy in eyes with DR and/or DME with lens opacities, to enable subsequent management of PDR and/or DME.

Recommendations for practice

- Counselling patients before treatment, regarding improving the control of their diabetes and comorbidities is essential.
- The procedure should be explained, including the likely outcome as well as the need for and timing and frequency of follow up, the likelihood of repeat treatment and the need for lifelong care.

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11. Management of diabetic macular edema

Summary

- Treatment of DME has evolved over time with the advent of new diagnostic techniques which have led to a revised classification of DME and a greater understanding of the pathogenesis and different types, and the indications for treatment.
- If suspected clinically, ischemic maculopathy should be excluded, as treatment can aggravate visual loss.
- There is evidence from a randomised clinical trial that DME with good visual acuity can be managed conservatively, with treatment if there is progression with loss of vision.
- A wide range of management options are available for DME i.e., focal or macular grid laser photocoagulation, intravitreal steroids and intravitreal AntiVEGF agents, alone or in combination.
- There is a good evidence that laser focal/macular grid photocoagulation can stabilise or even improve vision.
- There is good evidence of the benefits of intraocular steroids but follow up is needed to monitor intraocular pressure and cataract formation.
- There is good evidence that AntiVEGF agents can improve vision, but treatment needs to be repeated, with frequent follow up.
- Vitrectomy can be of benefit in the presence of vitreomacular traction, but cataract can develop or progress.
- The treatment offered needs to be tailored to the specific circumstances of the patient.

11.1 Sources of evidence

Diabetic Retinopathy Clinical Research Network (DRCRN) have undertaken a range of clinical trials of these management options over the last decade (See Appendix 1). Evidence for the effectiveness of different interventions for DME are summarised in the European Guidelines for the management of DME (2017),¹ and a large number of trials of different agents for DME have been undertaken over the last decade (Figure 11.1).²

Visual acuity in eyes with DME as an indicator for treatment

Until recently there has been little evidence on how to manage eyes with proven DME but where the visual acuity is good. This was addressed in the Protocol V trial of the DRCRN in which eyes with DME with a visual acuity of 6/9 (20/25) or better (702 eyes) were randomised to observation or focal/grid laser or Aflibercept as frequently as every four weeks.³ Eyes losing 10 or more letters during follow up in the observation or laser arm were treated with Aflibercept. At two years, 75% and 64% of eyes in the laser and observation groups respectively, received no further treatment, and there was no difference between treatment arms in visual acuity.

This trial suggests that observation is a reasonable strategy for DME with good visual acuity.^{3,4} Similar findings have been reported from an observational study.⁵

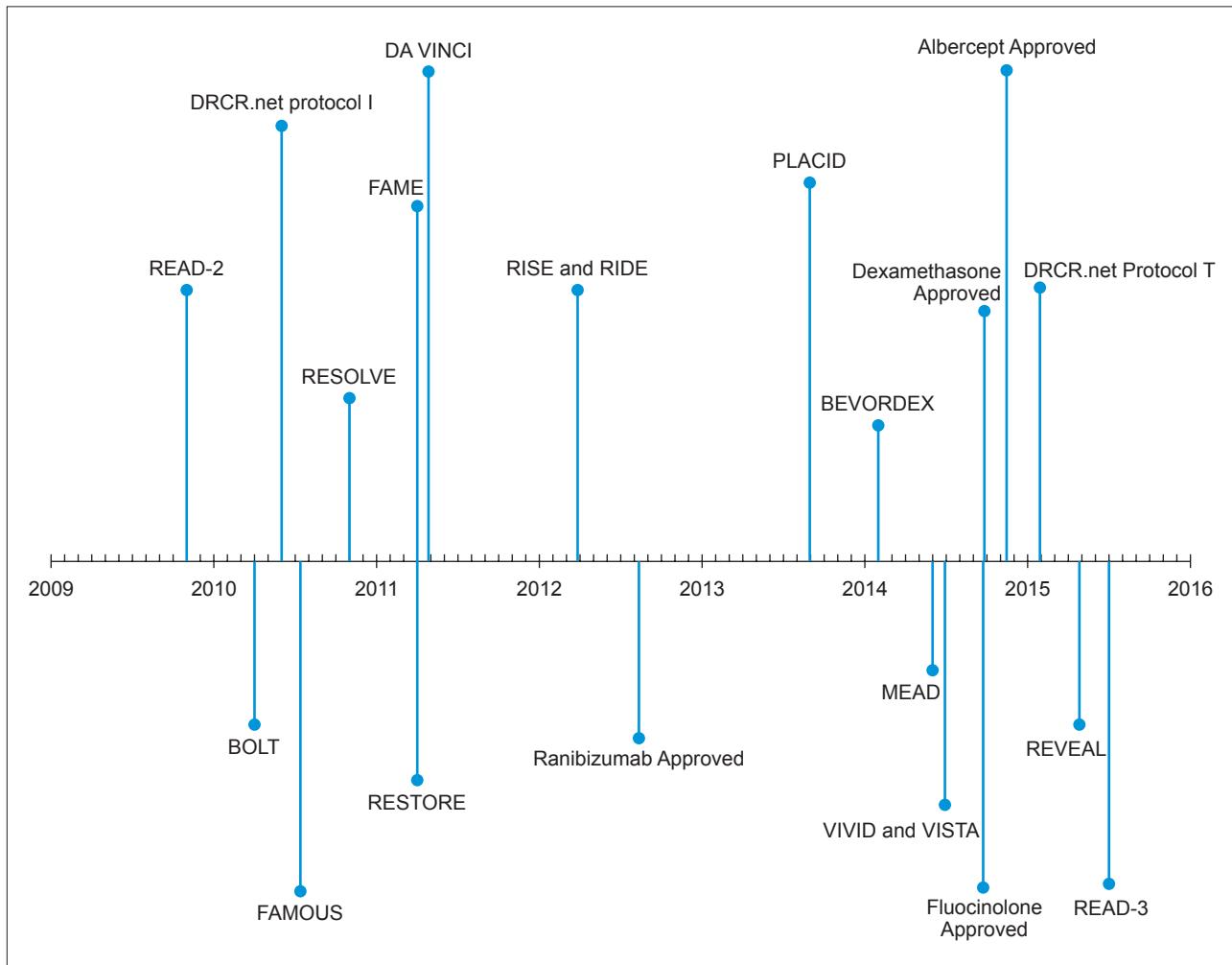


Figure 11.1 Timeline of trials of different treatment modalities for DME²

11.2 Indications for and efficacy of laser treatment for DME

The ETDRS trial of focal or grid laser photocoagulation of the macula for “clinically significant DME” prevented moderate visual loss, but the trial did not report on improvement in visual acuity.⁶ However, in these early trials treatment was often repeated and the intensity of the laser applications led to complications such as paracentral scotomas and choroidal neovascularisation. Mild macular grid laser treatment has been shown to give comparable results with fewer complications (Protocol A, DRCRN).⁷ A further study demonstrated that eyes with centre involving DME where the DME lessened but did not resolve after one session of laser treatment continued to improve over 32 weeks with no further treatment (Protocol K, DRCRN).⁸ Another study which treated non-centre

involving DME with focal or grid laser treatment reported no change in median visual acuity; vision improved by ≥ 5 letters in 32% of eyes but declined in 18%.⁹

In a recent Cochrane review (2018), 24 clinical trials of laser treatment were identified. Most were conducted in Europe (nine studies) and USA (seven), with other studies in Asia (four) and one each in Africa, Latin America, Europe and Asia, and Oceania.¹⁰ Four studies compared laser with no treatment; other trials compared standard treatment with subthreshold treatment (i.e., nonvisual conventional, micro-pulse and nano-pulse), or compared different types of macular grids, or different types of lasers.

In the first group of studies, treated eyes were significantly less likely to lose visual acuity than those than eyes that were not treated (RR 0.42, 95%

CI 0.20–0.90). There was some evidence that laser treatment led to partial or complete resolution of DME compared with no treatment at one to three years. The other trials did not provide conclusive evidence of the benefit of one intervention or laser type over the other, although subthreshold laser treatment may be superior to threshold.¹⁰

New lasers, such as sub-threshold micropulse diode (SDM) laser and selective retinal therapy (SRT) hold promise in terms of safety, efficacy and less tissue damage, although SRT is not yet available commercially.¹¹

11.3 Indications for and efficacy of intraocular steroids for DME

Intraocular steroids for longstanding or refractory DME include intravitreal injection (IVI) of triamcinolone, and intravitreal implants (IVIm)/drug delivery systems of fluocinolone and dexamethasone. [Reviewed in Schmidt-Erfurth U, et al. 2017]

In a Cochrane review (2013), seven trials were identified: four investigated IVI triamcinolone and three studied IVI/drug delivery systems.¹² In the first group of trials, treated eyes had significantly better visual acuity than untreated eyes at all time points during follow-up (three to 24 months). The relative risk (RR) for one or more lines of improvement in acuity was 2.85 (95% CI 1.59 to 5.10) at three months and 2.17 (95% CI 1.15 to 4.11) at 24 months.

Several other trials have been published since the Cochrane review. In one trial, eyes with DME were randomised to sham injections, or dexamethasone implants of 0.7 or 0.35 mg.¹³ At three years a significantly higher proportion of implanted eyes had gained ≥ 15 letters compared with sham injections (22%, 18.0% and 12% respectively). The mean number of treatments were 4.1, 4.4 and 3.3, and cataract developed in 68%, 64% and 20% in the 0.7 mg, 0.35 mg implant and sham groups, respectively. IOP was controlled medically in all but three eyes which required trabeculectomy (two 0.75 mg; one 0.35 mg).

In the IRGREL-DEX retrospective study, eyes with untreated DME, or with DME refractory to AntiVEGF agents, were treated with dexamethasone 0.7 mg or 0.35 mg implants.¹⁴ At two years, visual acuity had improved in both groups, with greater improvement in treatment of naïve eyes.

A case series from India gave promising results with dexamethasone implants for refractory DME,¹⁵ and a small trial of subtenons triamcinolone plus grid laser gave improvement in diffuse DME in the short term compared with grid laser alone.¹⁶

OCT biomarkers, such as hyper-reflective foci, cystoid spaces with hypo-reflective content and neurosensory detachment are indications for intravitreal steroids.¹⁷ Complications of intravitreal steroids include cataract and raised intraocular pressure.

11.4 Indications for and efficacy of AntiVEGF agents for DME

A large number of trials of different agents for DME have been undertaken over the last decade (Figure 11.1). Details of the trials are found in the Guidelines for the Management of Diabetic Macular Edema by the European Society of Retina Specialists (EURETINA) (2017).¹

A summary of the trials of AntiVEGF agents is shown in Appendix 2.^{18–27}

A recent Cochrane review (2018) of 24 trials used network analysis to compare different agents.²⁸ Network meta-analyses synthesise networks of direct and indirect comparisons of interventions, and enable researchers to simultaneously assess the effects of more than two interventions for the same condition.²⁹

This approach is considered to provide the highest levels of evidence of effectiveness. In this Cochrane review the main comparisons were for treatment of DME with Aflibercept (x3 trials), Bevacizumab (x8) and Ranibizumab (x14), and included the following trials: BOLT, Da Vinci, RELATION, RESOLVE, RESPOND, RESTORE, RISE-RIDE, READ, DRCR.net and LUCIDATE. The comparator arms were laser or sham injections. 41–64% of eyes were also treated with laser.

All three agents gave better improvement in vision (by three or more lines) than laser alone at one year, with rate ratios ranging from 2.47 for Bevacizumab to 3.66 for Aflibercept. These differences were not statistically significant (RR 1.11, 95% CI 0.87–1.43). Ranibizumab may have been more effective in reducing central retinal thickness at one year. There was no difference between agents in terms of serious systemic adverse events.²⁸

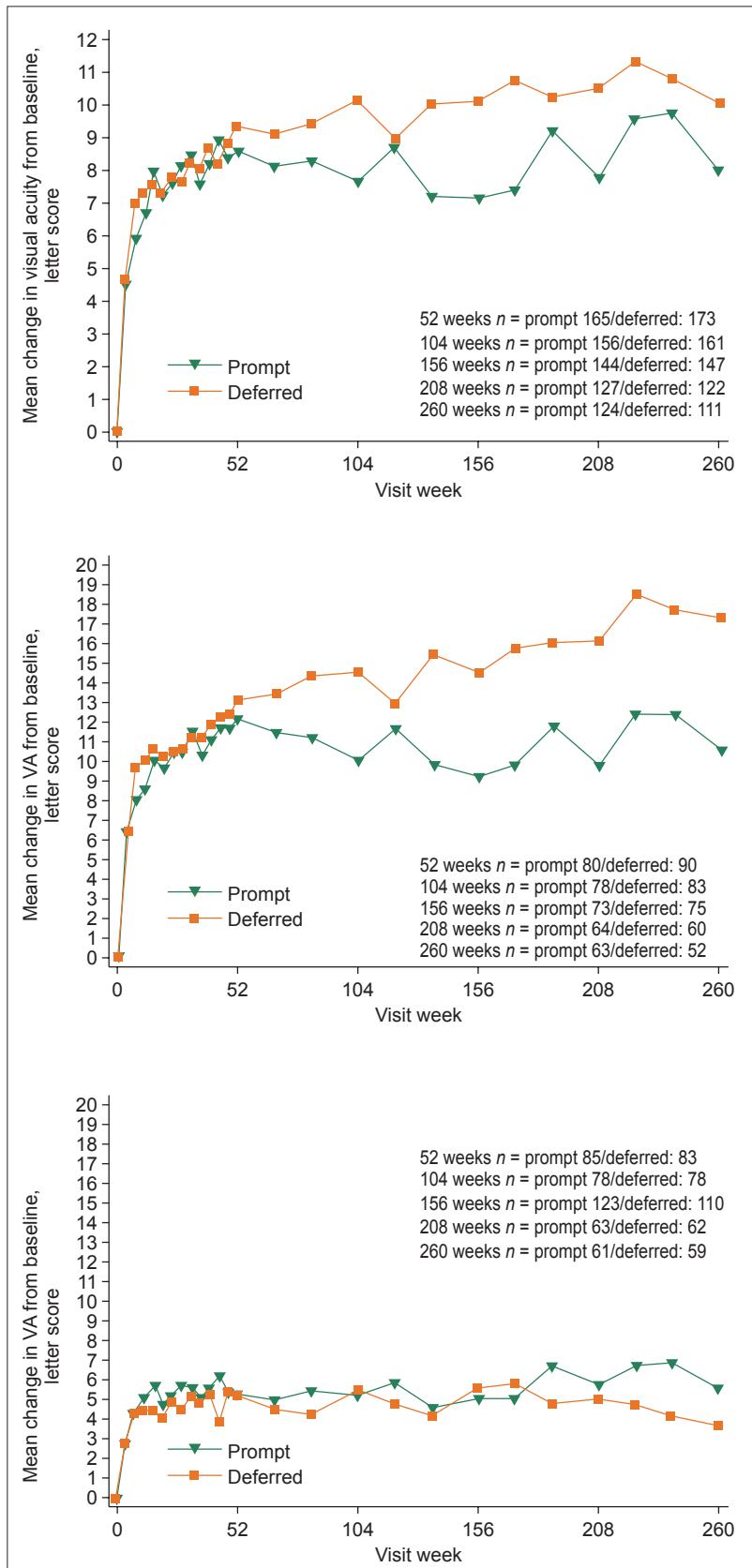


Figure 11.2 Change in visual acuity in DRCR Protocol I trial over five years follow, overall (top graph) worse (middle) and better visual acuity²⁰ (bottom).

A summary of the Cochrane review is that three to four of every 10 patients treated with AntiVEGF agents gained three or more lines of visual acuity at one year.

Since the Cochrane review a few other trials have been undertaken, and longer term outcomes of some of the included trials have also been reported.

In a small trial DME treatment-naïve eyes were treated with Bevacizumab with early or deferred macular grid laser treatment (one session only).³⁰ At five years there was no difference in visual acuity between the two groups.

In the trial which compared Ranibizumab with immediate or deferred laser, all eyes improved in the short term.²⁰ Those with worse baseline vision did better with immediate laser than those with deferred laser and better baseline vision at five years follow up (Figure 11.2). In this trial, eyes which did not respond to at least six injections of Ranibizumab were randomised to intravitreous dexamethasone or sham injection. There was no improvement in dexamethasone treated eyes.³¹

In the trial which compared all three AntiVEGF agents, with laser treatment if required (Protocol T, DRCRN), data at two years showed that in eyes with better pre-treatment vision there was no difference between agents overall.²⁶ Eyes with worse vision at baseline treated with Aflibercept had greater improvement (Figure 11.3). The rate of systemic adverse events, including vascular events, were comparable in all three treatment groups.

Several other trials are being conducted by the Diabetic Retinopathy Clinical Research network to assess the efficacy and safety of different treatment modalities for DME [See Diabetic Retinopathy Clinical Research Network website³²].

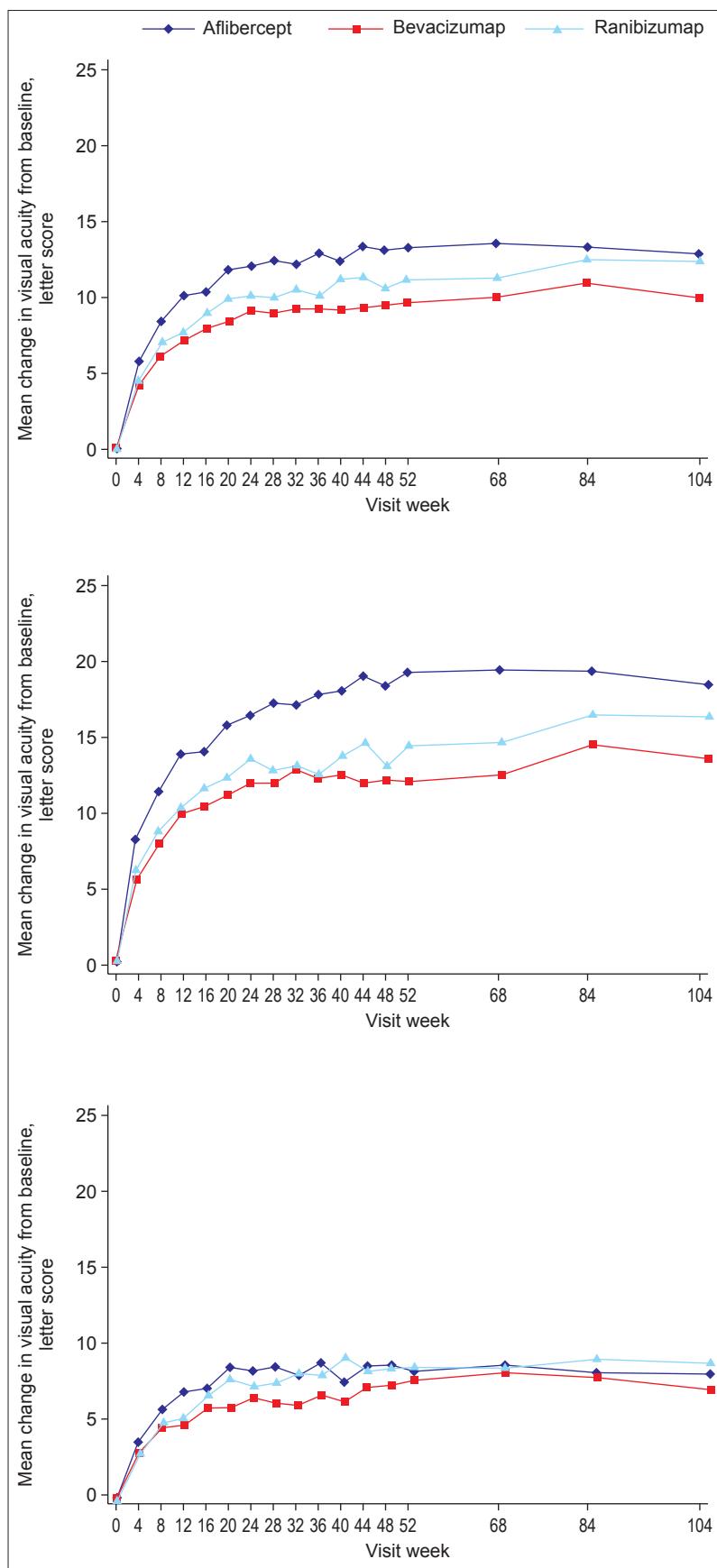


Figure 11.3. Change in visual acuity over time from the DRCR.net Protocol T study all participants (top graph); worse baseline vision (VA < 20/50) (middle); and better baseline vision (VA 20/32-20/40)²⁶ (bottom).

11.5 Indications for and efficacy of steroids combined with AntiVEGF agents

A Cochrane (2018) review included 8 trials of different AntiVEGF agents in combination with steroid preparations.³³ The conclusion was that combined treatment offered no clinical benefit in terms of improvement in visual acuity and signs of DME, but there was a greater risk of steroid induced complications.

The BEVORDEX trial, which was included in the review, compared the efficacy and safety of Bevacizumab versus dexamethasone implant for previously laser treated DME patients.³⁴ The visual acuity gains were comparable in the two groups, but dexamethasone treated eyes had fewer injections, and greater reduction in central macular thickness. Exudate area was also lower in the dexamethasone treated eyes.³⁵

In an observational study of eyes with hard exudates within 3mm of the fovea, hard exudates resolved with dexamethasone, with thinning of central retinal thickness but with no change in visual acuity.³⁶

11.6 Efficacy of combined treatments for DME

In the Protocol I trial of the DRCR, laser treatment alone (with sham injections) or in combination with intravitreal Ranibizumab (with prompt or deferred focal/grid laser treatment) or triamcinolone (with prompt laser) were compared for centre involving DME (four treatment groups).³⁷ At two years eyes treated with Ranibizumab with deferred laser had the best outcomes with a mean improve in visual acuity of 10 letters (Figure 11.4). Eyes treated with prompt laser alone had a mean improvement of 3 letters. Approximately 20% of eyes treated with triamcinolone and prompt laser lost a mean of 10 or more letters compared with 15% of laser only treated eyes.

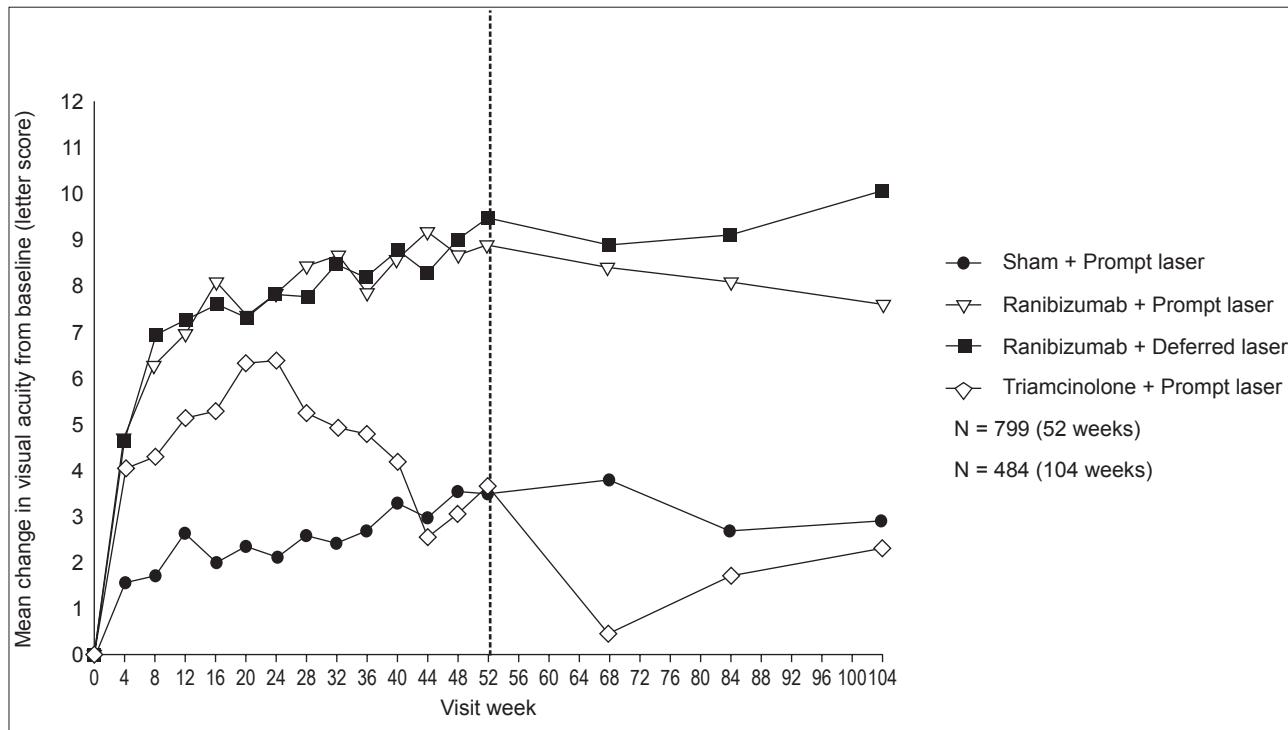


Figure 11.4 Mean change in visual acuity over a two-year follow-up in the Protocol I trial³⁷

Ranibizmab treated eyes had an average of eight to nine injections, and triamcinolone eyes had approximately three injections. Cataract surgery was much more frequent among eyes receiving triamcinolone and was lowest for laser alone. This trial demonstrates that laser alone remains a useful treatment for DME.

11.7 Indications for and efficacy of vitrectomy for DME

A systematic review and meta-analysis identified 11 trials which had different interventions and comparison groups.³⁸ The review concluded that vitrectomy gave better structural but not functional outcomes at six months than observation, with similar findings compared with laser. At 12 months vitrectomy was no longer associated with better structural outcomes, and had worse functional outcomes than laser. Similar findings were reported in a more recent review (2017) which concluded that vitrectomy is not indicated in the absence of vitreoretinal traction.³⁹

However, a large case series of eyes undergoing vitrectomy for DME with evidence of vitreo-macular traction had different findings.⁴⁰ Additional procedures during vitrectomy included membrane peeling (61%) internal limiting membrane peeling

(54%), PRP (40%) and injection of corticosteroids (64%). At six months 68% of eyes had at least a 50% reduction in central retinal thickness. Visual acuity improved by ≥ 10 letters in 38% and deteriorated by the same amount in 22%. Postoperative complications included retinal detachment (three eyes), vitreous haemorrhage (five eyes), raised IOP (seven eyes) and endophthalmitis (one eye).

Internal limiting membrane peeling can give some improvement in visual acuity in eyes where focal/grid laser has failed.⁴¹

Summary of vitrectomy for DME

- Vitreous traction may aggravate an underlying tendency for DME, and if severe may be the main cause.
- Some degree of traction occurs in 12% of eyes with DME.³⁹
- Indicators for surgical intervention in DME include evidence of epiretinal membranes, a taut posterior hyaloid and vitreo-macular traction.
- Studies report visual gains with reduction in macular thickness at three and six months, but a number of eyes lose vision and there are complications associated with surgery.

11.8 Efficacy of topical and systemic treatment for DME

Topical non-steroidal anti-inflammatory agents, which tend to be used for pseudophakic DME, have not been investigated in clinical trials.

The importance of controlling systemic factors for DR, such as hyperglycaemia and hypertension, have been outlined in earlier sections.

As DR and DME (particularly ischemic maculopathy and neurosensory detachment), are associated with poor renal function,^{42,43} patients should be assessed and referred for management, which might include enhanced control of glycaemia and hypertension and smoking cessation, and pharmacological agents such as renin-angiotensin system (RAS) inhibitors.⁴⁴ Lipid lowering agents should also be considered, particularly for individuals with dyslipidemia and hard exudates at the macula, as they has been shown to be of benefit in small case series.⁴⁵⁻⁴⁷ In the Protocol T trial, better control of HbA1c was associated with better visual acuity outcomes following treatment with AntiVEGF agents.⁴⁸

Counselling should therefore emphasise the impact of better control on visual outcomes.

11.9 Advantages, disadvantages and complications of the management options for DME

These are summarised in Table 11.1 (See next page).

Treatment of DME recommended for India

Recommendations for treating DME in India were agreed by a consensus of experts in 2016⁵² (Figure 11.5) and have been adapted below for different settings and patients in these Guidelines (Table 11.2).

In addition to likely effectiveness, which treatment is offered for the treatment of DME is influenced by two broad factors: the resources available, in terms of expertise, equipment, access to medication and cost, and the likelihood that patients will comply with repeated injections (AntiVEGF agents or steroids), and with the long-term follow up needed to monitor the condition and assess complications. The recommendations below take these variables into account.

IMPORTANT NOTE:

Treatment should be considered ONLY after excluding ischemic maculopathy. Fluorescein

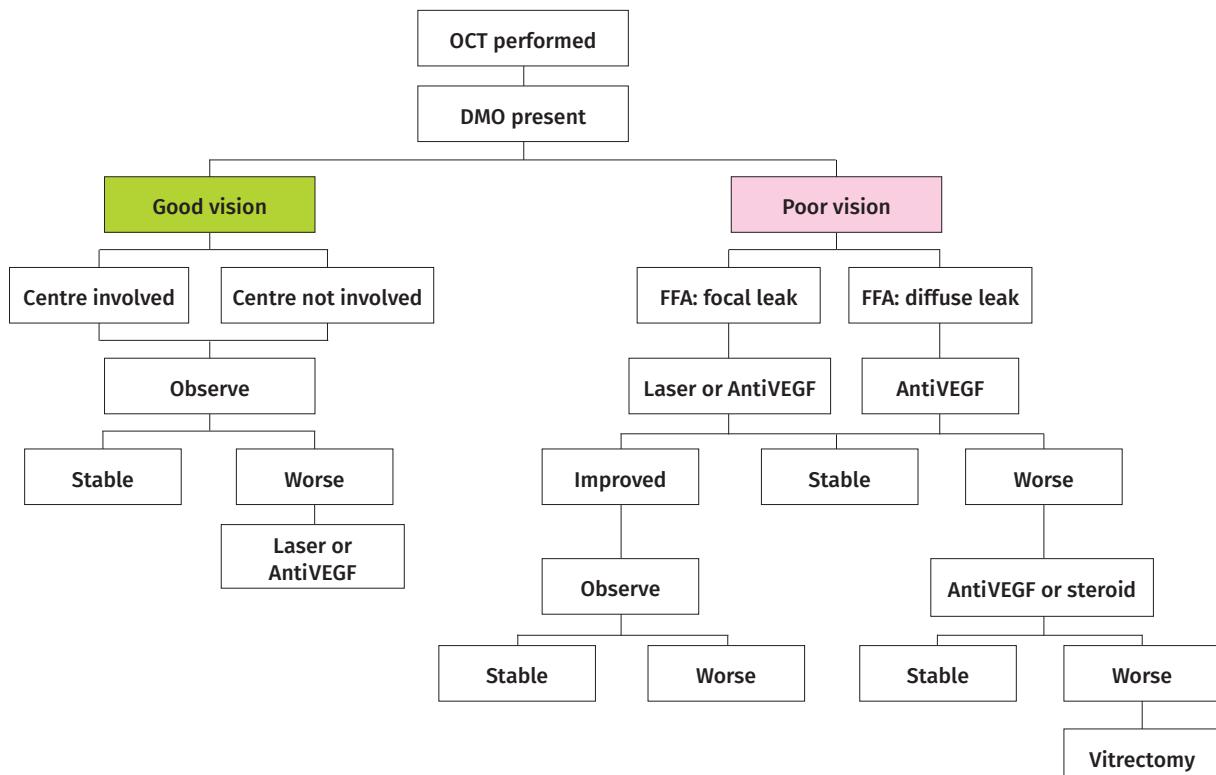


Figure 11.5 Recommendations for treatment of DME in India (from Das⁵²)

Table 11.1 Advantages, disadvantages and complications of the management options for DME (From AAO Guidelines⁴⁹)

Method and advantages	Disadvantages/complications
Control of risk factors	
<ul style="list-style-type: none"> Control of hyperglycaemia, hypertension, anaemia and proteinuria can reduce progression of DME, but ocular review should not be delayed 	Disadvantages <ul style="list-style-type: none"> Patients may not comply. Delay in treatment can lead to irreversible DME.
Focal or grid laser	
<ul style="list-style-type: none"> Usually a once off treatment; can be repeated Can prevent further loss of vision, or give some improvement Sustained effect 	Disadvantages <ul style="list-style-type: none"> Transient initial decrease in central vision. Complications <ul style="list-style-type: none"> Paracentral scotomas if laser burns close to the fovea, especially large or confluent burns. Permanent central scotomas from inadvertent foveal burns. Expansion of laser scar area (over many years). Choroidal neovascularisation.
AntiVEGF agents(50)	
<ul style="list-style-type: none"> More effective than laser in terms of structural and functional outcomes 	Disadvantages <ul style="list-style-type: none"> Very regular follow up with repeat investigations. Repeated intraocular injections needed over time: loading doses and then frequently during year one, tapering over time, but may be needed indefinitely. Complications <ul style="list-style-type: none"> Infectious endophthalmitis. Increased retinal traction. Cost to patients and providers. Other[#]
Laser plus Anti-VEGF agents	
<ul style="list-style-type: none"> More effective than laser in eyes with worse vision 	<ul style="list-style-type: none"> As above
Intravitreal steroids	
<ul style="list-style-type: none"> Useful for DME that does not respond to other treatment Good response based on specific OCT features 	Disadvantages <ul style="list-style-type: none"> Regular follow up with repeat investigations. Repeated intraocular injections. Complications <ul style="list-style-type: none"> Raised intraocular pressure/glaucoma. Cataract. Infectious endophthalmitis/inflammatory reactions.
Vitrectomy	
<ul style="list-style-type: none"> Can be of benefit if vitreoretinal traction from posterior hyaloid, or epiretinal membranes are present Refractory DME 	Disadvantages <ul style="list-style-type: none"> Limited indications. Improvement in VA may not be sustained. Complications <ul style="list-style-type: none"> Recurrent vitreous haemorrhage. Retinal tear or detachment. Vision loss. Infectious endophthalmitis. Cataract. Cost

Other. A recent review of systematic reviews and meta-analyses of trials of AntiVEGF treatment for range of conditions in adults (approximately 65,000 patients) concluded that AntiVEGF agents did not increase the risk of systemic complications.⁵¹ No data are available for the treatment of DME among people with diabetes who are at greater risk of cardiovascular disease.

angiography is the gold standard and should be performed as needed. In the absence of FFA, OCT features of ischemia i.e., disorganized inner retinal layers, external limiting membranes loss and ellipsoid zone loss, can be used to guide whether treatment is likely to be of benefit.

Factors considered in making the recommendations

Several different factors have to be taken into account when considering the optimal

management of DME in India. These include the type and severity of the DME, and the impact on visual acuity, the effectiveness of the different treatment modalities, the potential for complications and requirements for follow up. Other factors which need to be borne in mind are the facilities available for diagnosis and management, and whether patients are likely to comply with follow up. The latter is important for planned re-treatments and/or to assess complications.

The recommendations in the table below take these considerations into account.

11.10 PICO Question: What are the indications for and optimal management of DME in India?

Table 11.2 Recommendations for the treatment of DME by level of service provision and compliance of patients

Type of DME	Best corrected visual acuity	Sub-speciality retinal services##		Ophthalmologist trained in diagnosis and management of DR [#]	
		Compliant patients	Non-compliant patients	Compliant patients	Non-compliant patients
Non-centre involving	Good 6/12 or better*	Observe ^b ; control risk factors	Laser ^a based on angiography/OCT	Observe ^b ; control risk factors	Laser ^a based on clinical findings/OCT
	Poor <6/12	Investigate: exclude ischemic maculopathy	Investigate: exclude ischemic maculopathy	Refer for investigations	Refer for investigations
Centre involving	Good 6/12 or better*	Observe ^b ; control risk factors	Laser ^a based on angiography/OCT	Observe ^b ; control risk factors	Laser ^a based on clinical findings/OCT
• diffuse leak • focal leak	Poor <6/12	AntiVEGF ^a AntiVEGF/laser ^a	Laser ^a Laser ^a	AntiVEGF ^a	Laser ^a
With signs of vitreoretinal traction	Poor <6/12	Vitrectomy +/- AntiVEGF ^a	Vitrectomy +/- AntiVEGF ^a	Refer	Refer
Refractory DME**		Intravitreal steroids or vitrectomy ^a	Laser focal/grid laser [#]	Refer	Refer
DME in the presence of PDR or severe NPDR		AntiVEGF before laser PRP ^a	AntiVEGF before laser PRP ^a and focal/grid laser ^b	AntiVEGF before laser PRP ^a	AntiVEGF before laser PRP ^a and focal/grid laser ^a

(a) Level I; (b) Level II; (#) Limited evidence of effectiveness, but frequent follow up not required.

Fully equipped centre with fundus photography, fluorescein angiography, OCT, a trained team and facilities for vitrectomy (or referral).

Adequately equipped centre, with fundus photography and OCT, and a trained team *Also influenced by patient's requirement for good VA. **Refractory DME: received a minimum of three monthly injections of AntiVEGF with poor anatomical and functional response. PDR = proliferative DR; NPDR = non-proliferative DR.

11.11 Follow up after treatment for DME [from UK Guidelines⁵³]

Patients who have been treated for DME need regular follow up, with detailed clinical examination, including visual acuity measurement, and repeat OCT to assess whether the edema is resolving. Raised intraocular pressure after treatment with steroids can usually be managed medically. Cataract surgery may be required to monitor response to treatment.

11.12 PICO Question: What is the optimal follow up after management of DME in India?

Recommendations for practice – follow up after treatment

- Laser treatment: every three to four months as long as no other features require more regular follow up.
- Intraocular steroids: regular visits to monitor intraocular pressure and lens status – frequency dependent on findings.
- AntiVEGF agents: monthly during the first year.
- Vitrectomy: every two months.

11.13 PICO Question: How should patients be counselled about treatment of DME?

Recommendations for practice

- Patients need to be counselled before treatment that improving the control of their diabetes and comorbidities is essential.
- The procedure should be explained, including the likely outcome as well as the need for and timing and frequency of follow up, the likelihood of repeat treatment, and the need for lifelong care.

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12. Hyperglycaemia of pregnancy and pregnancy in women with diabetes

Summary

- Diabetic retinopathy, if present before conception or detected early in pregnancy, progresses more rapidly during pregnancy than among non-pregnant individuals, and may progress for up to 12 months after delivery.
- DME can also develop or progress during pregnancy.
- Frequent retinal examination by an ophthalmologist is recommended before and throughout pregnancy and following delivery.
- Urgent laser PRP of PDR is recommended during pregnancy.
- Management of DME needs to take into account the natural history during pregnancy, and the potential teratogenic effects of triamcinolone and AntiVEGF agents.

12.1 Epidemiology of diabetic retinopathy in women with hyperglycaemia of pregnancy and during pregnancy amongst known diabetics

Raised blood glucose which is first detected during pregnancy can be due to hyperglycaemia of pregnancy or overt diabetes.

Hyperglycaemia of pregnancy is defined as glucose intolerance which develops for the first time during pregnancy. Blood glucose levels are usually normal in early pregnancy but are raised during the second half of pregnancy. The blood glucose level returns to normal after delivery in the majority.

In overt diabetes the criteria which are used to diagnose diabetes in the non-pregnant state are met for the first time during pregnancy, often early in pregnancy, with higher HbA1Cs than in hyperglycaemia of pregnancy. The implications are that diabetes was present before pregnancy but was not diagnosed. Diabetes is likely to persist after delivery.

DR and DME in hyperglycaemia of pregnancy: Diabetic retinopathy does not develop during pregnancy.

DR and DME during pregnancy in women known to be diabetic/with overt diabetes

Diabetic retinopathy

Among women with diabetes before pregnancy, DR can progress during pregnancy,¹⁻⁴ at over twice the rate as in non-pregnant women, or can develop during pregnancy.⁵ In a recent review,¹ the prevalence of any DR in early pregnancy in Type 1 DM was reported as 34–72%, and 14% for Type 2. Progression of DR tends to occur during the first and second trimester, is usually worse at the end of the second trimester and in most tends to regress during the third trimester. However, DR can also progress for up to 12 months after delivery to severe NPDR or PDR, particularly amongst women with pre-eclampsia or pregnancy induced hypertension.^{1,6,7}

Table 12.1 Progression of retinopathy to proliferative retinopathy according to findings at baseline (before pregnancy or very early in pregnancy)¹

Author	Year of study	Type of DM	No DR at baseline: progression to PDR	NPDR at baseline: progression to PDR
Temple	2001	Type 1	1.2%	20.0%
Rahman	2007	Type 1	0	5.0%
Arun	2008	Type 1	0	6.7%
Vestgaard	2010	Type 1	0	7.3%
Rasmussen	2010	Type 2	0	9.1%
Egan	2015	Both, 68% Type 1	0	11.5%

The presence and severity of DR at baseline (before conception or very early in pregnancy) are predictors of the risk of progression to PDR.^{1,7} Findings in studies since 2000 are tabulated in Table 12.1.¹

Risk factors

Duration of disease is an independent risk factor for the progression of DR during pregnancy, and progresses in 10% of women who have had Type 1 DM for 10–19 years.^{1,7} Women who have had diabetes for 15 or more years are at particular at risk of progression to PDR.

Good control of risk factors is protective for progression of DR. In a cohort study of women with Type 1 DM, 71% those with an HbA1c of 6.6% and duration 20 years had minimal or no progression of DR during pregnancy. However, rapid control of glycaemia during pregnancy, to optimise outcomes for the mother and foetus, is also a risk factor for progression.^{1,4}

Hypertension before pregnancy, or pregnancy-induced hypertension increases the risk of progression.

In a recent study from India of 50 women known to have diabetes (most Type 2), 8% had DR and two women had PDR. There were no new cases of PDR during pregnancy, but in both cases with pre-existing PDR the retinopathy progressed during pregnancy, with worsening visual acuity.⁸ One patient required vitrectomy.

Diabetic macular edema

There are fewer data on DME, particularly for YO and early adult onset Type 2 DM.

The proportion of women with DME at any time during pregnancy ranges from 5 to 27% in Type 1 DM and is approximately 4% in Type 2 DM.¹ Pre-existing DME can progress during pregnancy, or can develop for the first time. In Type 1 DM, non-centre involving DME can progress to centre involving. DME can also regress after delivery once the blood volume returns to normal and fluid retention regresses.

12.2 Management of DR and DME during pregnancy

The indications for treatment of DR and DME during pregnancy are slightly different from the general population of people with diabetes, and there is a narrower range of management options because of safety concerns.

AntiVEGF agents, when injected into the eye, enter the systemic circulation where they can lower endogenous vascular endothelial growth factor, which in the case of Bevacizumab, can last up to two weeks.⁹ The degree and duration of this effect varies by agent. Animal models show there are potential teratogenic effects in rats, and the USA's Federal Food and Drug Administration recently issued safety labels for the use of two AntiVEGF agents during pregnancy.¹⁰ Although congenital anomalies attributed to AntiVEGF use during pregnancy have not been reported, the authors of a recent review advised against their use, particularly during the first trimester of pregnancy.

There are also concerns about the safety of triamcinolone during pregnancy, as in animal models it can lead to craniofacial malformations.^{11,12}

12.3 PICO Question: When and how often should retinal examinations be undertaken during pregnancy?

12.4 PICO Question: What are the indications for and optimal treatment of DR and DME in women with diabetes during pregnancy?

► **1. Before conception amongst women known to be diabetic – examination and management**

Recommendations for practice

- Counselling about the importance of controlling risk factors before and during pregnancy, with a target HbA1C as close to normal as possible.¹³
- Counselling about the need for dilated retinal examination throughout pregnancy and for up to 12 months after delivery.
- Visual acuity measurement and dilated retinal examination by an ophthalmologist to establish whether DR and/or DME are present.

Recommendations for treatment

- If DME is detected, follow the indications for treatment and treatment modalities in Chapter 11. If intravitreal injection of AntiVEGF agents or triamcinolone is the treatment of choice, advise the use of contraception for at least one month before, during, and for three months after the last treatment
- If severe NPDR or PDR are detected, treat with laser PRP (Level I). If AntiVEGF agents are the treatment of choice, follow the recommendation above regarding contraception advice.

► **2. During pregnancy**

Recommendations for practice

- Known to be diabetic: if preconception retinal examination was not possible, visual acuity measurement and dilated retinal examination by an ophthalmologist as early in pregnancy as possible.
- Known to have diabetes/overt diabetes: Repeat dilated retinal examination at least once in every trimester by an ophthalmologist, with the frequency being determined by the findings and the degree of control of risk factors.¹⁴

Recommendations for treatment

- Injections of AntiVEGF agents and triamcinolone are contraindicated during pregnancy because of their potential for teratogenic effects.
- PDR: laser PRP within four weeks of the diagnosis (Level I).
- Severe NPDR: laser PRP if an only eye, otherwise monthly follow up (Level I).
- Non-centre involving DME: observe for progression to centre-involving or regression (Level IV).
- Centre involving with loss of visual acuity: consider focal/macula grid laser photocoagulation (Level I), or observe throughout pregnancy and after delivery, and treat if required.

► **3. After pregnancy**

Recommendations for practice

- Dilated retinal examination of women with treated or untreated DME at one to two months, with management as required.
- Dilated retinal examination of women with mild, moderate or severe NPDR during pregnancy one to two months after delivery, with follow up for 12 months and management as required. The frequency of examination depends on the findings.

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13. Other eye diseases in people with diabetes

Summary

- People with diabetes have a higher incidence of other eye conditions, particularly cataract.
- Cataract surgery in people with diabetes can have poorer outcomes for a range of reasons, including the development or progression of DME.

Cataract surgery:

- There is some evidence that subconjunctival triamcinolone, or a 90 days course of topical NSAIs may reduce the incidence of DME after cataract surgery.
- Careful pre-operative assessment and meticulous surgical techniques reduce complications and the development of DME.
- There is good evidence that no benefit is derived from intravitreal AntiVEGF injections agents at the end of surgery.

As the population of India ages and the number of PwDM increases, an increasing proportion will develop other ocular complications of diabetes, including cataract needing surgery. As the risk of complications and poorer outcomes after cataract surgery is higher in PwDM, precautions are needed including detailed preoperative assessment of the anterior and posterior segments, meticulous surgical techniques, intracameral antibiotics to prevent endophthalmitis and intracameral or subconjunctival triamcinolone to reduce the risk of DME at the end of surgery.^{1,2} Cataract surgery may be needed to allow management of DR and/or DME.

13.1 Epidemiology of other eye diseases in people with diabetes

Individuals with diabetes are at greater risk of a range of other eye conditions, including cataract (particularly following vitrectomy), glaucoma,³ retinal vein occlusion, ischemic optic neuropathy and cranial nerve palsies, as has recently been reported in the India SPEED study, Report 1.⁴ There is no robust evidence that diabetes is associated with myopia.

In a population-based study in India of adults aged ≥40 years, 66% of PwDM had significant cataract with mixed opacities being the most frequent. Risk factors for any type of cataract were increasing age and poor glycaemic control.⁵

13.2 Outcomes and complications of cataract surgery in people with diabetes with and without DR

Cataract, particularly posterior subcapsular opacities, has an earlier age of onset in PwDM and can progress more rapidly. Multiple studies demonstrate the increased risk of cataract among PwDM and several pathogenic pathways have been described.⁵⁻⁷ Cataract surgery may be required to adequately examine the retina for DR and DME and to deliver treatment after surgery.

There are two broad considerations in relation to cataract surgery in PwDM: 1. surgery may worsen existing DR and DME or increase the incidence, and 2. cataract surgery has more complications than in people without DM. Both factors can lead to poorer visual outcomes.

Incidence and progression of DR and DME

[Note: The literature review is limited to studies published from 2000 onwards as surgical techniques and diagnostic methods have improved over time.]

Earlier studies, before modern surgical techniques, reported that DR progressed rapidly after cataract surgery in some eyes, leading to rubeosis and vitreous haemorrhage, with worsening visual outcomes compared to unoperated fellow eyes in people with diabetes. However, findings from recent studies using modern surgical techniques, such as phacoemulsification, show variation in the risk of developing or exacerbating DR or DME.

A large study in the UK (almost 82,000 phacoemulsification cataract operations) reported that DME developed more frequently after surgery in PwDM than in non-diabetics (RR 1.8 95% 1.4–2.4).⁸ The risk increased with increasing severity of DR (Figure 13.1).⁸

Some studies report no difference in the natural history or incidence of DR or DME by comparing fellow unoperated eyes, whereas other studies do report an increased incidence of PDR, and DME which has been attributed to poor glycaemic control after surgery.^{6,8–14} In a large multi-centre study, the following eyes were at increased risk of centre-involving DME after surgery: if DR was

present before surgery, and non-centre involving DME whether previously treated or not.⁹ Complicated surgery increases the risk of DME.¹⁵

OCT findings also show that DME can develop or progress after cataract surgery, with non-centre involving DME becoming centre involving.^{9,16,17} The edema may regress spontaneously within six months, suggesting that a proportion is due to the Irvine Gass syndrome i.e., inflammatory in nature.

A study from India compared PwDM who did or did not have DR before phacoemulsification surgery with non-diabetics.¹⁸ DME at eight weeks was more likely among PwDM than non-diabetics (51% vs 21%), and among PwDM with DR before surgery than those without 55% vs 47%. However, data were not presented on the presence of DME before surgery, and follow up was short. In this study, the development of DME and DR after cataract surgery was associated with poor glycaemic control and hypertension. However, there is no evidence on optimal levels of glycaemic control before cataract surgery.¹⁹

However, despite the increased risk of DME, cataract surgery generally improves visual acuity, with the presence of PDR and/or DME being associated with poorer outcomes.¹⁵

13.3 Efficacy of prophylaxis of DME

The findings from systematic reviews and trials exploring different interventions are shown in Table 13.1.

The available evidence suggests that subconjunctival triamcinolone or a course of topical NSAID may reduce the incidence of DME after cataract surgery,

Figure 13.1 Risk of developing DME after cataract surgery amongst people with diabetes⁸

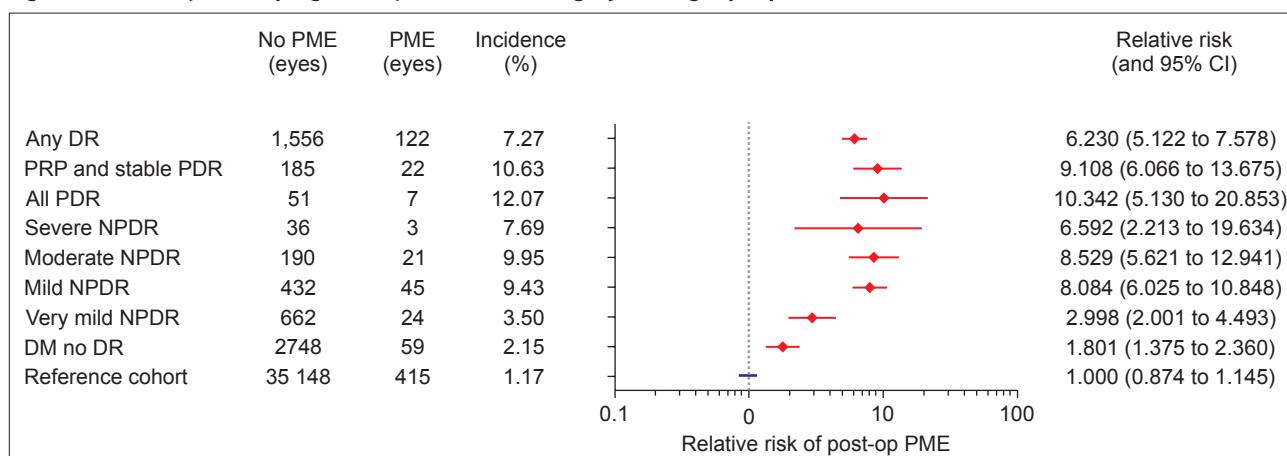


Table 13.1 Interventions for the prevention of DME after cataract surgery

Study design	Pre-operative DR/ DME status	Interventions / comparator	Outcome
Systematic review of five trials ²⁰	No DME and no DR	Topical NSAII and topical steroid vs topical steroid.	Combination better than steroids alone. Odds ratio 0.21 (95% CI-0.10–0.44).
		Intravitreal steroids alone.	No benefit.
		Intravitreal AntiVEGF agents alone.	No benefit.
Cochrane systematic review ²¹	Not enough data for analysis		
Trials not included in the systemic reviews			
RCT ²²	No DME; non-proliferative DR	Topical nepafenac from Day 1 pre-op, to Day 90 post op, vs sham drops.	DME within 30 days: <ul style="list-style-type: none"> • 5% intervention arm. • 17.5% control arm.
RCT ²³	No DME; mild non-proliferative DR	Intravitreal Bevacizumab at end of surgery vs no intervention.	Benefit short-lived.
RCT ²⁴	No DME; no DR in 85%	Four arms: <ol style="list-style-type: none"> 1. no intervention. 2. subconjunctival triamcinolone. 3. intravitreal Bevacizumab. 4. triamcinolone + Bevacizumab. 	Low rate of DME in untreated eyes <ul style="list-style-type: none"> • Triamcinolone-treated eyes had less macular edema than untreated eyes. • Bevacizumab of no benefit.

but robust evidence is lacking, including on which patients are the most likely to benefit and the duration of the effect, and more trials are needed. The available evidence seems to suggest no benefit with AntiVEGF agents.

Management of cataract in presence of DME and DR

The Diabetic Retinopathy Clinical Research Network (DRCRN) was not able to proceed with a trial to investigate the efficacy of interventions for PwDM with DME before cataract surgery due to very slow recruitment rates.²⁵ A literature search failed to find any published trials which specifically addressed this question.

13.4 Other complications of cataract surgery in people with diabetes

Patients with diabetes undergoing cataract surgery may have complications due to poor pupil dilation,²⁶ and an unstable corneal epithelium and endothelium.²⁷

Postoperatively, posterior capsule opacity, which can develop a year or more after surgery,²⁸ endophthalmitis^{29, 30} and anterior capsule phimosis are also more frequent in PwDM.⁶

Phacoemulsification surgery with IOL gives has fewer anterior segment complications than extracapsular cataract extraction in PwDM, and rates of DME were similar with both techniques.³¹ A study in India of phacoemulsification surgery in age matched diabetic and non-diabetic patients, reported similar degrees of PCO in both groups over four years of follow up. However, patients who were diabetic had hydrophobic IOLs and were given additional anti-inflammatory topical medication (diclofenac sodium) after surgery, which may explain the lack of difference.³²

Two non-randomised studies in India compared corneal endothelial cells loss after small incision cataract surgery in age-matched patients with and without diabetes. Both reported greater loss in PwDM and one reported greater central corneal thickness.^{33, 34}

Interventions to reduce complications

Intracameral antibiotics at the time of cataract surgery reduces the risk of endophthalmitis in all patients undergoing cataract surgery.³⁵ There is some evidence that topical and intracameral antibiotics give greater protection. Observational studies suggest that cefuroxime and moxifloxacin are equally effective and safe,³⁶ although adverse reactions have been reported.³⁷

13.5 PICO Question: What is the optimum management of cataract in people with diabetes before, during and after surgery?

► 1. Before surgery

Recommendations for practice – counseling

- If DR or DME are present before cataract surgery, patients should be counseled about the likelihood of a poorer outcome and the need for regular follow up.
- Patients should be informed that their vision may decline due to PCO months after surgery, and that additional treatments may be needed for the retinal complications of diabetes after cataract surgery.
- Good glycaemic control is considered best practice before cataract surgery but there are no evidence-based guidelines for this.

Recommendations for practice

- A dilated retinal examination, if possible, and OCT and ultrasound to assess the presence of DR and DME.
- The iris and angle should be assessed for neovascularisation with an undilated pupil, and intraocular pressure measured.
- Early surgery, to obtain a clearer view of the retina, allows timely management of DR and DME.
- Treat infection and defer surgery, to prevent endophthalmitis.
- Specular microscopy to assess the corneal endothelium.
- All patients should undergo dilated retinal examination and OCT less than 3 months before surgery to assess the presence of DR and DME.

Recommendations for treatment

- If PDR is detected, this should be treated with laser photocoagulation as far as possible, and completed as soon as possible after surgery (Level I).
- If DME is detected this should be treated, if possible, using an appropriate modality (see Chapter 11).
- For high risk patients (i.e., DR or non-centre involving DME present) consider a 90 day course of topical non-steroidal anti-inflammatory and steroids, starting before surgery (Level II).
- If vitreous haemorrhage is detected, combined cataract surgery with vitrectomy and endolaser photocoagulation is recommended.

► 2. During surgery

Recommendations for practice

- Meticulous aseptic and surgical techniques.
- The capsulorhexis should be larger than normal but smaller than the IOL optic diameter to prevent anterior IOL displacement and posterior capsular opacification.
- Iris hooks or a Malyugin ring may be needed to enlarge the pupil.
- Hydrophobic acrylic lenses should be used if vitrectomy is anticipated.

Recommendations for treatment

- At the end of surgery, if DME is detected before surgery, give subconjunctival triamcinolone or intravitreal preservative-free triamcinolone (Level II).
- At the end of surgery, give intracameral antibiotics (Level I).

► 3. After surgery

Recommendations for practice

- Retinal examination within a week of surgery, particularly if the view of the retina was poor before surgery. Treat DME and DPR as indicated (See Chapter 11).
- Recommendations for treatment.
- Topical steroids for as long as required to control inflammation.
- A course of topical antibiotics.

► 4. Recommendation for research

More trials are needed on subconjunctival triamcinolone or a course of topical NSAIs with or without topical steroids on the incidence/progression of DME after cataract surgery.

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14. Overview of operational issues in delivering services for DR and health system implications of implementing the guidelines

14.1 Operational issues in implementing a programme

For operational issues on how a programme for DR can be implemented, please see the Operational Guidelines for the Control of Visual Loss from Diabetic Retinopathy and Diabetic Eye Diseases in India (2019).

The Operational Guidelines summarise many of the less technical recommendations in these guidelines, and provide further details on how services for DR can be integrated into the Government of India's health system at different levels. The operational guidelines also outline the opportunities afforded by national programmes such as the National Health Mission, the National Programme for the Control of Cancer, Diabetes, Cardiovascular Disease and Stroke, and the National Programme for the Control of Blindness and Visual Impairment, outlining which healthcare professionals can play a role at different levels.

The Operational Guidelines also give estimates of the number of people with diabetes served by facilities at different levels (Table 14.1), and the number likely to have DR.

The operational guidelines highlight the importance of tracking individuals to ensure that they are screened and attend relevant healthcare facilities if they fail screening, and receive treatment if this is indicated. The importance of monitoring a programme for the control of visual loss from DR is emphasised, giving a list of suggested indicators for different aspects of the programme.

14.2 Health system implications

A programme for the control of visual loss from DR will impact on all components of the health system in India, including the health workforce, governance and leadership, health management information systems, technology and infrastructure and health

Table 14.1 Estimate of the number of people with diabetes who need screening for diabetic retinopathy and estimates of the number who need to be referred and managed.

Level	Population covered	At risk of DM (≥ 30 ys)	People with diabetes	PwDM with DR	PwDM with VTDR
		45% ¹²	8%	25%	7%
Health and Wellness Centres; Sub-Health Centre	5,000	2,250	180	45	3
Primary Health Centre	30,000	13,500	1,080	270	19
Community Health Centre	1,20,000	54,000	4320	1080	76
District Health Centre	10,00,000	4,50,000	36,000	9,000	630
Action needed		Screening for diabetes	Screening for DR	Failed screening: refer for diagnosis	Need treatment and follow up

PwDM=people with diabetes; VTDR=vision threatening diabetic retinopathy.

financing, all of which need to be adapted to deliver services to people with diabetes.

In terms of the health workforce, screening will entail training people who work in NCD clinics on how to take images of the retina, and training in how to grade the images or how to upload them onto a server for remote grading. In many instances this will require task sharing, which will need the endorsement of management. Eye care professionals may also need further training in how to grade retinal images and how to diagnose and manage diabetic retinopathy and diabetic macular edema.

Health management information systems will need to be adapted in order to monitor the programme,

and governance will be of vital importance to ensure policies are in place to support the programme and for quality assurance.

Technology and infrastructure in the form of equipment for screening, diagnosis and management will also need to be in place. Several different programmes in India provide opportunities for health financing by reimbursement of costs for treatment, and an initial capital outlay will be required.

For a programme to succeed, it is important that awareness is raised amongst people with diabetes and healthcare professionals about the importance of annual screening, and that treatment may be required even if their vision seems normal.

ANNEXURES

ANNEXURE 1. Terms of References for the Technical Expert Group

- Agree on the scope of the guidelines and the PICO (*Population, Intervention, Comparator, Outcome*) questions to be addressed.
- Review the evidence for prevention, detection/screening and management of sight threatening DR.
- Review existing guidelines from other countries and adapt to Indian needs for the prevention, detection/screening and management of DR, as required.
- Develop guidelines for implementation of screening and management programmes for DR.

ANNEXURE 2. Diabetic Retinopathy Clinical Research Network Manuscripts

General

1. Browning DJ, Glassman AR, Aiello LP, Bressler NM, Bressler SB, Danis RP, Davis MD, Ferris FL, Huang SS, Kaiser PK, Kollman C, Sadda S, Scott IU, Qin H; Diabetic Retinopathy Clinical Research Network. Optical coherence tomography measurements and analysis methods in optical coherence tomography studies of diabetic macular edema. *Ophthalmology*. 2008 Aug;115(8): 1366-71, 1371.e1
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Protocol A – Laser Photocoagulation for Diabetic Macular Edema

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Protocol AA – UWF Risk of DR Worsening Over Time

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Protocol B – Intravitreal Triamcinolone Acetonide versus Laser Study

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ANNEXURE 3. Summary of trials involving AntiVEGF agents for DME

RANIBIZUMAB (RBZ) vs laser			Reference
READ 2	0.5 mg RBZ alone vs laser alone vs RBZ + laser. In Year 3, RBZ as required.	RBZ had better visual acuity gains – sustained over 24–36 months. Frequent injections may be required.	Do, 2013
Protocol I	0.5 mg RBZ with prompt or deferred laser; sham injection with prompt laser; 4 mg IV triamcinolone + prompt laser.	RBZ with deferred laser had the best outcomes at five years.	DRCRN, Elman, 2015
RESTORE	1) 0.5 mg RBZ vs sham laser; 2) 0.5 mg RBZ vs laser; 3) sham injection vs laser. Monthly RBZ for three months, then as required.	RBZ with or without laser had better visual gains than laser alone at 12 months.	Mitchell, 2011
REVEAL (Asia)	1) 0.5 mg RBZ vs sham laser; 2) 0.5 mg RBZ vs laser; 3) sham injection vs laser. RBZ monthly for three months, then as required.	RBZ with or without laser had better visual gains than laser alone at 12 months.	Ishibashi, 2015
RIDE and RISE	RBZ 0.3 mg monthly vs RBZ 0.5 mg RBZ monthly vs laser for three years.	RBZ had better visual acuity gains with no differences between doses at two years.	Nguyen, 2012
RIDE RISE extension	RBZ 0.3 mg monthly vs RBZ 0.5 mg RBZ monthly vs laser for three years. RBZ 0.5 mg as required thereafter in all groups.	Visual acuity gains with RBZ maintained, with far fewer injections required	Boyer, 2015
BEVACIZUMAB (BCV) vs laser			
BOLT	BCZ at baseline and Weeks 6 and 12, vs laser. BCV as required thereafter for two years.	Better visual outcomes with BCZ sustained over two years.	Rajendran, 2012
AFLIBERCEPT (AFL) vs laser			
DA VINCI	AFL 1) 0.5 mg every four weeks; 2) 2 mg every four weeks; 3) 2 mg every eight weeks, after three initial monthly doses; 4) 2 mg as needed after three initial monthly doses; and 5) laser.	AFL superior to laser. Not large enough study to compare AFL treatment groups.	Do, 2012
VIVID (Europe, Japan, Australia) and VISTA (USA)	AFL 2 mg every four weeks vs 2 mg every eight weeks after five monthly doses vs laser. Cross-over rescue treatment as required from Weeks 24 and 100.	Initial AFL treatment gave better acuity gains than initial laser treatment at 148 weeks.	Heier, 2016
AFLIBERCEPT (AFL) vs BEVACIZUMAB (BCV) vs RANIBIZUMAB (RBZ)			
PROTOCOL T	2 mg AFL vs 0.3 mg RBZ vs 1.25 mg BCZ as frequently as monthly. Laser as required if no response at six months or thereafter.	BCZ had slightly lower visual gains than AFL and RBZ over two years. The gap in visual gains widened in eyes with poor baseline visual acuity. 15–16 injections required over two years.	DRCRN, Wells 2016

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