Perspective

Guidelines for the prevention and management of diabetic retinopathy and diabetic eye disease in India: A synopsis

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Diabetes mellitus now affects 65 million adults in India, which is likely to increase to over 130 million by 2045. Vision impairment and blindness from diabetic retinopathy (DR) and diabetic macular edema (DME) will increase unless systems and services are put in place to reduce the incidence of DR and DME, and to increase access to diagnosis and effective treatment. In India, sight-threatening DR (STDR) affects 5%–7% of people with diabetes, i.e., 3–4.5 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 hyperglycemia and hypertension. There is strong evidence that good control of hyperglycemia and hypertension reduce the incidence of STDR: interventions which lead to better self-management, i.e., a healthier diet and regular exercise, are required as well as taking medication as advised. There are highly effective and cost-effective treatments for STDR and up to 98% of blindness can be prevented by timely laser treatment and/or vitreous surgery. Given this increasing threat, the Queen Elizabeth Diamond Jubilee Trust endorsed the development of evidence-based guidelines for the prevention, detection, and management of DR and DME, and for cataract surgery in people with diabetes, specific to India as a component of the national DR project it has supported.

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In India, the number of people with diabetes mellitus (Type 2 and Youth-onset Type 2) is increasing, and there are estimated to be 128,500 people with Type 1 diabetes.[1] Approximately 5%–7% of people with diabetes have sight-threatening DR (STDR)[2] and the number of people with visual impairment from diabetic retinopathy (DR) is increasing. Indeed, DR is the commonest microvascular complications of diabetes. The number of people with diabetes is projected to continue to increase, and given the maturing of the diabetes epidemic, an increasing incidence of STDR is to be anticipated, as duration of disease is one of the most important risk factors.

Landmark clinical trials undertaken several decades ago showed that good control of hyperglycemia reduces the incidence of STDR,[3] and that laser treatment of DR and diabetic macular edema (DME)[4-6] are highly effective at preventing blindness or further loss of visual acuity. Systematic reviews of clinical trials also show that controlling hypertension can have a modest impact on the incidence of DR but little impact on progression.[7] The evidence is less compelling for dyslipidemia with only one small trial from India.

Over the last few decades, further insights have been gained regarding the pathogenesis of DR and DME[8] and new technologies have become available for diagnosis and management. These include high-resolution nonmydriatic imaging systems for screening, ocular coherence tomography (OCT) with or without angiography functions (OCT-A) for diagnosis, and different types of lasers and laser delivery systems, such as subthreshold laser, and multi-spot delivery, for treatment (anti-VEGF agents) other innovations in treatment include the use of biologicals, such as agents which block vascular endothelial growth factor (anti-VEGF agents), and slow-release intraocular systems for drug delivery, such as steroids. These new innovations have a lot to offer in the diagnosis and management of DR and DME. However, it can be challenging to keep up-to-date with these innovations, and there is a need to summarize the evidence of effectiveness from robust clinical trials to give guidance on the optimal management and under what circumstances. Indeed, this is the purpose of clinical guidelines such as those developed for DR and diabetic eye disease in India, which is "to improve the quality of care for patients and improve clinical effectiveness by the implementation of evidence-based care in daily practice." The guidelines include screening for DR and the management of DR/DME and cataract in people with diabetes and so will be of value to physicians and general ophthalmologists as well as vitreoretinal specialists.

In 2013, a national pilot project was launched in India with the goal of reducing avoidable blindness from DR, supported by the

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Queen Elizabeth Diamond Jubilee Trust, UK. After a National Summit in which strategies for control were agreed, a National DR Task Force was established by the Ministry of Health in 2014 to guide implementation. Several technical groups were established by the Task Force, one of which was to develop guidelines for DR/DME and diabetic eye disease in people with the following types of diabetes: Type 1, Type 2, and youth-onset. Recommendations were also made for screening and the management of DR/DME among pregnant women with diabetes.

Process of Guideline Development

The guidelines were developed following the steps recommended by the World Health Organization.[9] A development group was established comprising physicians, ophthalmologists, community physicians, policymakers, and public health professionals from the Government of India's health system and nongovernment service providers, and from schools of public health in India and the UK. It did not include primary level health care professionals nor patients. The group decided the scope of the guidelines, and delineated a list of 19 PICO (Population, Intervention, Comparator, Outcomes) questions to be addressed which covered the prevention, detection, diagnosis, and management of DR and DME and the management of cataract in people with diabetes. The PICO questions guided the evidence sought.

Table 1: Levels of evidence used in formulating the recommendations

Level I	Evidence obtained from a systematic review of all relevant randomized controlled trials
Level II	Evidence obtained from at least one properly designed randomized controlled trial
Level III-1	Evidence obtained from well-designed pseudo-randomized 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 randomized, 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 of 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

Based on the PICO questions, a rigorous literature search was undertaken by an Information Specialist, Cochrane Eyes and Vision, UK, 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 meta-analyses or network analyses, were preferentially drawn upon to formulate the recommendations whenever available. The literature was searched for additional and more recent evidence during development, as required.

A writing group was formed, and different members were allocated sections to draft.

Formulating and agreeing on the recommendations

To formulate the recommendations for each PICO question, the level of evidence was categorized into different levels [Table 1]. The guideline used extensive evidence and has 358 references, many of them Cochrane or other systematic reviews and meta-analyses. Guidelines from other countries and those produced by the International Council of Ophthalmology were also drawn upon. The balance of benefits and harms were also taken into consideration. Most of the recommendations relate to clinical management, whereas others are for clinical practice.

In India, there is considerable variability in the level of services for eye care between and within the government, private, and

Table 2: Recommendations for the treatment of DME by the level of service provision and compliance of patients

Type of DME	Best-corrected visual acuity	Subspecialty retinal services##		Ophthalmologist trained in diagnosis and management of DR#	
		Compliant patients	Noncompliant patients	Compliant patients	Noncompliant patients
Noncenter 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
Center 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	Poor <6/12	Anti-VEGF[a]	Laser[a]	Anti-VEGF[a]	Laser[a]
Focal leak		Anti-VEGF/laser[a]	Laser[a]		
With signs of vitreoretinal traction	Poor <6/12	Vitrectomy±Anti-VEGF[a]	Vitrectomy±Anti-VEGF[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		Anti-VEGF before laser PRP[a]	Anti-VEGF before laser PRP[a] and focal/grid laser[b]	Anti-VEGF before laser PRP[a]	Anti-VEGF 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 center with fundus photography, fluorescein angiography, OCT, a trained team, and facilities for vitrectomy (or referral). #Adequately equipped center, with fundus photography and OCT, and a trained team *Also influenced by patient's requirement for good VA. **Refractory DME: received a minimum of 3 monthly injections of Anti-VEGF with poor anatomical and functional response. PDR=proliferative DR; NPDR=nonproliferative DR

Table 3: Recommendations for treatment of DR by level of patient compliance and DME status

Type of DR	DME present	Patient likely to comply with follow-up	Patient not likely to comply with follow-up
PDR	No DME	Laser PRP[a] or Anti-VEGF monotherapy within 4 weeks[a] Consider Anti-VEGF injection 1 week before laser PRP to prevent DME[b]	Laser PRP[a] within 4 weeks Consider Anti-VEGF injection 1 week before laser PRP to prevent DME[b]
	DME present	Anti-VEGF injection before panretinal photocoagulation[b]	Laser PRP and focal/grid laser to the macula[a]
Severe NPDR	No DME	Regular follow-up	Laser PRP[a]
	DME present	Anti-VEGF or steroid injections[a]	Scatter laser PRP for PDR and focal/grid laser to macula[a]

(a) Level I evidence (b) Level II evidence, PDR=proliferative DR; NPDR=nonproliferative DR

Table 4: Recommendations for the management of cataract in people with diabetes

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 posterior capsule opacification months after surgery, and that additional treatments may be needed for the retinal complications of diabetes after cataract surgery
  - Good glycemic 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 neovascularization 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
  - For high-risk patients (i.e., DR or noncenter involving DME present) consider a 90-day course of topical nonsteroidal antiinflammatory and steroids, starting before surgery (Level II)
  - If vitreous hemorrhage is detected, combined cataract surgery with vitrectomy and endolaser photocoagulation is recommended

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)

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 PDR as indicated
- Recommendations for treatment
  - Topical steroids for as long as required to control inflammation
  - A course of topical antibiotics

Recommendation for research
- More trials are needed on subconjunctival triamcinolone or a course of topical NSAI with or without topical steroids on the incidence/progression of DME after cataract surgery

not-for-profit sectors. Some centers provide subspecialty retina services and are fully equipped to provide the full range of investigations and management options for DR and DME. Other centers provide general eye care, which includes conditions of the retina, but lack some of the expertise or equipment to implement the full range of treatments. The guidelines took account of this variability. As many of the newer treatments for DR and DME require extensive and frequent follow-up, the recommendations also allow clinicians to recommend the optimum treatment taking account of a particular individual's circumstances.

Once the recommendations had been drafted, they were agreed one by one using an anonymous voting system, followed by discussion if there was not unanimous agreement, in face-to-face meetings or remotely. Two sessions were held, one with endocrinologists and physicians who focused on the PICO questions on interventions to reduce the incidence of vision-threatening retinopathy and the timing of first screening, by type of diabetes. The second group, which comprised experts in the medical and surgical retina, focused on screening for DR, technologies for diagnosis, and the management of DR and DME, and the management of cataract. They also reviewed the recommendations on the timing of first screening, by type of diabetes. The document was then finalized by the Working Group; this group also decided the date for the next revision and agreed a plan for dissemination.

Examples from the Guidelines

The guidelines can be accessed here.[10]

Recommendations for screening

These include timing of the first screening, by type of diabetes, with the recommendation that nonmydriatic imaging is used. Screening people with Type 1 diabetes with onset before puberty should start at 10 years of age. People diagnosed with Type 1 diabetes after puberty should have a detailed eye examination at diagnosis. If there is no DR, screening should commence 5 years later. For people with Type 2 diabetes, including Youth-onset diabetes, screening should start at diagnosis.

Screening needs to be integrated into clinics where people with diabetes receive their care at all levels in the health system using nonmydriatic imaging systems, which is elaborated further in the Operational Guidelines.[10] Among those who fail screening, the International Classification of DR should be used to classify the stage of DR at clinical examination, to allow comparison of data with other countries.[11]

Recommendations for the management of diabetic retinopathy and diabetic macular edema

The recommendations for both of these PICO questions took account for different levels of service delivery as well as the likelihood that patients would comply with long-term follow-up and repeated treatments, which are required for anti-VEGF agents, for example [Tables 2 and 3].

Recommendations for the management of cataract in people with diabetes

People with diabetes develop significant cataract at an earlier age than those without, and surgery may be required to visualize and treat any retinopathy. Cataract surgery in people with diabetes is also likely to be more complicated, and DME can worsen or develop after cataract surgery. The recommendations regarding interventions to prevent and manage DME before, during and after cataract surgery are shown in Table 4.

Discussion

A limitation of the guidelines is that for many of the recommendations, there was little high-quality evidence from studies and clinical trials 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 for regular follow-up. In addition, in India, there is a different diabetes phenotype,[12] such as higher rates and severity of dyslipidemia, which may influence the pathophysiology and natural history of DR and DME as well as responses to treatment. More research is needed in India, particularly well-conducted randomized clinical trials to provide evidence where this is lacking, or where evidence from other populations may not be applicable.

Another limitation was that the views of patients and primary level health care professionals were not taken into consideration, and the guidelines were not pilot tested. Feedback by users on the utility of the guidelines will be of value for those drafting the next version, which should be undertaken in 3 to 5 years.

Conclusion

Increasing threat of diabetes-related blindness has prompted the development of India-specific evidence-based guidelines for the prevention, detection, and management of DR and DME, and for cataract surgery in patients with diabetes. The next logical step may be to clinically apply and validate these guidelines.

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Conflicts of interest

There are no conflicts of interest.

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