Special Focus on Diabetic Retinopathy, Original Article

Impact of treatment of diabetic macular edema on visual impairment in people with diabetes mellitus in India

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Purpose: The aim of this study was to report visual and anatomical outcomes following treatment for diabetic macular edema (DME) in clinical practice in India. **Methods:** Retrospective chart review of patients with DME who were initiated on treatment and followed up for at least 1 year at 9 tertiary eye care centers during 2016–2017 was performed. Data on demographics, systemic illnesses, visual acuity and anatomical characteristics of DME, treatment history were collated and analyzed for change in visual acuity level and central macular thickness at 1 year. **Results:** A total 1853 patients were diagnosed with treatable DME during study period, 1315 patients were treated and 556 patients (1019 eyes) followed up at one year. Although patients achieved significantly better anatomical outcome (central macular thickness of <300µ in 32.3% at baseline compared to 60.7% at 1 year, $P < 0.001$), visual impairment due to DME did not differ from baseline (mild visual impairment in 53.2% at baseline compared to 56% at 1 year, $P = 0.7$). Cystoid type of DME was the most common phenotype (432/1019, 42.4%) followed by spongy type (325, 31.9%) and cystoid plus spongy type (138, 13.5%). Bevacizumab monotherapy was the most common (388/1019, 38.1%) treatment followed by combination therapy (359, 35.2%). Mean number of anti-VEGF injections received per eye in a year was 2.1 (SD ± 0.9). **Conclusion:** Only about a third of treated DME patients complete one year follow up in India. Most patients receive suboptimal number of treatments. Treated DME cases largely show better anatomical outcome but not a better functional outcome.

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Increasing prevalence of diabetes mellitus (DM) is a major public health concern globally especially in middle-income countries such as in India.[1] Systemic and ocular complications of DM affect individuals in their most productive years of life.

Diabetic retinopathy (DR) is the most common microvascular complication of DM and is emerging as an important cause of visual impairment (VI) in the working-age group.[2-6] With increasing prevalence of DM, the absolute numbers of patients with DR are likely to increase in the next two decades in India.[1] Prevalence of DR in India ranges from 17.6% to 28.2%.[2-7] and less than 10% of the persons with diabetes (PwDM), suffer from sight-threatening DR (STDR) which includes diabetic macular edema (DME) and proliferative diabetic retinopathy (PDR).[2,5–7] Nevertheless, all PwDM need regular screening as they are at risk of progressing to STDR.[8] Lack of compliance is a major limiting factor in ensuring universal coverage of systematic DR screening. In a recent report,[2] nearly 70% of PWD had never had their eyes screened for DR. The same study reported the prevalence of any DME among PWD to be 8.9% and that of referable DME as 2.4%. Recent estimates suggest that there are 77 million PwDM in India.[1] Considering conservative estimate of 2% PwDM having DME, likely magnitude of treatable DME is 15,40,000 persons.

Macular laser photocoagulation (MLP) had been the mainstay of treatment in clinically significant DME until about a decade ago.[9,10] With the advent of optical coherence tomography (OCT), DME can now be quantified and further classified into non-center and center involving DME (Ci-DME). Anti-vascular endothelial growth factor (anti- VEGF) is superior to laser in the management of center-involving DME.[11–14] Bevacizumab was the first anti-VEGF therapy to be used for DME in India more than a decade back.[15] The standard of care for DME treatment has gradually shifted from MLP to anti-VEGF injections with more options becoming available over the years.[16] Different

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anti-VEGF agents and steroids have also been used in DME either alone or in combination with other therapies including MLP. The International Council of Ophthalmology (ICO) guidelines recommend monthly assessment with OCT.[17] Real-world studies[14] have shown that around 7–8 anti-VEGF injections per year have desirable impact on Ci-DME. Most of the health expenditure in India is out of pocket.[18] Treatments for DME are expensive. One major barrier to follow treatment frequency from other real-world studies[14] could be the financial burden, where yearly out of pocket expenses can be as high as INR 42000–70000 (≈USD 575–1000) (estimated mean cost of cheapest anti-VEGF injection INR 7000, range 6000–10000, mean seven injections per year) (personal communication). Therefore, treatment regimens and combinations are adapted to be more acceptable and affordable to patients. There is a paucity of data on visual outcomes when such treatment regimens have to be followed. Given that most patients with DME reside in middle-income countries, there is a need for evidence on real-life treatment outcomes of DME in such settings where screening for STDR is in its infancy and where public awareness of VI due to diabetes is limited.

This study was planned with the purpose of reporting characteristics of DME population, clinical profile of DME, treatment modalities used, and frequency of treatments in order to establish a real-world visual outcome of DME treatment in India.

Methods

This retrospective observational study was conducted in nine tertiary eye care centers between January and December 2019. Institutional ethics committees of each participating center granted a waiver for this study in view of the secondary nature of data analysis. Patient data were anonymized before transferring into excel sheet. Written informed consent is routinely obtained from patients before instituting any invasive treatment.

Retrospective chart review of consecutive PwDM was performed to identify treatment naïve DME cases initiated on various treatments during 2016-17 and who completed 1 year follow up. Those with hazy media, ocular co-morbidities, previous vitrectomy, lost to follow up before 1 year and incomplete ocular record at baseline, were excluded.

Sample size

The RISE and RIDE study[11] reported improvement of vision by two lines (10 ETDRS letters) in 40% of patients treated with monthly injections of intravitreal ranibizumab at 24 months after treatment. To assess the impact of DME on VI, our primary outcome was the proportion of eyes that moved up by one level from baseline VI category (mild/mod/severe VI and blindness) at 1 year. Assuming that 30% of treated patients would have achieved this in a real-world scenario, with alpha error of 0.05 and power of 80, sample size was calculated to be 165 and was increased to 190 to account for loss to follow up.

Data collection and analysis

The data collected included demography, duration of DM, type of DM, systemic comorbidities, type of treatment for DM, level of glycated hemoglobin (HbA1C), grade of DR, phenotype of DME, lens status. All these data were collected at baseline. Across all participating centers, international clinical DR severity scale[19] is used for grading of DR. Best-corrected visual acuity (BCVA) at baseline and at 1 year was recorded. Snellen visual acuity (VA) was categorized into various levels–: mild VI (BCVA <6/12–6/18), moderate VI (<6/18–6/60), severe VI (<6/60–3/60), blindness (<3/60–No PL).[20] Phenotype of DME was recorded at baseline as follows: cystoid, spongy, serous retinal detachment, combined (more than one phenotype), vitreomacular traction (VMT)/tractional detachment (TRD).[21] Central macular thickness (CMT) on optical coherence tomography (OCT) at baseline and at 1 year was categorized into- ≤300 microns (μ), 301–500 μ, 501–700 μ, >700 μ. Presence of ischemic maculopathy (either from fundus fluorescein angiography or OCT angiography) if recorded, was noted. Data on primary treatment, any change in treatment modality and frequency of injections during the 1-year period were collected. Combination treatment was defined as anti-VEGF plus other treatments (laser, cataract/vitreous surgery, topical medications, etc).

Information on all the variables was collected in a predesigned and pre-tested form. Data were entered into an excel sheet. A statistical tool (Stata IC 14, Tx, USA) was used to generate descriptive statistics. Age and gender distribution, proportion of subjects with systemic illnesses and with HbA1C >7 were calculated. Proportion of eyes with various categories of VI and CMT were calculated at baseline and at 1 year. Chi-square tests were performed to assess difference between these proportions at baseline and at 1 year. Proportion of eyes receiving 1, 2, 3 and >4 injections during one year period were calculated along with mean number of injections per eye per year.

Results

Total 59,798 PwDM were examined during the study period. Fig. 1 shows the process of sample selection. Five hundred and fifty-six PwDM fulfilling inclusion criteria were included in the study. Mean age of the sample was 58.8 years (SD 8.8, range 27–89). General characteristics of study population are shown in Table 1.

Significant number (302, 54.3%) of PwDM were on oral hypoglycemic agents (OHA) and 171 (30.8%) received insulin (±OHA). In the rest, treatment type was not recorded. A total 665/1112 eyes (59.8%) had cataract and 204 eyes (18.3%) were pseudophakic. Most patients (544/556, 97.8%) had some

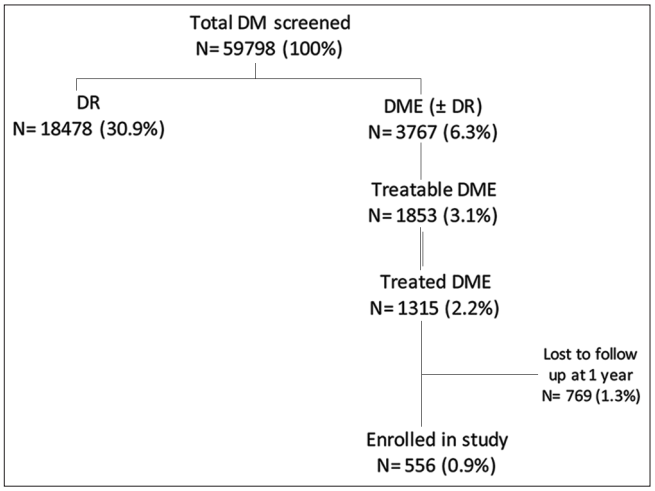

Figure 1: Sample selection from all work-in persons with diabetes mellitus

form of DR recorded and 163/556 (29.3%) had PDR. Of all the 556 cases, DME was bilateral in 465 (83.3%) and unilateral in 91 (16.7%) participants. Thus 1019 eyes with DME were included in the analysis. Records of 98/1019 (9.6%) eyes showed presence of ischemic maculopathy.

Record of VA at baseline and 1 year is shown in Table 2. One year record of VA was missing for 140 patients. The difference between proportion of persons with mild VI at baseline and at 1 year (53.2% versus 56%, $P = 0.7$) was statistically insignificant. Of the 879 patients with complete record at 1 year follow-up, on an individual basis, VA improved in 31 (3.5%), remained stable in 838 (95.3%) and worsened in 10 (1.1%). This proportion among cases treated with macular laser alone (complete follow up $n = 42$) was as follows: VA improvement (2, 4.8%), stable (31, 73.8%), worsened (9, 21.4%). Of the 98 eyes with documented ischemic maculopathy, 13 (13.3%) completed one year follow up. Of these 8 (0.8%) had stable vision and 5 (0.5%) showed worsening of vision.

Table 1: Characteristics of study population

Variables	*n* (%)
Age in years (Mean±SD)	58.8±8.8
Gender	
Male	405 (72.9)
Female	151 (27.1)
Type of DM	
Type 1 DM	51 (9.2)
Type 2 DM	505 (90.8)
Duration of DM	
≤5 years	102 (18.3)
>5 years	421 (75.7)
Unknown	33 (5.9)
Hypertension	
Yes	299 (53.8)
No	208 (37.4)
Unknown	49 (8.8)
H/o Dyslipidemia	
Yes	163 (29.3)
No	283 (50.9)
Unknown	110 (19.8)
H/o Ischemic Heart Disease	
Yes	72 (12.9)
No	411 (73.9)
Unknown	73 (13.1)
H/o Diabetic Nephropathy	
Yes	54 (9.7)
No	400 (71.9)
Unknown	102 (18.3)
H/o Anaemia	
Yes	38 (7.2)
No	330 (59.3)
Unknown	188 (33.8)
HbA1c %	
≤7%	57 (10.2)
>7%	214 (38.5)
Unknown	285 (51.3)

*SD - Standard deviation; H/o - History of; DM-diabetes; HbA1c - Glycated haemoglobin

Table 3 shows CMT for the entire cohort (first two columns) and complete case analysis for those who had both baseline and one year record (last two columns). OCT record at 1 year was missing for 205 eyes. Twice as many patients achieved CMT < 300 um at 1 year than at baseline (60.7% vs 32.3%, $P < 0.001$). Most common phenotype of DME was cystoid (432/1019, 42.4%) followed by spongy (325, 31.9%) and combined spongy plus cystoid (138, 13.5%), VMT/TRD in 112 (11%) eyes. Phenotype was undocumented in 12 (1.2%) eyes.

A total 969/1019 (95.1%) eyes received intravitreal pharmacotherapy and 50 (4.9%) eyes received only MLP as treatment. Various types of treatments are shown in Table 4. Bevacizumab monotherapy was the most commonly used treatment (38.1%). Number of injections received by eyes were as follows: 1 in 339 (35.2%) eyes, 2 in 245 (24.7%) eyes, 3 in 185 (19.1%) eyes and ≥ 4 in 146 (15.5%) eyes. Fifty (5.5%) eyes did not have record of number of injections received. A total of 2043 intravitreal injections were given for treatment of 969 study eyes. Mean number of injections received per eye per year were 2.1 (SD ± 0.9).

Discussion

This study represents the real-life management and outcome of DME based on data pooled from 9 tertiary care centers across south, east, north and west parts of India which makes it representative of India. It is seen from Fig. 1 that only about two-thirds of treatable cases sought treatment and less than a third continued follow up until 1 year which highlights several challenges. Patients with DME possibly cannot afford out of pockets expenses to cover high cost of DME treatment. This could be a major reason for poor uptake and follow-up of DME treatment in India. Other causes may be the lack of awareness, indirect costs and several unexplored barriers.

Nearly 3 out of 4 patients enrolled in this study were males. Previous reports[6,7,21] have shown higher prevalence of DR in males than in females. Higher proportion of males in this study cannot be explained by just this factor. Role of gender inequities in access to eye care has been reported earlier.[22,23] In

Table 2: Visual acuity at baseline and at 1 year

Visual acuity category	Baseline *n* (%) (including missing data)	1 year *n* (%) (including missing data)	Baseline *n* (%) Complete Case analysis	1 year *n* (%) Complete Case analysis
No VI	8 (0.8)	2 (0.2)	1 (0.1)	2 (0.2)
Mild VI	470 (46.1)	493 (48.4)	467 (53.2)	493 (56.0)
Mod VI	428 (42.0)	278 (27.3)	314 (35.7)	278 (31.7)
Severe VI	62 (6.1)	74 (7.3)	60 (6.8)	74 (8.4)
Blind	51 (5.0)	32 (3.1)	37 (4.2)	32 (3.7)
No record	0 (0.0)	140 (13.7)	NA	NA
Total	1019 (100)	1019 (100)	879 (100)	879 (100)

Table 3: Central macular thickness at baseline and at 1 year

Thickness (microns)	Baseline *n* (%) (including missing data)	1 year *n* (%) (including missing data)	Baseline *n* (%) Complete Case analysis	1 year *n* (%) Complete Case analysis
<300	354 (34.7)	494 (48.7)	264 (32.3)	494 (60.7)
301-500	397 (38.9)	227 (22.6)	335 (41.4)	227 (27.9)
501-700	199 (19.5)	83 (8.3)	171 (21.0)	83 (10.2)
>700	69 (6.7)	10 (0.9)	44 (5.3)	10 (1.2)
Unknown	0 (0.0)	197 (19.5)	NA	NA
Total	1019 (100)	1019 (100)	814 (100)	814 (100)

Table 4: Types of Treatment received

Type of treatment	*n* (%)	Number of eyes with 1 year data		
		VA	CST	Injection data
Bevacizumab	388 (38.1)	304	293	369
Ranibizumab	110 (10.8)	102	102	97
Aflibercept	12 (1.2)	6	7	12
Dexamethasone implant	17 (1.7)	10	12	12
Triamcinolone	15 (1.5)	11	11	11
Combination of >1 intravitreal injection	68 (6.6)	57	53	62
Macular laser alone	50 (4.9)	49	47	NA
Intravitreal injection plus others*	359 (35.2)	340	289	352
Total	1019 (100)	879	814	915

*'Others' included laser, vitrectomy, cataract surgery, topical medications etc

India, most health care expenditures are out of pocket[18] hence when it comes to spending money on eye care, males are more likely to seek treatment than females.[24] Proportion of type 1 DM in India has been reported to be 5-10%,[24,25] similar to that observed in the present study. Mean age of 58.8 years and a wide range of age suggest that high proportion of patients were in the working-age group.

Every fifth person in this study had a fairly recent onset DM of <5 years. The Diabetes Control and Complications Trial (DCCT) group reported that both type I and type II DM can have DME before 5 years of diagnosis and the prevalence increases with increasing duration of DM.[26] It is possible that those with recent-onset DM in the present study were diagnosed late.

Hypertension was the most commonly associated systemic disease followed by dyslipidemia, IHD, diabetic nephropathy and anemia in reducing order of frequency. Less than half of the subjects had their HbA1C checked and of them only a fifth had its value at normal level. Uncontrolled blood sugar levels are known to adversely impact incidence of DR/DME and its sight-threatening complications. The role of systemic risk factors in development of DR has been established.[8] With the help of physicians, importance of control of systemic risk factors needs to be stressed among PwDM.

Every third PwDM who visited hospital had DR perhaps due to the fact that this was a hospital-based study and patients with symptoms were likely to seek services. Proportion of DME cases among all PwDM was similar to that reported earlier.[8]

Most patients in the present study had either mild or moderate VI [Table 2]. If screening programs were universal, many would have been referred earlier. The proportion of VI did not change significantly at one year follow up. The proportion of patients showing better visual outcomes at 1 year was much lower (3.5% Vs 50%) than what was reported in a study where ranibizumab was injected in a serial well-timed manner.[11] This implies that treatment in most patients in the present study did not result in improved visual acuity at the end of first year. This study highlights the urgent need to screen and treat patients early as the current treatment for DME only stabilizes baseline visual acuity in most cases.

The proportion of participants with CMT of <300 µm showed a significant increase from nearly 32% to 60% [Table 3] at the end of one year implying good structural outcome. Most common phenotype of DME was cystoid in under half of participants followed by spongy type in a third. Every tenth subject had associated VMT/TRD who were all potential candidates for vitreo-retinal surgery in future. It has been reported that in DME, cystoid and VMT phenotypes are likely to have poorer visual outcomes.[27] Over half of the subjects in the present study had cystoid/VMT phenotypes hence had a guarded visual prognosis. This again implies that several PwDM in India seek treatment late in the course of the disease.

Nearly 4 out of 5 subjects had cataract which was operated in about a fifth. This suggests that in India most DME subjects are also likely to require cataract management. Just under a third subjects had concurrent PDR. Anti-VEGF therapy for DME can control PDR component temporarily. However, the gold standard for PDR treatment is pan-retinal photocoagulation and this alone can worsen DME further. Hence presence of both PDR and DME has a direct negative impact on visual prognosis. Presence of cataract can further complicate management and may entail multiple therapies (antiVEGF, lasers, surgery, etc). Lack of universal screening for DR and high proportion of cataract blindness in India[2,27,28] may mean several DME cases

are likely to present with other ocular comorbidities posing several challenges in management.

Treatment patterns

Over 95% subjects received intravitreal injections (mono/combination therapy) [Table 3]. Intravitreal bevacizumab was the most common therapy in over a third patients followed by combination therapy in another third. Low cost of bevacizumab explains this trend. High number of combination therapies also shows that co-morbidities (cataract/PDR) are common. Use of multiple anti-VEGF agents or steroids was seen in very few. Switching from one anti-VEGF to another is a viable option that is practiced in the management of persistent Ci-DME. Longer follow-up could have thrown more light in this regard.

Less than 3% of bevacizumab eyes and nearly 14.5% of ranibizumab eyes received them ≥4 injections. The higher proportion of ranibizumab eyes receiving ≥4 injections may mean these treatments were financed through insurance schemes. Vast majority of eyes (80%) received 3 or less intravitreal injections during one year period. Mean number of 2.1 injections per eye per year is far below the number recommended by international guidelines.[17] This implies that implementation of recommended guidelines in a real-world is a challenge in India. Various possible reasons for low number of injections noted in this study could be inability to pay for recurrent treatments, patients opting to continue treatment elsewhere, compliance fatigue due to the need of multiple visits at eye and diabetes facilities. Other causes for suboptimal treatment may include lack of awareness, lack of time, presence of other systemic complications and other unidentified barriers which need to be explored. Cataract in PwDM remains a significant cause of VI. This study highlights that treatment of DME alone may not result in better visual outcome.

This is possibly the first retrospective study from India that has looked at the DME management practices across some tertiary eye -care facilities in the country. Extrapolating data from this study to Indian population gives a figure of 15,40,000 (2% of 77 million PwDM)[1] DME cases needing treatment. Considering cost of average 12 bevacizumab injections for both eyes (INR 7000 per injection) in 1 year, the economic burden amounts to INR 129360 million (USD 1725 million). This cost is much higher for FDA approved drugs such as ranibizumab or aflibercept. In the recent times, the availability and use of biosimilars for ranibizumab has helped reduce the cost of intra-vitreal anti-VEGF therapy in India.[29] However, a consorted approach is required to deal with uncorrected refractive errors, cataract surgery backlog, screening and timely treatment of PDR/DME with optimal treatment regimens to have any impact on VI in PwDM.

Present study has several limitations. The study population represents those who sought treatment for DME at these eye care facilities. Findings from this study cannot be generalized to all DME patients across the country as there is no representation of those who did not avail treatment, were lost to follow up or had eye conditions such as advanced cataract, glaucoma, uveitis, etc., However, there is sufficient representation of the best clinical practice offered to DME patients in India.

Another limitation is the challenges associated with the retrospective nature of the study including information bias due to incomplete data. Data on systemic diseases/other risk factors such as HbA1C were not available for all patients. Hence analytical tests to establish association of these factors and final visual/structural outcome could not be carried out.

Measures of VA and CMT were collected in a qualitative manner hence mean values of these variables could not be assessed. It is possible that mean VA/CMT improved or deteriorated over study period which was not captured due to broad categorization. Only OCT parameters were used to categorize phenotypes of DME hence patients with central hard exudate plaques in whom visual outcome is often poorer despite reduction in the macular thickening were not studied separately. The OCT machines used at the study sites were different and could have resulted in minor variations in measurement of CMT. Lastly, there was no data on insurance coverage of study patients which could have helped in identifying 'out of pocket expenses' as a reason for poor uptake of injections. However, our study was aimed to evaluate the impact of treatment of DME on categories of VI and this was achievable with this study design. This study provides 'real world' scenario of characteristics of DME cases and treatment trends across the country. Findings of this study could provide a good starting point for policy makers to strengthen services, allocate resources and to plan research.

Conclusion

In conclusion, the study results call for urgent need to identify and treat DME optimally in India. A key research topic that has arisen from this study is to evaluate the barriers for uptake and compliance for DME treatment. There is also an urgent need for cheaper and longer lasting therapies for DME to have a positive impact on VI due to DME. Further studies on diabetic eye complications in middle-income countries are encouraged as the research priorities, training needs and clinical standards in high-income countries cannot be directly translated to resource-limited countries.

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Conflicts of interest

There are no conflicts of interest.

References

1. International Diabetes Federation. Prevalence and magnitude of diabetes as per country/region [Internet]. 2015. Available from: http://www.diabetesatlas.org/resources/2015-atlas.html. [Last accessed on 2019 Dec 21].
2. Kulkarni S, Kondalkar S, Mactaggart I, Shamanna BR, Lodhi A, Mendke R, *et al*. Estimating the magnitude of diabetes mellitus and diabetic retinopathy in an older age urban population in Pune, western India. BMJ Open Ophthalmol 2019;4:e000201.
3. Kusagur SR, K J G, Negalur N V. Prevalence of diabetic retinopathy in type II diabetes in relation to risk factors: A hospital based study. J Evol Med Dent Sci 2014;3:5513–21.
4. Gadkari SS, Maskati QB, Nayak BK. Prevalence of diabetic retinopathy in India: The All India Ophthalmological Society Diabetic Retinopathy Eye Screening Study 2014. Indian J Ophthalmol 2016;64:38–44.

5. Narendran V, John RK, Raghuram A, Ravindran RD, Nirmalan PK, Thulasiraj RD. Diabetic retinopathy among self reported diabetics in southern India: A population based assessment. Br J Ophthalmol 2002;86:1014–8.
6. Rema M, Premkumar S, Anitha B, Deepa R, Pradeepa R, Mohan V. Prevalence of diabetic retinopathy in urban India: The Chennai Urban Rural Epidemiology Study (CURES) eye study, I. Invest Ophthalmol Vis Sci 2005;46:2328–33.
7. Raman R, Rani PK, Reddi Rachepalle S, Gnanamoorthy P, Uthra S, Kumaramanickavel G, *et al*. Prevalence of diabetic retinopathy in India: Sankara Nethralaya Diabetic Retinopathy Epidemiology and Molecular Genetics Study report 2. Ophthalmology 2009;116:311–8.
8. Yau JWY, Rogers SL, Kawasaki R, Lamoureux EL, Kowalski JW, Bek T, *et al*. Global prevalence and major risk factors of diabetic retinopathy. Diabetes Care 2012;35:556–64.
9. Early treatment diabetic retinopathy study research group. Photocoagulation for diabetic macular edema: Early Treatment Diabetic Retinopathy Study Report no. 4. The Early Treatment Diabetic Retinopathy Study Research Group. Int Ophthalmol Clin 1987;27:265–72.
10. Early treatment diabetic retinopathy study research group. Treatment Techniques and Clinical Guidelines for Photocoagulation of Diabetic Macular Edema: Early Treatment Diabetic Retinopathy Study Report Number 2. Ophthalmology 1987;94:761–74.
11. Brown DM, Nguyen QD, Marcus DM, Boyer DS, Patel S, Feiner L, *et al*. Long-term outcomes of ranibizumab therapy for diabetic macular edema: The 36-month results from two phase III trials: RISE and RIDE. Ophthalmology 2013;120:2013–22.
12. Granström T, Forsman H, Lindholm Olinder A, Gkretsis D, Eriksson JW, Granstam E, *et al*. Patient-reported outcomes and visual acuity after 12 months of anti-VEGF-treatment for sight-threatening diabetic macular edema in a real world setting. Diabetes Res Clin Pract 2016;121:157–65.
13. Maggio E, Sartore M, Attanasio M, Maraone G, Guerriero M, Polito A, *et al*. Anti–vascular endothelial growth factor treatment for diabetic macular edema in a real-world clinical setting. Am J Ophthalmol 2018;195:209–22.
14. Patrao N V, Antao S, Egan C, Omar A, Hamilton R, Hykin PG, *et al*. Real-world outcomes of ranibizumab treatment for diabetic macular edema in a United Kingdom National Health Service Setting. Am J Ophthalmol 2016;172:51–7.
15. Kumar A, Sinha S. Intravitreal bevacizumab (Avastin) treatment of diffuse diabetic macular edema in an Indian population. Indian J Ophthalmol 2007;55:451–5.
16. International Council of Ophthalmology (ICO). Guidelines for Diabetic Eye Care in India Adapted from guidelines formed by International Council of Ophthalmology. 2015; (January). Available from: https://www.iapb.org/wp-content/uploads/ICO-Guidelines-for-Diabetic-Eye-Care-Adapted-to-India_VISION-2020-India.pdf. [Last accessed on 2020 Jan 15].
17. International Council of Ophthalmology. Updated 2017 ICO Guidelines for Diabetic Eye Care. ICO Guidel Diabet Eye Care 2017. [Last accessed on 2020 Aug 08].
18. Reddy KS. India's Aspirations for Universal Health Coverage. N Engl J Med 2015;373:1–5.
19. Americal academy of ophthalmology. International clinical diabetic retinopathy disease severity scale [Internet]. Int Counc Ophthalmol 2011. Available from: http://www.icoph.org/downloads/Diabetic-Retinopathy-Scale.pdf. [Last accessed on 2019 Apr 06].
20. World Health Organization. Blindness and vision impairment [Internet]. 2018. Available from: https://www.who.int/en/news-room/fact-sheets/detail/blindness-and-visual-impairment. [Last acessed on 2020 Apr 06].
21. Otani T, Kishi S, Maruyama Y. Patterns of diabetic macular edema with optical coherence tomography. Am J Ophthalmol 1999;127:688–93.
22. Namperumalsamy P, Kim R, Vignesh TP, Nithya N, Royes J, Gijo T, *et al*. Prevalence and risk factors for diabetic retinopathy: A population-based assessment from Theni District, south India. Br J Ophthalmol 2009;93:429–34.
23. Gilbert CE, Lepvrier-Chomette N. Gender inequalities in surgery for bilateral cataract among children in low-income countries. Ophthalmology 2016;123:1245–51.
24. Rius A, Lansingh VC,Guisabola VL, Carter MJ, Eckert KA. Social inequalities in blindness and visual impairment: A review of social determinants. Indian J Ophthalmol 2012;60:368–75.
25. Kumar KMP. Incidence trends for childhood type 1 diabetes in India. Indian J Endocrinol Metab 2015;19:S34–5.
26. White NH, Sun W, Cleary PA, Tamborlane WV, Danis RP, Hainsworth DP, *et al*. Effect of prior intensive therapy in type 1 diabetes on 10-year progression of retinopathy in the DCCT/EDIC: Comparison of adults and adolescents. Diabetes 2010;59:1244–53.
27. Kim NR, Kim YJ, Chin HS, Moon YS. Optical coherence tomographic patterns in diabetic macular oedema: Prediction of visual outcome after focal laser photocoagulation. Br J Ophthalmol 2009;93:901-5.
28. Neena J, Rachel J, Praveen V, Murthy GVS, for the RISG. Rapid assessment of avoidable blindness in India. PLoS One 2008;3:e2867.
29. Sameera V, Apoorva A, Joshi S, Guruprasad A. Safety and efficacy of Razumab – The new biosimilar in India: Our experience. Kerala J Ophthalmol 2016;28:180–5.