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To cite this article: Charumathi Sabanayagam, WanFen Yip, Daniel S. W. Ting, Gavin Tan & Tien Y. Wong (2016) Ten Emerging Trends in the Epidemiology of Diabetic Retinopathy, Ophthalmic Epidemiology, 23:4, 209-222, DOI: [10.1080/09286586.2016.1193618](https://doi.org/10.1080/09286586.2016.1193618)

To link to this article: <http://dx.doi.org/10.1080/09286586.2016.1193618>



Published online: 29 Jun 2016.



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MINI REVIEW

Ten Emerging Trends in the Epidemiology of Diabetic Retinopathy

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ABSTRACT

Purpose: Diabetes is a major public health problem affecting 415 million people worldwide. With the increasing prevalence of diabetes, diabetic retinopathy (DR) is emerging as the leading cause of avoidable blindness worldwide.

Methods: We reviewed previous and recent literature to provide an overview of emerging trends on the burden, epidemiology, risk factors, and prevention of DR.

Results: First, there is clear evidence of a global increase in the prevalence of diabetes. Second, there is a decline in the incidence of blindness due to DR, particularly in developed countries. Third, diabetic macular edema (DME) rather than proliferative diabetic retinopathy (PDR) is the increasingly common cause of visual impairment. Fourth, DR awareness remains patchy and low in most populations. Fifth, hyperglycemia remains the most consistent risk factor for DR in type 1 diabetes across different studies and populations. Sixth, in contrast, blood pressure is an important risk factor for DR in type 2 diabetes. Seventh, the relationship between dyslipidemia and DR remains unclear, with inconsistent results from different studies and trials. Eighth, the utility of predictive models incorporating multiple risk factors for assessing DR risk requires evaluation. Ninth, photographic screening of DR using tele-ophthalmology platforms is increasingly recognized as being feasible and cost-effective. Finally, DR prevention in low-resource settings cannot follow models developed in high-resource countries and requires different strategies.

Conclusions: The ten trends we observed in the current review may guide planning of public healthcare strategies for the management of DR and prevention of blindness.

ARTICLE HISTORY

Received 29 January 2016

Revised 15 March 2016

Accepted 19 March 2016

KEYWORDS

Awareness; burden; diabetic retinopathy; prevention; risk factors

Introduction

Diabetes currently affects an estimated 415 million people worldwide, and the number is expected to rise to 642 million by 2040.¹ With the rising prevalence of diabetes, the number of persons with diabetic retinopathy (DR) has also increased. In view of the increasing burden of diabetes and DR, there has been substantial global public attention and research in recent years on understanding the epidemiology, risk factors and burden of diabetes and DR, in an effort to develop long-term strategies to manage this major public health problem.^{1–8}

Over the last decade, there have been some major developments in the diagnosis and care of patients with diabetes and DR. For example, the results of landmark clinical trials in the 1980s and 1990s such as the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) showed that the development and progression of DR can be significantly reduced by controlling blood glucose^{9–11} and blood

pressure (BP).¹² Other major trials demonstrated the effectiveness of laser photocoagulation in preventing vision loss in patients with DR.^{13,14} In the last decade, three developments are particularly important. First, the development of the non-invasive optical coherence tomography (OCT) has improved the assessment of DR, particularly diabetic macular edema (DME). Second, the introduction of intraocular administration of anti-vascular endothelial growth factor (anti-VEGF) agents has changed the paradigm in the management of DME from “preventing vision loss” to “improving vision.”¹⁵ Finally, the increasing use of photographic screening of DR with the development of high quality digital fundus cameras and the transmission of images and information over the internet has allowed the development of tele-ophthalmology as an increasingly used, viable and cost-effective option in the screening of DR.^{16–19} These developments have reduced the prevalence of DR and occurrence of new cases of blindness due to DR globally and improved the diagnosis and management of DME. For example, with the increasing availability of OCT devices together with their improved accuracy and

precision for identification of subclinical DME, OCT has been recognized as the new reference standard for assessment of DME and proven valuable for monitoring progression and treatment response for DME.^{20,21} Implementation of telemedicine-based DR screening resulted in improved screening rates and less vision loss from DR.²² Treatment with anti-VEGF drugs have improved vision outcomes and reduced the worsening of DR in patients with DME.^{23,24} In this article, we review past and current literature to understand and highlight emerging trends in the epidemiology of DR, with a particular focus on the burden, awareness, risk factors and screening of DR.

Materials and methods

We searched Medline (PubMed), and EMBASE databases up to December 2015. Gray literature was searched using Google, and citation lists of relevant publications were manually searched. Search terms included “diabetes,” “retinopathy,” or “diabetic retinopathy,” “macular edema” or “diabetic macular edema,” in combination with search terms related to epidemiology (e.g. “prevalence,” “incidence,” “awareness”), risk factors (e.g. “blood pressure,” “glucose,” “glycated hemoglobin,” “HbA1c,” “cholesterol,” “predictive model”), and screening (e.g. “telemedicine”). Only studies published in English were included in this review.

Results and discussion

Our study findings listed in Table 1 may guide future research, and planning of public healthcare strategies for the management of DR and prevention of blindness.

Trend 1: There is a global increase in the prevalence of diabetes

The total number of persons with diabetes continues to increase worldwide from 135 million in 1995,²⁵ to 171 million in 2000,²⁶ to 415 million in 2015.¹ This number is projected to increase dramatically to 642 million by 2040,²⁷ with the greatest increases expected in developing countries, particularly in Asia and Africa.²⁸ Diabetes estimates from developing countries show marked trends toward younger ages of onset, and rural communities being affected as much as urban ones. While the majority of those with diabetes in developed countries were aged over 64 years, most people with diabetes in developing countries were found to be much younger, between the ages of 45 and 64 years.²⁹ In addition, risk factors contributing to the increased prevalence of diabetes have been shown to be different between developed and developing

Table 1. List of emerging trends in the epidemiology of diabetic retinopathy.

- 1 There is a global increase in the prevalence of diabetes.
- 2 There is a decline in the incidence of blindness due to PDR, particularly in developed countries.
- 3 DME, rather than PDR, is an increasingly common cause of visual impairment.
- 4 Awareness of DR remains poor in most communities.
- 5 Hyperglycemia remains the most consistent risk factor for DR in type 1 diabetes.
- 6 In contrast, BP is an important risk factor for DR in type 2 diabetes.
- 7 The relationship between dyslipidemia and DR remains unclear.
- 8 Photographic screening of DR using a tele-ophthalmology platform is increasingly being recognized as a feasible and cost-effective screening strategy.
- 9 An accurate predictive model of patients at risk of DR remains to be developed.
- 10 DR prevention in low-resource settings requires different public healthcare models and strategies.

BP, blood pressure; DME, diabetic macular edema; DR, diabetic retinopathy; PDR, proliferative diabetic retinopathy.

countries. In developing countries, weight gain and obesity due to sedentary lifestyle, unhealthy diet (e.g. easier access to fast food), high BP and high cholesterol have been shown to contribute to the rising prevalence of diabetes.^{3,30} On the other hand, the main reason for the increasing prevalence of diabetes in developed countries has been attributed to the increased life expectancy of the population.³¹ These differences suggest that healthcare systems of countries with different economic status should focus on different strategies to control the prevalence of diabetes. While many studies have reported on the prevalence of diabetes, there is still a lack of data in certain developing regions such as Eastern Europe, Africa, and Southeast Asia.³⁰ Understanding the prevalence of diabetes in these regions is important for relevant authorities to estimate the needs of medical facilities and to plan resource allocation for managing the increasing number of patients with diabetes. In addition, as the prevalence of diabetic micro- and macrovascular complications including retinopathy, nephropathy, foot complications, and cardiovascular disease are set to increase paralleling the rising prevalence of diabetes, organized public health efforts are needed to detect diabetes early in the course of the disease through screening programs and to educate the public on diabetes-related risk factors and complications in order to tackle the epidemic. However, this will require political will, commitments at all levels, and adequate resources.

Trend 2: There is a decline in the incidence of blindness due to proliferative diabetic retinopathy, particularly in developed countries

With increasing prevalence of diabetes and increasing life expectancy of those with diabetes, DR is set to be the leading cause of vision loss in many countries.³² In 2010, of an estimated 285 million people worldwide with

diabetes, over one-third were found to have signs of DR.⁸ Despite the increasing prevalence of diabetes across all countries, epidemiological evidence from developed countries (Table 2) suggested a declining trend in the prevalence of DR-related blindness in people with both type 1^{5,33–35} and type 2³⁶ diabetes due to concerted public health efforts. In the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), a population-based prospective study of diabetic persons living in 11 counties of the state of Wisconsin in the US with 25-year follow-up, the annualized estimates for the progression of DR and the incidence

Table 2. Trends in the incidence and prevalence of diabetic retinopathy (DR).

Author, year, ref. no.	Definition of retinopathy	Findings
<i>Type 1 diabetes</i>		
Klein and Klein, 2010 ⁵	Modification of the Early Treatment Diabetic Retinopathy Study	Annual incidence of proliferative retinopathy 1980–1982 to 1990–1992 cohort: 3.5% 1994–1996 to 2005–2007 cohort: 1.5%
Pambianco and colleagues, 2006 ³⁵	Modified Airlie House System	Cumulative incidence of proliferative retinopathy 1965–1969 cohort: 38% 1975–1980 cohort: 26.5%
Nordwall and colleagues, 2004 ³³	Graded by ophthalmologist using independent DR grading protocol	Cumulative incidence of severe retinopathy (laser-treated retinopathy) 1961–1965 cohort: 47% (95% CI 34–61%) 1966–1970 cohort: 28% (95% CI 15–40%) 1971–1975 cohort: 24% (95% CI 12–36%)
Hovind and colleagues, 2003 ³⁴	Graded by ophthalmologist	Cumulative incidence of proliferative retinopathy 1965–1969 cohort: 31.2% (95% CI 22.2–39.8%) 1970–1974 cohort: 30.3% (95% CI 22.2–38.4%) 1975–1979 cohort: 19.3% (95% CI 11.2–27.4%) 1979–1984 cohort: 12.5% (95% CI 5.2–19.8%)
<i>Type 2 diabetes</i>		
Cugati and colleagues, 2006 ³⁶	Modified Airlie House Classification	Prevalence of moderate-severe NPDR BMES I (1992–1994): 8.3% BMES II (1997–2000): 4.5% Prevalence of PDR BMES I: 1.4% BMES II: 1.2%

CI, confidence interval; BMES, Blue Mountains Eye Study.

of proliferative diabetic retinopathy (PDR) was higher in the first 12 years of the study (1980–1992) than in the later 13 years of the study (1994–2007).⁵ Similarly, in the Linköping Diabetes Complications Study,³³ the cumulative incidence of severe retinopathy was reported to have declined from 47% in the 1961–1965 cohort to 28% in the 1966–1970 cohort and 24% in the 1971–1975 cohort.³³ Similar findings were observed in a Danish study where the cumulative incidence of PDR declined progressively from 31.2% in participants whose onset of diabetes was in 1965–1969 to 12.5% in participants whose onset of diabetes was in 1979–1984,³⁴ and in the Pittsburgh Epidemiology of Diabetes Complications Study from 38% in the earlier cohort to 26.5% in the latter cohort although the decline was not statistically significant.³⁵ In a meta-analysis including 28 studies and 27,120 type 1 and type 2 diabetic participants, the pooled incidence of PDR was found to be lower in participants in 1986–2008 (2.6%) compared to participants in 1975–1985 (19.5%),³⁷ and in the Pittsburgh Epidemiology of Diabetes Complications Study from 38% in the 1965–1969 cohort to 26.5% in the 1975–1980 cohort.³⁵ A similar decline was also observed in the pooled incidence of non-proliferative DR (NPDR, 47% in 1975–1985 to 20.5% in 1986–2008).³⁷ Additional evidence to support this trend comes from screening studies conducted in Europe which have shown more than two-thirds reduction in the prevalence of visual impairment and blindness after the introduction of free screening services.³⁸

Although developed countries have documented a decreasing trend in the prevalence and progression of severe DR despite increasing prevalence of diabetes, a similar trend was not observed in developing countries where public health programs targeting diabetes prevention and management face significant challenges due to poor healthcare systems and lack of resources. In addition to diabetes, as the prevalence of other risk factors of DR, including hypertension and high cholesterol, are on the rise in developing countries such as China and India,^{39,40} it will be important to investigate the trend of DR in these countries.^{39,41,42}

Trend 3: Diabetic macular edema, rather than proliferative diabetic retinopathy, is an increasingly common cause of visual impairment

With the rising prevalence of type 2 diabetes, the prevalence of DME (commonly seen in type 2 diabetes) is also on the rise.^{43–45} In a recent study in the US, DME was shown to be twice as common as PDR suggesting DME to be a more common cause of vision loss in persons with type 2 diabetes.⁴³ In the WESDR, the overall prevalence of DME was shown to be 11.1% and 8.4% in the younger and older

onset groups, respectively. In the same cohort, the 10-year incidence of DME was highest in the older-onset patients on insulin (25.4%), followed by the younger-onset patients on insulin (20.1%) and older-onset patients not requiring insulin (13.9%).⁴⁶ Nevertheless the incidence of DME among those with type 1 diabetes was lower in the later follow-ups compared to the earlier ones, largely attributed to better glycemic and BP control.^{5,46,47} However, the WESDR data needs to be interpreted with caution as the data was collected in the early 1980s. It is therefore unclear whether the reduction in incidence is due to early detection or recent medical advances in diabetes care. Incidence of DME in type 1^{44,46,48–53} and type 2 diabetes^{44,51,52,54–56} are listed in Table 3. In addition, the decline in the incidence of DME was reported among those with type 1 diabetes only^{46,48} and no data is available to support this trend in those with type 2 diabetes.^{51,55,56} As the number of persons with DME is expected to increase with the rising prevalence of type 2 diabetes worldwide, large population-based studies with recent data are needed to understand the epidemiology, and treatment pattern of DME.

Trend 4: Awareness of diabetic retinopathy remains poor in most communities

Early detection and timely treatment can prevent DR-related blindness. However, lack of patient awareness is a major hurdle to patients attending eye screenings and receiving treatment. Surprisingly, poor awareness of DR has been reported in both developed and developing countries. In the 2005–2008 National Health and Nutrition Examination Survey (NHANES) in the US, 73% of individuals with DR⁵⁷ and 55.3% of those with DME⁵⁸ were unaware of their condition. In Tokyo, 32% of those with type 2 diabetes were unaware of their DR status.⁵⁹ In Singapore, while 90% of those with diabetes were aware of their diabetic status, more than 80% of those with DR were unaware of their DR status, including 25% of those with sight-threatening DR.⁶⁰ Few studies have documented awareness of DR in developing countries. Awareness of DR among those with diabetes was reported to be 27%⁶¹ in the Andhra Pradesh Eye Disease Study in India, and 63% among newly diagnosed diabetic patients who presented to a tertiary eye care center in Nepal.⁶² In Egypt, 60.2% of participants presenting with advanced DR were not aware that diabetes could be sight-threatening.⁶³ These findings suggest that despite the high prevalence of diabetes and impact of DR on vision, awareness of DR remains low. As a consequence, these patients are less likely to be detected early or receive timely interventions for DR,⁶⁴ which is important for the prevention of visual impairment and blindness.

Lack of awareness of DR has been shown to be associated with poor health literacy, low socioeconomic status, and poor control of HbA1c and BP levels.^{65–67} These findings indicate that public health education should be more targeted towards persons with lower educational levels and lower socioeconomic status. In addition, it should also be highlighted that more follow-up sessions could be set aside by primary care professionals for patients with poorly controlled HbA1c and BP levels.

Trend 5: Hyperglycemia remains the most consistent risk factor for diabetic retinopathy in type 1 diabetes

Hyperglycemia has consistently been shown to be a risk factor for DR and DME in both type 1^{41,48,49} and type 2 diabetes.^{68,69} In the WESDR, higher HbA1c at baseline and an increase in HbA1c level between baseline and follow-up were associated with progression of DR and incidence of PDR at both 14 and 25 years of follow-up.^{41,49} Baseline HbA1c was associated with incidence of DME at both time points and an increase in HbA1c level between baseline and follow-up was associated with incidence of DME at 25 years in those with type 1 diabetes.⁴⁸ Data from several randomized controlled trials provided strong evidence supporting the effectiveness of tight glycemic control in reducing the risk of DR in those with type 1 diabetes. The DCCT demonstrated that intensive therapy reduced the risk of DR by 75% and progression of DR by 54% over a mean follow-up of 6.5 years in patients with type 1 diabetes.^{70–73} In a meta-analysis of 16 trials from 12 cohorts of type 1 diabetic patients, Wang and colleagues reported that intensive treatment decreased risk of DR progression by 51% compared to conventional treatment.⁷⁴ Although tight glycemic control reduces the risk of microvascular complications, it has two clinically important adverse effects, namely early worsening of DR and hypoglycemia. In the DCCT, tight glycemic control led to risk of early worsening of DR⁷⁵ which was subsequently reversed after 18 months, with no cases of serious vision loss reported subsequently.⁷⁵ A similar finding was also reported in the meta-analysis by Wang and colleagues.⁷⁴ In another meta-analysis of 14 randomized controlled trials (RCT) of type 1 diabetic participants, intensive treatment was found to be associated with a 3-fold increased risk of hypoglycemia and a nearly 2-fold increased risk of ketoacidosis.⁷⁶

Hyperglycemia has been shown to be a risk factor for DR in those with type 2 diabetes in several cross-sectional studies.^{77–81} In addition, higher HbA1c was associated with both incidence and progression of DR over a 4-year follow-up in patients with type 2 diabetes in a Hong Kong study.⁶⁹ However, the benefits of tight glycemic control in reducing the risk of DR in patients with type 2 diabetes is

Table 3. Incidence of diabetic macular edema (DME).

Author, year, ref. no.	Study population, country	Method of scan	Definition of ME	Follow-up, years	Findings
Martin-Merino and colleagues, 2014 ⁵¹	Type 1 & 2 diabetes, United Kingdom	–	Maculopathy; inclusive of ME, exudative maculopathy or any other non-specific maculopathy	9	Cumulative incidence 1-year follow-up: Type 1 diabetes: 0.6% Type 2 diabetes: 0.3% 9-year follow-up: Type 1 diabetes: 4.4% Type 2 diabetes: 3.6% Cumulative incidence of DME 5-year follow-up: 0.59% 10-year follow-up: 1.2% Annual incidence of Referable retinopathy Year 1: 2.02% Year 2: 2.82% Year 3: 3.24% Year 4: 3.54% Cumulative incidence of DME 11.07% Cumulative incidence of DME 5.4%
Jones and colleagues, 2012 ⁵⁵	Type 2 diabetes, United Kingdom	Fundus photo	Independent grading scale; English National Screening Program	10	
Thomas and colleagues, 2012 ⁵⁶	Type 2 diabetes, United Kingdom	Fundus photo	Maculopathy; exudates within 1 disc diameter of the fovea Referable retinopathy; pre-proliferative or proliferative retinopathy (with or without maculopathy), or maculopathy with background retinopathy	4	
Romero-Aroca and colleagues, 2011 ⁵⁰ Varma and colleagues, 2010 ⁴⁴	Type 1 diabetes, Spain United States	Fundus photo, FA, OCT Stereoscopic photographs	DME; retinal thickening and hard exudates in the macular area ME; thickening of the retina with or without partial loss of transparency within 1 disc diameter from macular center or the presence of focal photocoagulation scars in the macular area ME; retinal thickening in the macular area	10 4	
Klein and colleagues, 2009 ⁴⁸	Type 1 diabetes, United States	Stereoscopic photographs		25	Annualized incidences of DME Follow-up 1: 2.3% Follow-up 2: 2.1% Follow-up 3: 2.3% Follow-up 4: 0.9% Cumulative incidence of DME 8.7%
Leske and colleagues, 2006 ⁵²	Type 1 & 2 diabetes, Barbados	Stereoscopic photographs	Clinically significant macular edema (CSME), which was defined as (1) thickening of the retina at or within 500 µm of the center of the macula, (2) hard exudates at or within 500µm of the center of the macula associated with thickening of the adjacent retina (but not residual hard exudates remaining after the disappearance of retinal thickening), and (3) a zone or zones of retinal thickening 1 disc area or larger in size, any part of which was within 1 disc diameter of the center of the macula Maculopathy; ring of exudate within macula ≥1 disc area in size but not within 1 disc diameter of center of macula, or exudates within 1 disc diameter of fixation and/or presence of focal or grid photocoagulation scars	9	
Younis and colleagues, 2003 ⁵³	Type 1 diabetes, United Kingdom	Fundus photography		6	Cumulative incidence of DME 3.2%
Younis and colleagues, 2003 ⁵⁴	Type 2 diabetes, United Kingdom	Fundus photography	Maculopathy; ring of exudate within macula ≥1 disc area in size but not within 1 disc diameter of center of macula, or exudates within 1 disc diameter of fixation and/or presence of focal or grid photocoagulation scars	6	Cumulative incidence of DME 4.8%

(Continued)

Table 3. (Continued).

Author, year, ref. no.	Study population, country	Method of scan	Definition of ME	Follow-up, years	Findings
Klein and colleagues, 1998 ⁴⁹	Type 1 diabetes, United States	Stereoscopic photographs	ME: thickening of the retina with or without partial loss of transparency within 1 disc diameter from macular center or the presence of focal photocoagulation scars in the macular area CSME: retinal thickening at or within 500 µm from the center of the macula, or hard exudates within 500 µm of the center of the macula associated with thickening of the adjacent retina, or zone or zones of retinal thickening at least 1 disc area in size, at least part of which is 1 disc diameter from the center of the macula, or signs of past focal photocoagulation treatment	14	Cumulative incidence of DME 26.1% Cumulative incidence of CSME 17.0%
Klein and colleagues, 1995 ⁴⁶	Type 1 & 2 diabetes, United States	Stereoscopic photographs	ME: thickening of the retina with or without partial loss of transparency within 1 disc diameter from macular center or the presence of focal photocoagulation scars in the macular area	10	Annual incidence of DME over first 4 years: Younger-onset: 2.3% Older-onset: 1.4% Annual incidence of DME over next 6 years: Younger-onset: 2.0% Older-onset: 2.4%

ME, macular edema; CSME, clinically significant macular edema; FA, fluorescein angiography; OCT, optical coherence tomography.

not clear. In the UKPDS trial involving patients with newly diagnosed type 2 diabetes, the group that received intensive therapy had 25% reduced risk of microvascular end points (retinopathy requiring photocoagulation, vitreous hemorrhage, and/or fatal or non-fatal renal failure) compared to the conventional treatment group.⁸² A similar finding was also observed in two Japanese studies.^{83,84} In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial involving type 2 diabetic patients,⁸⁵ although intensive glycemic control (HbA1c <6.0%) did not reduce the progression of DR defined by development of “need for retinal photocoagulation or vitrectomy to treat retinopathy,” intensive control did reduce deterioration of visual acuity defined by “3-line change in visual acuity” associated with DR.⁸⁶ In contrast, in the Action in Diabetes and Vascular Disease (ADVANCE) trial,⁸⁷ aggressive glycemic control (HbA1c <6.5%) showed no significant benefit in terms of onset or progression of retinopathy in type 2 diabetes. A recent meta-analysis involving participants with type 2 diabetes from seven trials showed that intensive glycemic control reduced the risk of DR by 20%⁸⁸ but increased the risk of hypoglycemia by 30%. In addition, an increased risk of death due to cardiovascular causes was reported with intensive glycemic control in the ACCORD and the Veterans Affairs Diabetes trials.⁸⁹

In summary, while hyperglycemia is a risk factor for DR in both type 1 and type 2 diabetes, benefits of tight glycemic control were more evident in type 1 diabetes. It should be noted that strict glycemic control may be effective in preventing or delaying the onset of DR in patients with diabetes, but rapid reductions in HbA1c should be cautioned considering the adverse effects.

Trend 6: Blood pressure is an important risk factor for diabetic retinopathy in persons with type 2 diabetes

BP has been shown to be associated with DR in several prospective studies.^{50,68,90–95} In the WESDR type 1 diabetes cohort, baseline hypertension was associated with incidence of PDR at 14 years follow-up,⁴⁹ higher systolic BP at baseline with incidence of PDR at 25 years follow-up, and baseline systolic BP with incidence of DME at 25 years follow-up.⁴¹ Higher diastolic BP between baseline and 4-year follow-up was associated with progression of DR at both 14 years and 25 years follow-up,^{41,49} and baseline systolic BP was associated with 25-year DME incidence.⁴⁸ Interestingly, this finding was not observed in those with type 2 diabetes in the WESDR cohort,⁹² possibly due to selective mortality of those with both DR and high BP as those with type 2 diabetes are older than those with type 1 diabetes.⁹² In a 5-year community-based prospective study conducted among Chinese adults with type 2 diabetes in

Shanghai, high BP was independently associated with incident DR.⁶⁸

Evidence from RCTs have consistently shown the effectiveness of BP control in reducing the risk of DR. The UKPDS,⁹⁶ including hypertensive patients with type 2 diabetes, reported that patients allocated to tight BP control (<150/85 mmHg) had 37% reduced risk of microvascular disease, 34% decreased risk of DR progression and 47% reduced risk of deterioration in visual acuity of three lines over a 9-year period.^{97,98}

In addition to the effect of BP on DR risk, the effect of anti-hypertensive medication use on DR has also been investigated. In the EURODIAB Controlled Trial of Lisinopril in Insulin-Dependent Diabetes Mellitus,⁹⁹ after a 2-year follow-up, the group assigned to treatment with lisinopril, an angiotensin-converting enzyme (ACE) inhibitor, had a 50% reduction in the risk of progression of retinopathy compared to participants who were on placebo. In the Diabetic Retinopathy Candesartan Trial (DIRECT), the group assigned to candesartan, an angiotensin II receptor antagonist, had 18% reduction in incidence of retinopathy and 35% reduction in progression of retinopathy in persons with type 1 diabetes, and 34% increase in regression of retinopathy in those with type 2 diabetes.^{100,101} In the Renin-Angiotensin System Study, treatment with ACE inhibitors, enalapril and losartan, was reported to reduce retinopathy progression by 70% after 5 years of follow-up.¹⁰² In the ADVANCE Preterax and Diamicon MR Controlled Evaluation Retinal Measurement Study, while lowering BP with an ACE inhibitor and diuretic combination (perindopril-indapamide) did not significantly reduce the incidence or progression of retinopathy in patients with type 2 diabetes, fewer patients experienced new or worsening DR in the BP lowering treatment group compared with placebo after 4.5 years of follow-up.¹⁰³ Although several clinical trials have shown that ACE inhibitors are effective in controlling BP in patients with diabetes, ACE inhibitors were not found to be superior to other anti-hypertensive agents for controlling BP in patients with hypertension and DR.⁹¹

In summary, while well-controlled BP was associated with decreased incidence and progression of DR, more studies are needed to establish a clear BP cut-off before BP targets are incorporated into clinical practice.

Trend 7: The relationship between dyslipidemia and diabetic retinopathy remains unclear

Several population-based studies have examined the association between dyslipidemia and DR.^{81,104–107} In the Madrid Diabetes Study including 3443 persons with type 2 diabetes, higher levels of low

density lipoprotein (LDL) cholesterol increased the 4-year risk of DR 8-fold.¹⁰⁶ Findings from cross-sectional studies were inconsistent. While higher levels of triglycerides were marginally associated with DR in those with type 2 diabetes in an Indian study,¹⁰⁵ higher levels of total and LDL cholesterol were found to be protective of any retinopathy in a Singapore study,⁸¹ and serum lipids (high density lipoprotein cholesterol, LDL cholesterol, triglycerides) failed to show significant associations with DR in a US study.¹⁰⁷

In contrast to observational studies, evidence from two major RCTs show that fenofibrate, a peroxisome proliferator activated-receptor alpha (PPARα) agonist used to reduce cholesterol levels mainly in patients at risk of cardiovascular disease, had an effect on DR progression. A retrospective study comparing the progression of DR in persons with type 2 diabetes treated with and without fibrates in the UK reported a 22% reduction in rates of new onset of DR in the fibrate-treated group.¹⁰⁸ In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) Study,¹⁰⁹ 3.6% of participants with type 2 diabetes who received fenofibrate required laser therapy for retinopathy compared to 5.2% in the placebo group ($p = 0.0003$) over a 5-year period. In the ACCORD Eye Study,¹¹⁰ therapy with 160 mg of fenofibrate plus simvastatin daily in those with type 2 diabetes, reduced the progression of DR by 40% compared to placebo plus simvastatin. However, in these trials, the mechanism of the beneficial effect of fenofibrate did not appear to be attributable to the observed changes in the circulating levels of lipid. Mechanisms unrelated to lipids have currently been postulated to be attributable to the beneficial effect on DR. Fenofibrate has been hypothesized to protect the retina from the adverse effects of oxidative stress by preventing lipid deposition and lipotoxicity by upregulating apolipoprotein A-1 production,¹¹¹ and by promoting expression of antioxidant enzymes (such as superoxide dismutase and glutathione),¹¹² by activating PPARα. There is also evidence to suggest that fenofibric acid, an active metabolite of fenofibrate, prevents apoptosis (programmed cell death) of retinal endothelial cells¹¹³ by downregulating stress-mediated signaling and induction of autophagy and survival pathways of the retinal pigment epithelium,¹¹⁴ and prevents inflammatory disruption of the retinal epithelium pigment by suppressing the activation of adenosine monophosphate-activated protein kinase (AMPK).¹¹⁵

In summary, although fenofibrate has been shown to be effective in reducing the progression of DR in type 2 diabetes, it is unclear if the same effect will be observed in patients with type 1 diabetes,¹¹⁶ and the mechanisms of action are not well understood.

Trend 8: Photographic screening of diabetic retinopathy using a tele-ophthalmology platform is increasingly being recognized as a feasible and cost-effective screening strategy

As DR remains asymptomatic until advanced, and there is strong evidence that laser treatment prevents vision loss, regular eye examinations are recommended for people with diabetes. In the long term, early detection of DR also motivates patients to better manage their diabetes with improved glycemic and BP control.¹¹⁷ Compelling data from Sweden and England where a DR screening service is offered for free, showed that vision loss from DR could largely be prevented by regular eye screening.^{38,118} Incidence of vision loss from DR has been shown to be reduced by more than a third in Stockholm county¹¹⁸ and by more than two-thirds in the Newcastle district in England,³⁸ a decade after the introduction of the DR screening service. The American Diabetes Association and the American Academy of Ophthalmology recommend that people with type 2 diabetes should have an initial dilated eye examination at the time of their diabetes diagnosis and subsequent examinations should be yearly or more frequently if retinopathy is progressing.¹¹⁹ Despite the recommendations and guidelines, adherence to DR screening has been reported to be low possibly due to lack of awareness, lack of healthcare resources or poor access to care. Telemedicine-based DR screening, where digital retinal photographs taken with non-mydriatic cameras at the point-of-care are transmitted for remote interpretation by trained readers and consultation by ophthalmologists is gaining popularity due to improved access with wider coverage, improved accuracy, efficiency, and cost-effectiveness.^{16–19}

Trend 9: An accurate predictive model of patients at risk of diabetic retinopathy remains to be developed

While large epidemiological studies have identified poor glycemic control, higher BP, and dyslipidemia as important risk factors associated with progression of DR, studies integrating these risk factors into a DR risk score to improve prediction of DR are scarce. A precise prediction model is important as it allows clinicians to identify individuals at high risk for early treatment and counseling, thereby reducing the risk of progression from non-proliferative DR to vision-threatening DR.¹²⁰ In addition, risk scores help efficient allocation of healthcare resources, for example, in initiating treatment or to schedule follow-up.¹²¹ Using data from health insurance enrollees of a large managed care network in the US, Harris and colleagues attempted to

construct a risk model based on risk factors such as age at first diagnosis of non-proliferative DR, sex, race, comorbid hypertension, dyslipidemia, diabetic nephropathy, neuropathy, non-healing foot ulcers, HbA_{1c} level, and treatment with ACE inhibitors, statins, sulphonylureas, metformin, and insulin.¹²² The 5-year probability of DR progression from non-proliferative DR to PDR was reported to be as low as 5% for those with few risk factors and as high as 38% for those with multiple risk factors.¹²² However, the findings of this study should be interpreted with caution as the study was limited by lack of information on other important risk factors of DR such as diabetes duration, BP, body mass index etc, and the authors did not perform empirical testing for the efficacy of their prediction model.

Trials that examined the effect of intensive treatment against multiple risk factors in patients with diabetes have also shown inconsistent findings with respect to DR. In the Steno-2 Study, long-term intensive treatment against multiple factors including hyperglycemia, hypertension, dyslipidemia, and microalbuminuria in patients with type 2 diabetes reduced the risk of macro- and microvascular events including DR by about 50%.¹²³ Nonetheless, the same benefits of multifactorial treatment (medications targeting hyperglycemia, hypertension, and dyslipidemia together with promotion of a healthy lifestyle) on microvascular complications were not observed in a subsequent multicenter cluster RCT conducted across 343 primary care practices in Europe.¹²⁴ Compared to routine care, target-driven multifactorial intervention failed to show significant reductions in the prevalence of any of the three microvascular outcomes including nephropathy, neuropathy, and DR at 5 years.¹²⁴ Clearly, there is a paucity of prediction models for DR and more studies developing accurate models for predicting risk of DR in multiple diverse populations and validating the developed equations are needed before being put to clinical use.

Trend 10: Diabetic retinopathy prevention in low-resource settings requires different public healthcare models and strategies

Although the prevalence of diabetes is increasing worldwide, the overwhelming burden of diabetes has been shown to affect low-middle income countries, where four out of five people with diabetes are living, and is a major concern.²⁷ Despite the increasing burden of diabetes in low-middle income countries, epidemiological data for DR in these countries is limited or non-

existent. Available estimates suggest that the estimates of DR in these countries are comparable to those reported from developed countries. The prevalence of any DR among those with diabetes in low-middle income countries has been shown to range from 18–22% in India,¹²⁵ 23% in China,¹²⁶ 30% in Latin America and 30–32% in Africa.² Prevalences in rural populations were reported to be 18% in rural India¹²⁷ and 43% in rural China.¹²⁸ Prevention of DR in low-middle income countries face significant challenges due to lack of resources. The World Health Organization (WHO) and International Diabetes Federation have initiated programs and projects to improve prevention of blindness from diabetes globally and in particular in low-middle income countries by supporting the adoption of effective measures for the surveillance, prevention and control of blindness due to DR.^{7,129–132} These include: (1) Establishing and maintaining a web-based source to assist policy makers in the implementation of national diabetes programs including educational materials, treatment guidelines, training manuals developed in different settings, evidence-based information, and online access to expert advice; (2) educating diabetic patients about risk factors of DR and promoting a healthy lifestyle at primary care level; (3) adding dilated ophthalmoscopic exams to assess the magnitude of DR to Rapid Assessment of Avoidable Blindness (RAAB) studies, a screening method originally designed to enumerate causes of avoidable blindness due to cataract, refractive error, trachoma and corneal scarring in low-resource settings; (4) capacity building by empowering and training primary healthcare workers with skills to perform screening and counseling; (5) use of low-cost screening technologies such as digital retinal imaging and remote grading; (6) strengthening secondary-level centers for laser photocoagulation and tertiary-level facilities for retinal surgery; (7) improving access to care using mobile health vans or health-care services that move closer to patients' homes; (8) to ensure sustainability, integrating DR screening programs into existing public health programs such as the healthy lifestyle initiative, primary health care, disease control program etc; (9) encouraging the commitment and support of nongovernmental organizations and private sectors in strengthening and promoting DR control programs. Although adopting the public health approach has been accepted as a priority by several member countries of WHO,^{131,133–135} challenges in implementation remain, including poor health-care systems, lack of awareness about DR among persons with diabetes, lack of well-trained personnel, lack of tertiary eye-care services, logistical constraints for screening, treatment and follow-up, and difficulty in ensuring compliance with treatment.

Conclusion

In conclusion, we provide a current overview of the trends in the epidemiology of DR in the last few decades. An epidemic of diabetes is imminent; consequently the absolute numbers of DR cases will increase worldwide, in particular in low-middle income countries. Awareness of DR remains alarmingly low and concerted efforts are needed to educate patients, physician, policy makers, and the population. The decline in blindness due to DR in the last decade in developed countries in the US and Europe suggest comprehensive and well-organized public health efforts may help curtail the burden of blindness due to DR. Public health initiatives in low-middle income and low resource setting countries are gaining momentum but significant challenges remain.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the writing and content of this article.

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