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Review

# Diabetic retinopathy: global prevalence, major risk factors, screening practices and public health challenges: a review

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## Abstract

Diabetes retinopathy (DR) is a leading cause of vision loss in middle-aged and elderly people globally. Early detection and prompt treatment allow prevention of diabetes-related visual impairment. Patients with diabetes require regular follow-up with primary care physicians to optimize their glycaemic, blood pressure and lipid control to prevent development and progression of DR and other diabetes-related complications. Other risk factors of DR include higher body mass index, puberty and pregnancy, and cataract surgery. There are weaker associations with some genetic and inflammatory markers. With the rising incidence and prevalence of diabetes and DR, public health systems in both developing and developed countries will be faced with increasing costs of implementation and maintenance of a DR screening program for people with diabetes. To reduce the impact of DR-related visual loss, it is important that all stakeholders continue to look for innovative ways of managing and preventing diabetes, and optimize cost-effective screening programs within the community.

## Introduction

Diabetes mellitus (DM) is one of the world's fastest growing chronic diseases and a leading cause of acquired vision loss.[1] According to the World Health Organization, it is estimated that the total number of people with diabetes will double from 171 million in 2000 to 366 million by 2030.[2] Diabetic retinopathy (DR), a specific microvascular complication of DM, remains the leading cause of acquired vision loss worldwide in middle-aged and therefore economically active people.[1,3,4] With the increasing number of people with diabetes, the number of DR and vision-threatening DR (VTDR), which includes severe non-proliferative DR, proliferative DR (PDR) and diabetic macular edema (DME), has been estimated to rise to 191.0 million and 56.3 million, respectively by 2030.[5]

Over the past few decades, there have been major advances made in understanding the epidemiology of DR, systemic control of DM to prevent DR development and progression, clinical assessment, diagnosis and management of DR and VTDR. There is widespread knowledge that screening, early detection and prompt treatment of VTDR allow prevention of diabetes-related visual impairment.[6] Randomized controlled trials have shown that early treatment can reduce an individual's risk of severe visual loss by 57%.[7] However, DR screening services in developing and developed countries remain patchy, and are constantly challenged by unclear guidelines on the most appropriate method to screen (e.g. clinical examination *vs* fundus photography), and the increasing resources needed for implementation and maintenance of a comprehensive DR screening programs.[8] Thus, DR is an increasingly significant major public health problem, especially in many middle-to-low income countries where access to trained eye-care professionals and secondary and tertiary eye-care services (e.g. access to laser and intra-vitreal therapies) may be suboptimal. It is,

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therefore important that all public and private stakeholders continue to look for innovative ways of managing DM, improve access to DR screening, and plan and optimize cost-effective screening programs within the community.

This review article aims to explore the global prevalence and incidence of DR, the major risk factors for DR, DR screening practices worldwide and the challenges in public health in implementing appropriate DR screening and management strategies.

## Global Epidemiology of DR

### Global prevalence of DR

According to the World Health Organization (WHO), it is estimated that DR accounts for 4.8% of the number of cases of blindness (37 million) worldwide.[9] A pooled analysis of 22 896 people with diabetes from 35 population-based studies in the U.S., Australia, Europe and Asia (between 1980–2008) showed that the overall prevalence of any DR (in T1DM and T2DM) was 34.6% (95%CI 34.5–34.8), with 7% (6.9–7.0) VTDR.[10]

### Type 1 Diabetes (T1DM)

The prevalence of DR was reported to range from 10 to 50%, depending on the population and methods used to screen for DR, and the duration of diabetes.[11] Given the significant variation in management of T1DM in different health care systems, the comparison of prevalence of T1DM-related DR should be analysed with caution. The EURODIAB study, a multicentre study involving 31 clinics in 16 European countries, reported the prevalence of DR among T1DM patients ranged from 25% in Austria to 60% in Portugal.[12] In 2004, the pooled data from two US studies of T1DM (Wisconsin Epidemiologic Study of Diabetic Retinopathy – WESDR, and the New Jersey 725 study) found the prevalence for any DR and VTDR of 82% and 32%, respectively.[13] The DR prevalence among the T1DM was reported to be lower in Asia with the lowest prevalence in India (13.4%),[14] followed by China (14%).[15] In Australia and New Zealand, the DR prevalence rate ranged from 25% to 42%.[16–19] The prevalence of DME is related to the disease duration, with low rates of DME within 5 years of T1DM diagnosis, increasing to 29% at 20 years.[20] The prevalence was found to vary over time, likely because of the improved health care for T1DM over time and the incidence studies can provide better insights into these temporal changes.

### Type 2 Diabetes (T2DM)

The overall prevalence DR and VTDR in T2DM were 25.2% and 6.9%, respectively.[10] According to Liverpool Diabetic Eye Study[21] and the United Kingdom Prospective Diabetes Study (UKPDS),[22] the DR prevalence for T2DM in United Kingdom ranged from 25% to 27%. The prevalence of DR in other European countries such as Sweden, Denmark and Italy were slightly higher, ranging from 30% to 40%.[23–25] In the United States, there were several large population-based studies reporting on DR prevalence and incidence (San Luis Valley Study,[26] Los Angeles Latino Eye Study [LALES],[27] Multi-ethnic Study of Atherosclerosis [MESA][28] and Veterans Affairs Diabetes Trial [VADT][29]). The prevalence of DR ranged from 30 to 50%, with the highest prevalence seen in the Hispanic population.[30] Various population-based studies in Australia (e.g. AusDiab study,[31] Blue Mountains Eye Study [BMES],[32] Melbourne Visual Impairment Project [MVIP][33] and Newcastle Diabetic Retinopathy Study)[34,35] reported DR and VTDR prevalence rate of 22%–35% and 1.2%–7.1%, respectively among T2DM patients.

In the past, DR prevalence had been relatively low in Asia.[36,37] In China, the prevalence of DR in T2DM ranged from 28% to 43%.[38,39] Because of poorer access to screening services, the prevalence of DR was higher in the rural than the urban areas in China.[38] On the contrary, the Indians who lived in urban areas had higher prevalence of diabetes (28.2% *vs* 10.4%) and DR (18% *vs* 10.3%) as compared to the rural Indians.[37,40] In a multi-ethnic Asian population-based study, Chiang et al. also reported racial differences in the prevalence of diabetes but not diabetic retinopathy, with the highest prevalence seen in the Indian (28.9%) and, followed by the Malay (24.8%) and Chinese (20.1%).[41]

The Singapore Indian Eye Study reported a higher DR prevalence (33%) amongst the migrant Indians who lived in Singapore (a newly urbanized Asian country) than those living in urban India.[42] It had been postulated that new migrant Indians in Singapore frequently experience new lifestyle patterns and dietary habits with calorie-dense/lower-fiber foods, further complicated by the psychological stressors, shortage of financial resources and/or other unmeasured inequalities.

### Incidence and Progression of DR

#### *Type 1 Diabetes (T1DM)*

In Europe, 50% of T1DM with no DR at baseline had been shown to develop retinopathy by 5 to 7 years, and 9% with mild NPDR would develop PDR by 5 years.[43] On the other hand, the US WESDR showed the 10-year DR incidence in T1DM was 74%, increasing to 97% after 25 years. Of those who had any DR at baseline, the incidence of DR progression (2+ steps progression on Early Treatment Diabetic Retinopathy Study [ETDRS] scale) was 64% at 10 years and 83%

at 25 years.[44] Annual estimates of the 25-year WESDR study have shown a decline in PDR and DME incidence in the latter half of the study compared to the first 12 years.[44,45]

## Type 2 Diabetes (T2DM)

In UK, the 5-year cumulative DR incidence in T2DM was 4%, rising to 16.4% after 10-years follow-up (from no retinopathy to pre-proliferative retinopathy).[46] The annual incidence of retinopathy in US (LALES) was 7.1%,[27] similar to WESDR (8.6%)[44] and the Barbados Incidence Study of Eye Diseases (7.5%),[47] but was higher than the rates found in the non-US studies, predominantly on white population. In Australia, the BMES reported the 5-year DR cumulative-incidence and DR progression (1+ ETDRS steps) were 22.2% and 25.9%.[48] In Hong Kong, the 4-year cumulative DR incidence, DR progression (2+ ETDRS steps) and VTDR incidence for T2DM were 15.2%, 45.5% and 0.03%, respectively.[49]

## Declining Prevalence and Incidence of DR

With the increased awareness of DR risk factors, better glycaemic control and access to the screening programs in the community, there is a decline in the prevalence and incidence of DR in the developed countries such as US, Australia and the European countries. A systematic review and meta-analysis covering 1975–2008 showed a significant decline in prevalence of DR, as compared to the rates before 1985.[50] The 10-year incidence of PDR and severe visual loss (SVL) were substantially lower in the studies published between 1986 and 2008, compared to the ones before 1985 (PDR: 6.6% [95% CI: 0.0–18.3%] *vs* 11.5 [0.0–25.7%]; SVL: 2.6 [0.0–7.1%] *vs* 6.0 [0.9–11.1%]).[50] In US (WESDR), the annual incidence of PDR declined from 3.4% to 1.4% whereas for clinically significant macular edema (CSME), it decreased from 1.0% to 0.4% in T1DM.[44] There is lack of follow-up study that evaluates the subsequent trend in DR incidence and prevalence over the last 10 years. In addition, more recent rural population-based surveys have shown a higher DR prevalence rate as compared to the metropolitan area, because of limited access to the health care facilities.[37,40] Although studies have documented a decline in the incidence of DR among those with T1DM, the DR trend of T2DM patients still remains unknown.

## Major Risk Factors For DR

The risk factors of DR can be broadly divided into modifiable and non-modifiable factors (Table 1). The modifiable risk factors include hyperglycaemia, hypertension, hyperlipidemia and obesity (Fig. 1). In contrast, duration of diabetes, puberty and pregnancy are the non-modifiable risk factors for DR development and progression.

## Hyperglycaemia

The Diabetes Control and Complications Trial (DCCT) and UKPDS were the two landmark clinical trials that showed tight glycaemic control [HbA1c value of 7% or less] could reduce the risk of DR development and progression in T1DM and T2DM patients, respectively.[22,51] In DCCT for T1DM, intensive treatment (median HbA1c of 7.2%) reduced the DR incidence (2+ ETDRS steps) and progression (3+ ETDRS steps) by 76% (95%CI 62–85%) and 54% (95%CI 39–66%), respectively, as compared with conventional treatment (median HbA1c of 9.1%).[52,53] In T2DM, UKPDS showed a reduction of DR by 25%, including the need for laser photocoagulation.[54] For every 1% decrease in HbA1c, there was a reduction in 40% of DR development, 25% progression to VTDR, 25% need for laser therapy and 15% blindness in people with diabetes.[55] In addition, intensive glycaemic control had been shown to reduce the 4-year incidence of DME by 58%.[53] These effects (intensive glycaemic control) appeared long lasting because of metabolic memory, also known as 'legacy effect'. It is a term used to describe the beneficial effects of immediate intensive treatment of hyperglycaemia with a sustained benefit with respect to the outcomes for many years, regardless of glycaemia in the later course of diabetes.[56] It is suggested that early glycaemia normalization can halt hyperglycaemia-induced pathological processes associated with enhanced oxidative stress and glycation of cellular proteins and lipids.[57] In the Action to Control Cardiovascular Risk in Diabetes Eye study, intensive control of HbA1c (median of 6.4%) decreased the progression of DR from 10.4% to 7.3% over 4 years. However, the results may carry limited clinical relevance as the author defined progression of DR as 3+ ETDRS steps on a 17-point scale, and this finding was only applicable to those with mild retinopathy.

Tight glycaemic control, however, has two potential adverse effects – early worsening of DR and hypoglycaemic attacks.[55] In DCCT, the intensive group had more T1DM patients with DR worsening (3+ ETDRS) as compared to the conventional treatment group (13.1% *vs* 7.6%, OR 2.1; $P < 0.001$) but this effect was reversed by 18 months.[58] On the other hand, intensive treatment is also associated with a three-fold risk of hypoglycaemia as compared with conventional treatment in a meta-analysis.[59] The incidence of severe hypoglycaemia increased by 9.1 episodes per 100 person-years in the intensively treated patients.[59] In fact, the Action to Control Cardiovascular Risk in Diabetes trial was stopped prematurely after 3.5 years prior to study completion given the fact that the intensive therapy group

**Table 1.** Risk factors for diabetic retinopathy

| | |
|---|---|
| *Modifiable* | |
| 1. HbA1c[55] | Decrease in every 1% = reduction in 40% of retinopathy, 25% need for retinal laser and 15% of blindness |
| 2. Systolic Blood Pressure[44,45] | Decrease in every 10 mmHg = reduction in 35% of retinopathy, 35% need for retinal laser and 50% blindness<br>However, two Asian clinic-based studies did not show association of blood pressure with the incidence and progression of DR |
| 3. Hyperlipidemia[73] | DR is associated with triglycerides level whereas DME is associated with LDL, high non-HDL cholesterol and high HDL/LDL ratio |
| 4. Body Mass Index (BMI)[78] | i. Increased waist–hip ratio, BMI >31 kg (men); BMI >32 kg (women) and BMI <20 kg were associated with increased risk of DR development |
| *Non-modifiable* | |
| 1. Puberty[88] | Post pubertal period has 30% increased risk of DR development and the onset to any DR was faster (2 years shorter) compared to the prepubertal period |
| 2. Pregnancy[84,85] | i. Pregnancy could increase risk of DR progression by 2.3 times<br>ii. During postpartum period, 29% would have DR regression<br>iii. Pregnant women with retinopathy is at much higher risk of DR progression, with 47% progression and 50% of those required laser treatment |

DME, diabetic macular edema; DR, diabetic retinopathy; HbA1c, glycated haemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

(targeting at HbA1c level of less than 6%) has significantly higher mortality rate (hazard ratio, 1.22; 95% CI, 1.01–1.46%, $P=0.04$) and more hypoglycaemic attacks (10.5% *vs* 3.5%, $P<0.001$), compared with the standard treatment group.[60]

The Action in Diabetes and Vascular Disease (ADVANCE) trial, however, did not demonstrate an increase in risk of death associated with intensive treatment. This was a multicentre trial involving over 10 000 patients with T2DM from 215 collaborating centres in 20 countries from Asia, Australia, Europe and North America. The study found that the HbA1c threshold for macro-vascular events and death was 7%, whereas for micro-vascular events, it was 6.5%.[61] Above these thresholds, the risks increased significantly; every 1% higher HbA1c level was associated with a 38% higher risk of a macro-vascular event, a 40% higher risk of a micro-vascular event

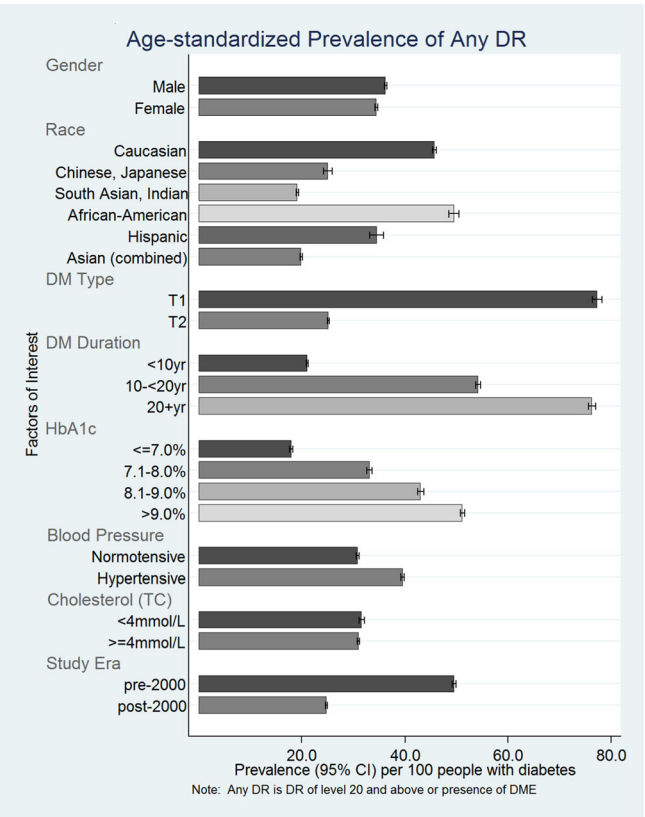


**Figure 1.** Age-standardized prevalence of any diabetic retinopathy by subgroups of interest, in diabetic subjects aged 20 to 79 years. (Bar indicates prevalence estimate, and capped line indicates 95% confidence interval).[10]

and a 38% higher risk of death (all $P < 0.0001$). On the other hand, there was no evidence of achieving additional benefit in reducing macro- and micro-vascular complication below these thresholds, but neither was there clear evidence of harm. Thus, it is crucial to gradually optimize the HbA1c level, aiming for a level between 6.5% and 7% as a long-term management goal, to reduce the incidence of DM-related macro- and micro-vascular complications.

## Hypertension

In spite of several epidemiologic studies not finding blood pressure to be a consistent risk factor for DR incidence and progression,[62–64] multiple randomized controlled trials (RCTs) have demonstrated the benefits of tight blood pressure (BP) control as a major modifiable factor for DR incidence and progression. The UKPDS was the first RCT that showed the importance of tight BP control in reducing retinopathy.[22] A total of 1048 hypertensive T2DM patients were randomized into intensive BP control (target systolic/diastolic BP: <150/85 mmHg) *versus* conventional control group (target BP: <180/<105 mmHg). After 9 years of follow-up, patients with tight BP control had a reduction of risk in DR progression by 34% (99%CI 11–50) and visual acuity deterioration by 47% (99%CI 7–70). It has been shown that every 10 mmHg increase in systolic blood pressure was associated with 10% increased risk of early DR and 15% risk of PDR or DME.[44,45]

On the other hand, anti-hypertensive medications that target the renin–angiotensin system, including angiotensin II receptor antagonists (Candesartan[65,66] and Losartan[67]) and angiotensin-converting-enzyme inhibitor (Enalapril),[67] may have additional benefit in slowing DR progression, independent of their hypotensive properties. The Diabetic Retinopathy Candesartan Trials (DIRECT) is a multicentre (309 centres) RCT involving 5231 patients with T1DM or T2DM who were assigned into placebo or 32-mg candesartan, an angiotensin II receptor blocker.[66,68] In T1DM (DIRECT-Prevent-1, $n = 1421$ and DIRECT-Protect 1, $n = 1905$),[66] the candisartan group had a marginal effect on lowering incidence of DR (2+ ETDRS steps) by 18%, but not on DR progression (3+ ETDRS steps). In post-hoc analyses, candesartan had been shown to reduce incidence of DR by 35% (hazard ratio 0.65, 95% CI 0.48-0.87%). For T2DM, candesartan reduced DR progression by 13% in the primary outcome, though it was not statistically significant. For secondary outcome, the treatment was shown to increased DR regression by 34% in participants with early retinopathy.[65,66] The results from DIRECT trial suggested overall beneficial effects of candesartan in reducing retinopathy in T1DM and T2DM (with more obvious effect seen in the early retinopathy group), but it did not achieve either of the pre-specified primary endpoint of both studies.[65]

In the Renin–Angiotensin System Study, both Enalapril and Losartan were able to reduce risk of DR progression by 65% and 70%, respectively in T1DM, irrespective of their blood pressure lowering actions.[69] The EURODIAB Controlled Trial of Lisinopril in Insulin-Dependent diabetes Mellitus showed that the Lisinopril, an angiotensin converting enzyme inhibitor, could reduce DR progression by 50% in the first year and 80% in the second year, for those normotensive and normoalbuminuric cases.[70] However, this study was confounded by the baseline differences in glycaemic level of the treatment *versus* the control group. In addition, neither UKPDS nor the Appropriate Blood pressure Control in Diabetes (ABCD)[71] study reported superiority of angiotensin converting enzyme inhibitor over other anti-hypertensive agents to prevent DR progression. Despite of conflicting results reported on the effect of blood pressure on DR incidence and progression, it is crucial for the primary health care physicians to monitor and optimize the blood pressure for patients with diabetes to prevent DM-related complications in the long term.

## Hyperlipidemia

Various studies have reported inconsistent results on the effect of lipid on the development and progression of DR and DME.[72–74] DCCT showed that the severity of DR correlated positively with increasing triglycerides and inversely with high-density lipoprotein (HDL) in T1DM.[75] However, there was no association between total cholesterol and DR shown in the Multi-Ethnic Study of Atherosclerosis (MESA)[28] and the Chennai Urban Rural Epidemiology Study (CURES) Eye Study.[74] Of the subset in the lipid panel, triglycerides were shown to be related to the presence of DR and the low-density lipoprotein was related to DME.[74] In Sankara Nethralaya-Diabetic Retinopathy Epidemiology and Molecular Genetic Study (SN-DREAMS), high serum low-density lipoprotein (OR: 2.72), high non-high density lipoprotein cholesterol (OR: 1.99) and high cholesterol ratio (OR: 3.08) were related to DME.[73]

The subgroup of Action to Control Cardiovascular Risk in Diabetes Eye study has also demonstrated that fenofibrate reduced the DR progression at 4 years in T2DM patients, compared to placebo group (6.5% *vs* 10.2%).[60] The 5-year Fenofibrate Intervention and Event Lowering in Diabetes study randomized 9795 people with T2DM to daily fenofibrate (a triglyceride-lowering agent) or placebo. The requirement for first laser treatment for all retinopathy was significantly lower in the fenofibrate group than in the placebo group (3.5% *vs* 4.9%, hazard ratio = 0.69; 95% CI 0.56–0.84%,

absolute risk reduction 1.5% [0.7–2.3%], $P=0.0002$). The primary endpoint of 2+ ETDRS progression was similar between the two groups and in the subset of patients without pre-existing retinopathy. In patients with pre-existing retinopathy, fewer patients on fenofibrate had a 2+ ETDRS progression than did those on placebo (3.1% *vs* 14.6%, $P=0.004$), and fewer had macular edema or laser treatments.[76] The use of fenofibrate, however, did not seem to correlate with the lipid level in the same study, suggesting that there may be an unknown protective effect of fenofibrate in DM patients.

## Body Mass Index (BMI)

Although the influence of BMI on DR had shown conflicting results,[77–79] more recent reports showed positive correlation of increased BMI and waist to hip ratio (WHR) with increased risk of DR.[80–82] In WESDR, the association between obesity (BMI >31 for men and >32 for women) *versus* DR severity and progression (2+ ETDRS steps) was not statistically significant ($P>0.05$).[78] In the same study, the underweight patients (<20 kg/m$^2$) were associated with increased DR incidence ($P=0.04$),[78] suggesting that patients with poor overall systemic health may experience concomitant weight loss. The mean BMI of each quartile, however, was not available in that study. The Diabetes Incidence Study in Sweden reported significant association between baseline high BMI and severe NPDR and PDR ($P=0.001$), after 10 years of follow-up.[80] The EURODIAB Prospective Complications study showed increased WHR was associated with DR severity and progression in T1DM (hazard ratio: 1.3; 95%CI 1.0–1.6%, $P<0.05$).[83] Even though the evidence is still equivocal between BMI and DR, it is, however, still critical for people with diabetes to maintain an optimal BMI and WHR to prevent development and progression of DR and other diabetes-related complications.

## Puberty and Pregnancy

DR can worsen rapidly during puberty and pregnancy, especially in T1DM.[84–89] In WESDR, there was a 30% excess risk of developing DR, comparing the period before and after menarche.[86] The mean time to development of DR is significantly shorter for subjects with T1DM diagnosed after puberty than for those diagnosed before puberty. (9.4 years *vs* 11.8 years, $P=0.0004$).[88] In WESDR, pregnancy increased the risk of DR progression by 2.3 times (adjusted OR: 2.3; $P<0.005$).[90] Other similar studies have shown increased DR progression including development of VTDR during pregnancy.[84,85] Severity of DR at the beginning of pregnancy has been shown to influence the risk of progression. For patients with absent DR at baseline, DR progression in pregnancy was shown to be low.[91] Of those with NPDR, 47% progressed to a more severe spectrum with 50% requiring laser treatment.[92] During the postpartum period, 29% had regression of DR.[92] Therefore, non-mydriatic photography should be performed for T1DM after puberty, early onset T2DM during childhood and during the course of pregnancy. For those pregnant women with PDR, they may benefit from early pan-retinal photocoagulation treatment and close review during the pregnancy and postpartum period.[85]

## Cataract Surgery

The ETDRS showed DR progression was associated with intra-capsular extraction and extra-capsular cataract extraction surgery.[93] With the adoption of the phacoemulsification surgeries, fewer patients were found to have DR progression postoperatively, compared to intra-capsular extraction or extra-capsular cataract extraction patients.[94] Pre-operative poor glycaemic control was associated with postoperative DR progression.[95] In patients with PDR, panretinal photocoagulation performed less than 6 months preoperatively was shown to increase the risk of postoperative DME.[96] Thus, it is recommended that patients with VTDR should ideally be stabilized with panretinal photocoagulation before cataract surgery. In patients with significant cataract obscuring the fundus view, cataract surgery should be offered with postoperative surveillance of DR or DME progression.

## Inflammatory Biomarkers

Chronic or low-grade inflammation and endothelial cell dysfunction are thought to play a role in the pathogenesis of DR.[97–99] Various studies have measured the concentrations of many different inflammatory chemokines in the serum, vitreous of aqueous of patients with DR. These chemokines include prostaglandins (PgE1, PgE2), stromal cell-derived factor (SDF-1α),[100] high-sensitivity C-reactive protein (hsCRP),[101] intercellular adhesion molecule 1 (ICAM-1)[102] and vascular cell adhesion molecule 1 (VCAM-1)[102] and tumour necrosis factor alpha (TNF-α).[103] In DCCT study, the baseline hsCRP level may be associated with higher risk of incident CSME and macular hard exudate, and the increased ICAM-1 level was ssociated with the development of retinal hard exudates.[104] However, baseline VCAM-1 or TNF-α receptor 1 levels were not shown to be associated with risk of DR development in that study.[104] The markers of endothelial function can be measured using von Willebrand factor, tissue-type plasminogen activator and soluble E-selectin. Of those, the soluble E-selectin (a marker of endothelial function) was also found to

be associated with progression of retinopathy in a population-based study.[98]

## Genetic Risk Factors

Given the complexity of the disease, the field of genetic risk factors for DR is still in its infancy.[105] The attempts to identify genes in the development of DR have been limited to twin studies,[106] family studies,[107–113] candidate gene studies[114–118], linkage studies[109,118,119] and small-scale Genome Wide Association Study (GWAS).[120–122] In twin studies, more concordant twins with T2DM (95%, 35 of 37) were found to have same degree of DR severity, as compared to twins with T1DM (68%, 21 of 31).[106] The familial aggregation studies showed that siblings or relatives of T1DM or T2DM patients with DR had up to three-fold increased risk of developing DR, compared to those with no DR.[108–112] The heritability scores are the score used to estimate the amount of genetic influence on a particular behavior or trait by comparing how similar these different types of twins are, with 0 means that genes have no influence, and 1 being the sole influence of genes. The familial linkage is more consistently seen in the presence of more severe retinopathy, with heritability score of 0.18 to 0.27 for any DR,[109,113] and 0.25 to 0.52 for PDR,[108,113] in either T1DM or T2DM.

The severity and rapidity of DR onset had been associated with several genetic factors,[123] including chromosome 1p,[109] chromosomes 3 and 9,[119] aldose reductase gene (ALR2),[124] receptor for advance glycation endproducts (RAGE) gene,[125] transforming growth factor beta 1 (TGF-beta1) gene,[126] vascular endothelial growth factor (VEGF) gene,[127,128] endothelial nitric oxide synthase (eNOS) gene,[128] vitamin D receptor[128] and insulin-like growth factor 1 (IGF-I) gene.[129] However, these associations had been weak, inconsistent and lack of standardization of DR phenotype across different populations. It is difficult to draw any conclusions from these studies because the sample sizes of individual studies were often small. The *P* values obtained from these efforts are sometimes nominally significant but cannot withstand corrections for multiple testing. Also, the other limitation of candidate gene approach is that it depends on a priori hypothesis that implies that a particular gene has a functional explanation in DR pathophysiology, and if the hypothesis is wrong, the genetic association will be negative or inconsistent.

Linkage analysis and GWAS approaches are driven by chromosomal location without a need for any biochemical or pathophysiological association between the gene and the disease. Chromosomes 1, 3 and 12 had been linked with DR in Pima Indians and Mexican Americans.[109,118,119] However, none of the regions reached genome-wide statistical linkage significance. In GWAS, various single-nucleotide polymorphisms (SNPs) are had been proposed to be associated with DR traits.[120–122,130] A single-nucleotide polymorphism is a deoxyribonucleic acid sequence variation occurring commonly within a population in which a single nucleotide – A, T, C or G – in the genome differs between members of a biological species or paired chromosomes. In one of the GWAS studies, [121] DR was found to be associated with five novel chromosomal regions (chromosome 1p, 10p, 10q, 13q and 5q). Nevertheless, none of the regions reached genome-wide statistical significance. The limitations in the GWAS studies were inconsistency and low reproducibility of the single-nucleotide polymorphisms in different population, combining heterogeneous phenotypes (patients with PDR, NPDR and DME), poor characterization of health individuals (those with no DR) and poor DR standardization.

## Dr Screening Programs

Early detection and prompt treatment allow prevention of up to 98% of diabetes-related visual impairment.[6] To date, DR screening is performed in various ways by different health care professionals such as optometrists,[131,132] GPs,[132,133] screening technicians and clinical photographers, using direct ophthalmoscopy,[134] dilated slit lamp bio-microscopy with a hand-held lens (90 D or 78 D),[135] mydriatic or non-mydriatic retinal photography,[134] tele-retinal screening,[136] and retinal video recording (Table 2).[137] Irrespective of the screening methods, the International Council of Ophthalmology Guidelines recommend the examiners to assess patients' best-corrected visual acuity, obtain a thorough diabetes history including HbA1c (glycosylated haemoglobin), blood pressure profile, lipid profile, smoking status and other diabetes-related complications, as these risk factors may affect the urgency for referral by primary eye care providers to ophthalmologists.[138]

## Classification System

At present, various DR screening programs around the world use different DR classification systems.[7,139,140] For research studies, the most commonly used retinal photography screening method is the Airlie House seven standard 30° stereoscopic fields[139], graded using the ETDRS grading system (Table 3), which consists of six levels of retinopathy for one eye or 11 levels for both eyes.[140] Nevertheless, this system is rather complicated to be utilized by the primary health care physicians. To simplify the DR classification system, the WHO divided the DR severity into three levels: (i) lesions that could be reviewed in the clinic in a few

**Table 2.** The methods, sensitivity and specificity of diabetic retinopathy (DR) screening by different practitioners[19,135,137,147,151,192–194]

| Methods of DR screening | Practitioners | Outcome measure | Sensitivity % (95% CI) | Specificity % (95% CI) |
|---|---|---|---|---|
| 1. Direct ophthalmoscopy[192] | GPs | Any DR | 63 (56–69) | 75 (70–80) |
| | Optometrists | | 74 (67–81) | 80 (75–85) |
| | GPs | Referrable DR | 66 (54–77) | 94 (91–96) |
| | Optometrists | | 82 (68–92) | 90 (87–93) |
| 2. Dilated slit lamp examination[135,151] | Ophthalmologist | Referrable DR | 87 (84–92) | 95 (92–98) |
| | Optometrists | Referrable DR | 73 (52–88) | 90 (87–93) |
| 3. Retinal still photography | | | | |
| i. Mydriatic | | | | |
| Singe field (35°) colour[192] | GPs | Any DR | 79 (74–85) | 73 (68–79) |
| | Optometrists | | 88 (83–93) | 68 (62–74) |
| | Diabetologist | | 73 (67–79) | 93 (90–96) |
| Two fields (50°) – Colour[151] (Optic disc and macula) | Retinal photographers | Referrable DR | 96 (87–100) | 89 (86–91) |
| Two fields (50°) – Red free[151] (Optic disc and macula) | Retinal photographers | Referrable DR | 93 (82–98) | 87 (84–90) |
| Three fields (30°) – Colour[193] (Optic disc, macula and temporal) | Ophthalmologist | Any DR | 95 (87–98) | 99 (95–99) |
| | Medical Officer | | 92 (83–96) | 96 (92–98) |
| ii. Non-mydriatic | | | | |
| Single field (35°) – Colour[194] | Trained grader 1 | Any DR | 72 (66–79) | 96 (92–99) |
| | Trained grader 2 | | 64 (57–71) | 99 (95–100) |
| Single field (35°) – Red free[147] | Trained grader | Referrable DR | 78 | 86 |
| 4. Retinal video recording – Colour[137] (Optic disc, macula and temporal) | Ophthalmologist 1 | Any DR | 94 (84–98) | 99 (95–99) |
| | Ophthalmologist 2 | | 93 (83–98) | 95 (89–98) |

DR, diabetic retinopathy; GPs, general practitioners.

months; (ii) lesions that need a referral as soon as possible; and (iii) sight-threatening retinopathy, which requires immediate referral.[141] Furthermore, Wilkinson et al. published the International Clinical Diabetic Retinopathy and Diabetic Macular Edema Disease Severity Scales in 2003 (Table 3).[142] This classification is much simpler and more user-friendly among primary eye care physicians, allowing better communication between ophthalmologists and other health care professional.

## Retinal Photography

According to the UK National Institute for Clinical Excellence (NICE) guidelines, DR screening tests should have sensitivity and specificity of at least 80% and 95% respectively, with a technical failure rate of less than 5%.[143] At present, the Public Health England has published various guidelines on National Health Service diabetic eye screening programmes, with the aim to improve the DR screening in the primary health care setting. A two-field mydriatic retinal still photography, centering on (i) the optic disc and (ii) the macula, has been recommended as the preferred screening method to increase the screening accuracy and reduce the unwarranted referrals to the ophthalmologist in the tertiary eye care setting.[144]

Mydriatic retinal photography, with additional use of ophthalmoscopy for un-gradable cases, had been shown to be the most effective DR screening strategy.[134] It allows not only better-quality retinal images but also a minimum sensitivity of at least 80% in the detection of any grade of DR.[143] For VTDR, sensitivity and specificity increased to 97% and 92%, respectively. However, the safety of pupil dilation remains one of the fearful complications among primary eye care physicians. Nevertheless, the incidence of mydratics-induced acute angle-closure attack was reported as 6 in 20 000 Caucasians.[145] However, this may be higher among the Asian populations because of the difference in eye anatomy.

Non-mydriatic retinal photography is a popular screening technique in the primary eye care setting, as it does not require any dilating drops. Nevertheless, the drawbacks include a higher technical failure rate resulting from media opacity or small pupils, and difficulty in obtaining stereoscopic views. In detection for VTDR requiring referrals, the sensitivity was reported between 78% and 98% with the specificity of 86% and 90%[146,147] It has been proven to be a cost-effective screening method to be utilized in the primary health care setting.[148]

Recently, ultra wide-field fundus imaging technology has been implemented for DR screening. It is able to capture a 200° wide-field image in a single photograph by combining an ellipsoid mirror with a scanning laser ophthalmoscope. This technology is available in various imaging devices, including Optos (Marlborough, MA), Optomap 200Tx, Daytona imaging systems and Heidleberg Engineering (Carlsbad, CA). As compared to the

**Table 3.** The Proposed International Clinical Diabetic Retinopathy and Diabetic Macular Edema Disease Severity Scales with the corresponding levels from Early Treatment Diabetic Retinopathy Study (ETDRS), clinical findings and referral guidelines[7,142]

| Proposed disease severity level | Clinical findings | Derivation from ETDRS levels | Management options |
|---|---|---|---|
| No apparent retinopathy | No abnormalities | Levels 10: DR absent | Optimize vascular risk factors* |
| Mild NPDR | MAs only | Level 20: Very mild NPDR | Optimize vascular risk factors |
| Moderate NPDR | More than MAs,<br>less than severe NPDR | Levels 35,43, 47: moderate NPDR<br>less than 4:2:1 | Optimize vascular risk factors<br>and refer to an Ophthalmologist |
| Severe NPDR | Any of the following (4:2:1)<br>i. Extensive (>20) intraretinal haemorrhages<br>in each of 4 quadrants<br>ii. Definite venous beading<br>in 2+ quadrants or more<br>iii. Prominent IRMA<br>in 1+ quadrant ore more<br>AND no signs of PDR | 53A-E: severe to very severe NPDR<br>4:2:1 rule | Optimize vascular risk factors,<br>refer to an Ophthalmologist for<br>scatter (panretinal) laser treatment |
| PDR | One or more of the following:<br>i. Neovascularization<br>ii. Vitreous/preretinal haemorrhage | Levels 61,65,71,75,81,85:<br>PDR, high-risk PDR, very severe<br>or advanced PDR | Optimize vascular risk factors,<br>refer to an Ophthalmologist for<br>scatter (panretinal) laser treatment |
| DME apparently absent | No apparent retinal thickening or<br>hard exudates in posterior pole | | Review in 1–2 years |
| DME apparently present | Some apparent retinal thickening<br>or hard exudates in posterior pole | | |
| i. Mild DME | Some retinal thickening or hard exudates<br>in posterior pole but distant from the<br>centre of the macula (diameter 1000 μm) | Non-CSME | Optimize vascular risk factors<br>and refer to an Ophthalmologist |
| ii. Moderate DME | Retinal thickening or hard exudates<br>approaching the centre of the macula,<br>but not involving the centre of the macula | Non-CSME | Optimize vascular risk factors<br>and refer to an Ophthalmologist for<br>consideration of focal/grid lasers |
| iii. Severe DME | Retinal thickening or hard exudates<br>involving the centre of the macula | CSME<br>i. Thickening of the retina at or within<br>500 μm of the centre of the macula<br>ii. Hard exudates at or within the centre<br>500 μm from the centre of macula, if<br>associated with thickening of retina<br>iii. A zone or zones of retinal thickening<br>1 disc area or larger, any part of whic is<br>within 1 disc diameter of the centre of<br>the macula | Optimize vascular risk factors<br>and refer to an Ophthalmologist for<br>intravitreal anti-VEGF or focal/grid lasers |

CSME, clinically significant macular edema; DME, diabetic macular edema; IRMA, intraretinal microvascular abnormalities; MA, microaneurysms; NPDR, non-proliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

standard imaging, the ultra wide-field imaging was reported to improve DR diagnostic accuracy by 15% to 17% by detecting more peripheral lesions, with a lower technical failure rate of 3% and quicker image evaluation time.[149,150] This screening modality may improve the physicians' ability to diagnose and manage diabetic eye disease, given that 10 to 15% of standard fundus images captured in multiple retinal locations is incorrect.[150]

The technical failure rate has been reported to be higher in non-mydriatic and wide-angle field (e.g. 50°) retinal photography.[147,151] At present, few studies have reported on the technical failure rate of screening devices, which may have an impact on the clinical- and cost-effectiveness of a screening programme. Unreadable or ungradable retinal images usually warrant mydriasis and repeat imaging either at the same session or subsequently. Failing which, the patients will warrant referrals to see ophthalmologists because of the undetermined DR state and other co-existing visually significant pathologies such as dense cataracts, rubeotic glaucoma with hazy cornea or vitreous haemorrhages.

## Tele-Retinal and Mobile Eye Screening

Tele-retinal and mobile eye screening had been shown to be cost effective for DR screening in various countries including Australia, United States, United Kingdom and India.[152–155] Tele-retinal screening involves digital retinal imaging with remote image interpretation as a means of improving access to eye care. It improves the access to DR screening service for the people who live in the rural and remote areas. In United States, a national tele-retinal imaging diabetic retinopathy screening program was set up between the Veterans Health Administration, Joslin Vision Network and the Department of Defense and the Veterans Integrated Service Network.[155–157] Similarly, the National Health Service has also set up a National Diabetic Retinopathy Screening Program in United Kingdom with the aim to achieve a 100% screening rate for the patients with diabetes.[158]

In Singapore, the national screening program – Singapore Diabetic Retinopathy Program had been set up using the tele-medicine model with centralized reading centre based in Singapore Eye Research Institute. This screening program provides a national coverage of 600 000 persons with diabetes with in-built quality assurance processes. The retinal still photography is interpreted within an hour by the professional graders and the report will be subsequently sent back to the primary care physicians. This program aims to minimize the patients' follow-up and to reduce the unwarranted tertiary eye care referrals. Further research may be invaluable to assess the cost-effectiveness of such programme.

## Major Public Health Challenges

Diabetes imposes a substantial public health burden. Once diagnosed with diabetes, a patient will have the disease for life. The most recent data from the International Diabetes Federation indicate that diabetes affected 387 million people worldwide in 205, a number that is expected to grow to 592 million by 2035.[5] In United States, the total estimated cost of diagnosed diabetes in 2012 is $245 billion, including $176 billion in direct medical costs and $69 billion in reduced prodcutivity.[159] The annual costs of a US diabetic population were approximately double those of matched case–controls and for those with micro- and macro-vascular complications, their costs were 3 times higher than those without.[160] However, savings of $624 million and 400 000 person-years of sight could be achieved annually for United States if everyone with diabetes underwent regular diabetic retinopathy screening and received treatment according to the severity of their condition.[161–163]

Despite having various DR screening programs, DR remains the leading cause of blindness among working-age adults in the world, ranging from 3 to 7% in the developing countries (South-East Asia and the Western Pacific region) to 15–17% in the developed regions (America and Europe).[1] Limited data is available on the cost for diabetic eye diseases. It is often difficult to segregate the eye cost from the total diabetes health-care cost, as diabetes is a metabolic disorder that affects multiple systems in people with diabetes. In US,[164] the direct annual cost for DR was estimated to be USD$493 million dollars whereas in Sweden, the annual average healthcare cost of a patient with any DR, PDR and DME was reported to be USD$93.6, USD$334.1 and USD$280.8, respectively.[165] In a recent Australian health economic report, the annual indirect costs of DME in Australia were estimated at approximately $2.07 billion, with a significant portion of this to be because of a reduced capacity at work and lost wellbeing secondary to visual impairment.[166]

Public education on diabetes plays an important role to raise the awareness of people with diabetes. Wang et al. reported a surprising low number of patients with diabetes (less than 50% of the survey respondents) who were aware of HbA1c,[167] with merely 17% understood its ideal level (<7%), significance and the physiology. Younger age and post-secondary education were shown to be significantly associated with people who understood HbA1c.[167] A meta-analysis also showed that the enforcement of patient education and self-management strategies reduced HbA1c levels by 0.8% compared to the control group at immediate follow-up.[168]

To prevent diabetes and diabetic retinopathy, it is critical to educate the public on the diet and lifestyle factors, optimization of vascular risk factors (i.e. BP,

lipid, smoking), improve their awareness about diabetes and the associated complications. Lifestyle counseling in the primary care setting plays a crucial role in helping the patients with diabetes in optimization their glycaemic and other vascular risk factors control. Morrison et al. showed that ≥1/month face-to-face counseling between the doctors and patients with diabetes (compared to less than once per 6 months) were able to enable faster achievement of HbA1c (3.5 months *vs* 22.7 months), blood pressure <130/85 mmHg (3.7 weeks *vs* 5.6 months) and low-density-lipoprotein cholesterol <100 mg/dL (3.5 months *vs* 24.7 months), with $P < 0.0001$ for all.[169] Furthermore, the primary health care physicians will need to be kept updated on the current DR screening and referral guidelines, ensuring early detection and prompt intervention for patients with VTDR. However, personalized education and structured interventions had recently been shown to have minimal effect on long-term HbA1c control.[170] This study suggests that HbA1c control still remains a substantive challenge in the real world, outside the confines of a clinical study. Further research will be invaluable to explore more alternative and effective lifestyle interventions in optimizing the glycaemic controls for these patients.

Many studies had shown that DR could be associated with patients' psychosocial well-being.[171,172] Increased severity of DR and DME had been shown to be associated with negative impact on quality of life and depression.[172,173] Patients with DR were more likely to have difficulty maintaining social interaction and disintegration of their social lives.[171] They reported to have anxiety over maintaining friendships or acquaintances, or meeting new people because of difficulty recognizing faces.[171,174,175] Younger patients with DR found visual impairment as a major deterrent to finding potential partners and forming romantic relationships.[171] Moreover, visual impairment secondary to DR could also result in unemployment and loss of income.[171]

Non-adherence to medication, a common problem for patients with diabetes, is associated with poor glycaemic control, increased risk for hospitalization and mortality.[176] Increasingly, cognitive behavioural therapy (CBT), combined with a series of diabetes self-management and adherence interventions, has been shown to be an effective intervention for people with diabetes.[173,177] The people with diabetes who underwent a total of 12 sessions of CBT consisting of different modules are 27% and 30.2% more adherent to the oral medication and self-monitoring of blood glucose, respectively ($P = 0.000$) and has lower HbA1c by 0.6 units ($P = 0.03$) than the non-CBT group.[173]

## Prevention of diabetes-related visual impairment

Early detection is crucial to prevent diabetes-related visual impairment. Primary prevention could be undertaken to prevent the occurrence of diabetes by raising the public awareness to avoid obesity, increase physical activity and to consume low fat/high complex carbohydrate diet.[178] All of these strategies had been shown to increase insulin sensitivity and reduce the prevalence of diabetes in the general population.[179,180] However, it is rather challenging to prevent the development of diabetes with the primary prevention as mentioned earlier. Once patients develop diabetes, secondary prevention should then focus on maintaining good glycaemic control, optimization of vascular risk factors (e.g. hypertension, hyperlipidemia, cessation of smoking) and ensuring early eye screening.[178] Failing which, these patients with poor glycaemic control will develop vision-threatening DR (severe NPDR and PDR), requiring prompt scattered retinal laser to prevent blinding complications.[181,182] At present, research and clinical resources are heavily invested on the VTDR area. More focus and resources should be redirected to the research related to primary and secondary prevention in order to reduce the permanent visual loss secondary to diabetes.

A successful DR screening program involves various factors including high sustainability and accessibility of the screening service in the community with highly trained health providers in DR screening.[144,183,184] The National Health Service has set out operational guidance (e.g. screening settings, role definition of clinical leads, standardization of grading thresholds, equipment guidance, photographic methods, referral intervals) for diabetic eye screening program in England.[185] It is also crucial to evaluate the health economic data on the cost-effectiveness of various different business models for a screening program, based on the existing infrastructure and clinical service.[186] Tele-retinal screening, using digital photography with telemedicine links, has been shown to be a cost-effective method to improve early access of DR screening services to rural, remote and hard-to-reach populations.[187] Scattered delivery systems may be transformed into a comprehensive DR network. This enables the capitalization of the resources, tools and training available in urban areas.

Globally, there is a mismatch between the capacity to implement DR screening services *versus* the number of people with diabetes, especially in the low and middle-income countries. Retinal still photography, mydriatic and non-mydriatic, has been shown to be the cost-effective DR screening strategy.[148,188] The cost-effectiveness of a screening program is sensitive to the program size because of high fixed cost of the camera methods, but not to prevalence.[188] For the resource-rich developed countries, further research

should also be directed to evaluate interventions for DME, in addition to prevent visual loss from PDR.[181,189] For the management of fovea-involving DME, anti-vascular endothelial growth factor (aflibercept, ranibizumab or bevazicumab) has become the primary treatment to improve vision.[189,190] More resources should be directed towards exploring more alternative novel therapeutics for DR and DME. On the other hand, the fundamental problems of the resource-poor low to middle income countries are the lack of access to high-quality ophthalmologists and limited health care resources such as the lasers machines and anti-VEGF therapy.[191] It is, therefore, extremely crucial to channel the finite resources to develop innovative strategies to improve the disease awareness and access to the screening services and treatment in these countries. [188] The overall cost-effectiveness of a screening program is influenced by variation in compliance rates, age of onset of diabetes, glycaemic control and screening sensitivities.[186]

## Conclusion

Diabetes retinopathy (DR) remains a global health issue. Early detection and prompt treatment allow prevention of diabetes-related visual impairment. Patients with diabetes require regular follow-up with primary care physicians to optimize their glycaemic, blood pressure and lipid control to prevent development and progression of DR and other diabetes-related complications. In spite of the major understanding of epidemiology and risk factors of DR, more research is required to the awareness of DR among the people with diabetes. A better understanding of the type and extent of the psychosocial impact of DR may assist policy planners and rehabilitation workers to improve quality of life for patients with diabetes. With the rising incidence and prevalence of diabetes and DR, it is challenging to maintain the costs and running of DR screening programs for people with diabetes. To reduce the impact of DR-related visual loss, it is important that all stakeholders continue to look for innovative ways of managing and preventing diabetes, and optimize cost-effective screening programs within the community.

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