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The Journal of Community Health Management

Journal homepage: https://www.jchm.in/

Review Article

# Unravelling epidemiological trends and risk disparities in diabetic retinopathy

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## Abstract

Diabetic retinopathy (DR) remains a leading cause of blindness worldwide, driven by the epidemic rise in diabetes mellitus. The epidemiology of DR is reflected as global trends in lifestyle, urbanization, and health disparities, with variation between populations and regions. Socioeconomic differences contribute to the burden of DR, making imperative need for integrated public health interventions. The pathogenesis of DR is multifactorial and is characterized by common risk factors including hyperglycaemia, diabetes duration, hypertension, dyslipidaemia, smoking, genetic predisposition, obesity, albuminuria, and pregnancy. Of these, control of glycemia plays an important role, with elevated levels of glycated haemoglobin (HbA1c) imparting a high risk for the development and onset of DR. Also, longer duration of diabetes has a very high correlation with greater prevalence of DR, affecting 100% of type 1 DM patients at 30 years and 90% of type 2 DM patients in the same duration. The disease is manifested as non-proliferative (NPDR) or proliferative (PDR) DR, by the presence of neovascularization. Diabetic macular oedema (DME) can occur at any time and results in serious vision loss. This review explores the multifaceted epidemiology and determinants of risk of DR, synthesizing current evidence to inform opportunities for tailored interventions. It is crucial to elucidate the multifactorial interaction of metabolic, vascular, genetic, and environmental determinants, to tailor prevention efforts, early detection, and effective management approaches. Policy and clinical practice based on evidence for these determinants are key to preventing the public health burden of DR and preserving vision in affected individuals.

**Keywords:** Diabetic retinopathy, Epidemiology, Risk factors, Population, Statistical trends

**Received:** 13-03-2025; **Accepted:** 27-03-2025; **Available Online**: 16-08-2025



## 1. Introduction

Diabetic retinopathy (DR) is a significant public health issue and a major cause of blindness among adults worldwide. With diabetes mellitus entering epidemic trends, the spread of DR underscores the new imperative for understanding its epidemiology and etiologic risk factors. The statistical trends in DR closely reflect the rising worldwide number of patients with diabetes driven by urbanization, physical inactivity, and dietary changes. As diabetes rises, DR prevalence also increases with varying trends observed between regions, populations, and groups (Teo et al. 2021).

The differences in healthcare access, socioeconomic standing, and ethnicity also contribute to the burden of DR, highlighting the importance of addressing disparities in healthcare systems. Identification and awareness of DR risk factors are essential. In addition to the common relationships with duration of diabetes and blood glucose control, numerous metabolic, vascular, genetic, and environmental factors influence DR susceptibility. Hypertension, dyslipidaemia, smoking, genetic predisposition, pregnancy, ethnicity, obesity, and albuminuria all play roles in disease development and disease progression (Klein and Klein 2021). The interplay among these factors is the cause of heterogeneity in DR presentation and the rationale for individualized treatment. Hence, this review explores the intricate relationships between epidemiological patterns and risk determinants that cause DR. Through this analysis, it can contribute to the development of evidence-based strategies for the prevention of DR, early detection, and management, ultimately working toward preserving vision and improving the quality of life for those affected by this vision-threatening condition.

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http://doi.org/ 10.18231/j.jchm.v.12.i.2.4

## 2. Discussion

### *2.1. Epidemiology and types*

The prevalence of DR among diabetic patients is around 35% globally, and approximately 10% of them is vision-threatening (Yau et al. 2012). Similar figures have also been reported in Malaysia, where between 30% to 40% of diabetic patients develop DR and around 15% of them are above the age of 40 years (Ooyub et al. 2004, Abougalambou and Abougalambou 2015, Li et al. 2016). Beagley et al. (2014) estimated that there will be a 70.5% increment in diabetes mellitus (DM) cases from the year 2013 to 2035 in Southeast Asia, and this figure might be underestimated. According to an estimate by WHO, Malaysia is expected to have a 164% increase in DM cases within 30 years from 2000 to 2030 (Mafauzy 2006). With the increasing prevalence of DM worldwide, a corresponding increase in the number of DR cases is expected in the future (Saadine et al., 2008).

DR is usually diagnosed within 5 to 7 years after the onset of DM in around 20% of type 1 DM patients. After 10 years, the incidence of DR in type 1 DM patients increases up to 60% and up to 100% after 30 years (Gubitosi-Klug et al. 2021). Among type 2 DM patients, around 30% present with DR when the initial diagnosis of DM is made (Nentwich and Ulbig 2015). Type 2 DM patients may present with DR at the time of initial diagnosis because the diagnosis is often ignored or delayed, which allows hyperglycaemia-induced damage to vessels and nerves to continue. Around 50% to 70% of type 2 DM patients have DR symptoms after 10 years, which increases to 90% after 30 years of the onset of DM (Dedov et al. 2009). A study by Romero-Aroca et al. (2017) showed that the prevalence of DR was 7.03% higher in type 1 DM compared to type 2 DM. The Scottish National Diabetic Retinopathy Screening Programme showed a comparable result where type 1 DM patients have 8.4% higher cumulative incidence compared to type 2 DM patients in the community without DR during the initial diagnosis of diabetes (Looker et al. 2014).

In Malaysia, no association between ethnicity and DR has been observed despite the data showing that Indians have the highest prevalence of diabetes (Letchuman et al. 2010, Tee and Yap 2017, Hussein et al. 2015). The progression of retinopathy in this country has been influenced by independent risk factors such as duration of diabetes (Shriwas et al. 1996, Abougalambou and Abougalambou 2015, Mallika et al. 2011, Rani et al. 2009, Abougalambou and Abougalambou 2013, Jew et al. 2012), high total cholesterol (Abougalambou and Abougalambou 2015, Addoor et al. 2011, Jew et al. 2012), lower body mass index (BMI) (Mallika et al. 2011, Rani et al. 2009) and creatinine clearance (Abougalambou and Abougalambou 2015, Shriwas et al. 1996, Jew et al. 2012).

DR is categorised into two types; non-proliferative (NPDR) and proliferative (PDR) that are distinguished by the absence or presence of neovascularisation, respectively (Al-Jarrah and Shatnawi 2017). Diabetic patients develop NPDR before progressing to PDR, which accounts for 3%-10% of DR cases (Kim et al. 2014). The main features of NPDR include microaneurysms, haemorrhages, exudates and macular swelling. Weakened retinal capillaries form microaneurysms. Over time, microaneurysms rupture and the fluid and blood leakage cause the formation of haemorrhages and exudates. The fluid and blood leakage also cause swelling of the macula. NPDR can be further sub-classified into mild, moderate, and severe NPDR as defined by Early Treatment Diabetic Retinopathy Study (ETDRS) (**Table 1**). PDR occurs after neovascularisation has taken place and is usually followed by complications such as vitreous haemorrhage and retinal detachment. With vitreous haemorrhage and retinal detachment, DR patients experience severe blurring and dark spots in the central eye, resulting in vision loss and blindness. Diabetic macular oedema (DME), which is the major cause of vision loss in DR (Lee et al., 2015) can be observed either in NPDR or in PDR stage. With the changes happening in the retina, DR patients usually experience a variety of symptoms such as blurry vision, colour vision impairment, and transparent and colourless spots known as floaters.

**Table 1:** Types of diabetic retinopathy as defined by early treatment diabetic retinopathy study

| Types | Retinal Findings |
|---|---|
| Mild NPDR | Micro aneurysm only |
| Moderate NPDR | At least one haemorrhage or micro aneurysm and/or at least one of the following: |
| | Retinal haemorrhages |
| | Hard exudates |
| | Cotton wool spots |
| | Venous beading |
| Severe NPDR | Any of the following but no signs of PDR: |
| | More than 20 intraregional haemorrhages in each of the four quadrants |
| | Definite venous beading in two or more quadrants |
| | Prominent intraretinal microvascular abnormalities in one or more quadrants |
| PDR | Neovascularization or/and |
| | Vitreous haemorrhage |

NPDR: Non-Proliferative Diabetic Retinopathy
PDR: Proliferative Diabetic Retinopathy

## 3. Risk Factors

### *3.1. Glycaemic control*

Hyperglycaemia is a modifiable risk factor for DR and good glycaemic control has been shown to prevent DR development and progression (Hautala et al. 2018). Elevated levels of glycated haemoglobin (HbA1c), in addition to being associated with the incidence and progression of any type of

DR, are positively correlated with the presence of macular oedema (Vilsbøll et al. 2018). An increment of one point in HbA1c is associated with an increase of ~30% chance of DR development in both type 1 and type 2 DM. Other than that, patients with good HbA1c control (less than 8%) showed greater regression of DR advancement with the help of pan-photocoagulation 'laser' treatment (Almutairi et al. 2021). The relationship of elevated HbA1c and DR is independent of other risk factors, such as the duration of DM and the severity of DR (Klein et al. 1984).

### *3.2. Duration of DM*

Other than impaired glycaemic control, a strong association between chronic hyperglycaemia has been identified with DR development and progression. The frequency of DR increased significantly with increasing duration of diabetes (Anwar et al. 2019, Voigt et al. 2018, Elwali et al. 2017, Endo et al. 2019). According to Shaikh and Gillani (2010), DR was observed in 25.5% of type 2 DM patients after ten years, and 4% of these patients had proliferative retinopathy.

### *3.3. Hypertension*

Apart from poor glycaemic control, blood pressure (BP) has been shown to be an important causative factor for DR (Liu et al. 2020). The 2017 Guidelines for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults, recommend a BP level of less than 130/80 mm Hg in adults with diabetes for prevention of further complications (Whelton et al. 2018). Investigation from clinical trials have proven the positive effect of tight BP control on the risk of DR in patients with diabetes and hypertension (Mohammadi et al. 2019, Wang et al. 2015). In population-based trials, while systolic blood pressure (SBP) has been consistently shown to be associated with DR (Wang et al. 2011, Sasongko et al. 2012, Solomon et al. 2017, Chisha et al. 2017), association of diastolic blood pressure (DBP) was less coherent with the majority showing no significant association of DBP with DR (Cardoso et al. 2017, Smith et al. 2020, Liu et al. 2020).

### *3.4. Hyperlipidaemia*

DM is strongly associated with hypercholesterolemia and hypertriglyceridemia (Shi et al. 2018, Chang and Wu 2013, Li et al. 2020). A similar association was observed in DR where elevated serum total cholesterol and low-density lipoprotein (LDL) cholesterol correlated with the severity of retinal hard exudation (Zhou et al. 2018). High serum triglyceride and LDL also influenced the progression to PDR (Wright and Dodson 2011). Lipid-lowering drugs, particularly statins and fibrates, have been demonstrated to ameliorate DR (Chou et al. 2020). However, it is worth noting that the relationship between major serum cholesterol types and the development of DR, published by other studies, was inconsistent (Kajal Seema et al. 2021, Chou et al. 2020). The discrepancies in outcomes may be attributed to the different detection methods and the variations in the diagnostic criteria for DR (Chou et al. 2020).

### *3.5. Obesity*

A meta-analysis showed an association between obesity and higher DR incidence. However, no significant association was noted between the risk of PDR development and obesity. The significant harmful effect of obesity was particularly detected in the Type 1 DM group but not in the Type 2 DM group (Zhu et al. 2018). However, there are still controversies regarding this association as recent studies have reported the absence of such an association (Han et al. 2021) or negative association between BMI and the prevalence of DR (Paik et al. 2020, Han et al. 2021, Looker et al. 2012). Additionally, the possible beneficial effects of weight loss on DR have not been evaluated.

### *3.6. Smoking*

Smoking was found to have deleterious effects on diabetic retina as the increase in carbon monoxide concentration, increased platelet aggregation and vasoconstriction, which lead to poor retinal vascularization (Śliwińska-Mossoń and Milnerowicz 2017). It is also showed higher risk of DR development in smokers compared to non-smokers, especially among type 1 DM patients. Smoking also was shown to increase the incidence of macular oedema among type 1 DM patients (Kramer et al. 2008).

### *3.7. Gender*

Most studies show a higher prevalence of DR in men compared to women (Cherchi et al. 2020, Deshpande et al. 2008, Mehlsen et al. 2011). However, some smaller scale studies have shown no gender differences in the incidence of DR (Stratton et al. 2001, Mazhar et al. 2011, Hammes et al. 2011, Zhang et al. 2010). It also suggested that sex hormones may play a role in the higher incidence of advanced stages of DR in men (Sun et al. 2020).

### *3.8. Pregnancy*

Around a 2.50-fold higher risk of developing DR was observed in pregnant women when compared to non-pregnant women in the Diabetes Control and Complications Trial (DCCT) (Esteves et al. 2008). The risk was greater in the second trimester and remained high until the end of the first postpartum year (Esteves et al. 2008). Correlation between pregnancy has also been proven in other studies (Bourry et al. 2021, Egan et al. 2015, Morrison et al. 2016, Scanlon 2017, Vestgaard et al. 2010). However, Verier-Mine et al. (2005) did not observe any significant association between pregnancy and DR subjects, as was also observed in other studies (Temple et al. 2001, Toda et al. 2016, Rasmussen et al. 2010). Despite the inconsistent data on the association of pregnancy with the development and progression of DR, intensive eye care for diabetic patients during pregnancy is highly recommended (Association 2006, Makwana et al. 2018).

## 4. Future Perspectives

The way forward in the management of DR is heading in the direction of early detection strategies, precision medicine, and novel therapeutic strategies aimed at decreasing disease progression and improving patient outcomes. The most promising development is perhaps the use of artificial intelligence (AI) in screening and diagnosis. AI-powered retinal imaging has been shown to have excellent sensitivity and specificity in the detection of DR and is therefore a useful adjunct to large-scale screening programs, especially in resource-poor environments where ophthalmologist access is limited (Yao et al. 2024). The integration of deep-learning algorithms into telemedicine systems is another plus point for accessibility, with the potential to facilitate earlier intervention and better disease monitoring.

Aside from technology, the emerging discipline of personalized medicine has enormous potential in the precision of DR management. Identification of molecular and genetic biomarkers of disease progression can enable treatment strategies to be customized according to the risk profile of the patient. This would enable more targeted therapy, prevent unnecessary exposure to therapy, and minimize side effects. The exploration of systemic and local biomarkers, including inflammatory cytokines, markers of oxidative stress, and genetic polymorphisms, can result in early prognostic indicators and novel therapeutic targets.

Therapeutic innovation continues, with an increasing focus on regenerative medicine and targeted pharmacological treatments. The introduction of gene therapy, stem cell transplantation, and neuroprotective agents represents a paradigm shift in the management of DR, with the aim not only to halt disease progression but to restore retinal function. The therapeutic potential of antioxidants in mitigating oxidative stress-induced retinal damage remains an active field of investigation, with tocotrienols and other vitamin E analogues showing promise in preclinical and early clinical studies. Additional trials should be conducted to establish their long-term efficacy and optimal dosing schedules.

Comprehensive approach to DR management also necessitates control of systemic risk factors, particularly glycaemic control, hypertension, and dyslipidaemia (Kropp et al. 2023). The integration of multidisciplinary models of care among endocrinologists, ophthalmologists, and primary care providers is also imperative in aligning patient outcomes. Digital health innovations, including mobile apps and remote monitoring systems, can also potentially enhance patient engagement and adherence to treatment regimens.

Studies in the future will also need to cover the impact of DR treatments on quality of life and functional visual outcomes rather than solely anatomical gains. Patient-centred interventions that tackle the psychosocial impact of vision loss and that involve rehabilitation interventions will be critical in delivering holistic care. Continued investment in randomized controlled trials and large-scale real-world studies will be required to validate emerging treatments and to transfer experimental findings to clinical practice.

## 5. Conclusion

This review provides an overview of the epidemiology and risk factors of DR. Through a division of the global burden of DR by its prevalence, incidence, and distribution across different populations, valuable information regarding the magnitude of this vision-threatening complication has been obtained. Besides, elucidation of the complex array of risk factors for DR susceptibility and progression, ranging from vascular and metabolic to genetic and environmental determinants, has further demonstrated the intricate interaction underlying disease pathogenesis.

The implications of this review's findings are profound for clinical practice, public health policy, and research. Identification of high-risk populations and modifiable risk factors enables healthcare professionals to implement population-targeted screening, prevention, and management programs that can limit the occurrence and severity of DR complications. Furthermore, the integration of telemedicine, artificial intelligence, and multidisciplinary care models has the potential to improve access to early diagnosis and treatment, particularly in needy populations. However, health disparities in access and outcomes remain an ongoing challenge that requires joint efforts at the individual, community, and policy levels. Health equity activities should take a high priority and be reinforced by promoting policies to secure universal access to quality eye care services and diabetes care as urgent steps to alleviating the DR burden among individuals with the disease and healthcare systems.

## 6. Source of Funding

None.

## 7. Conflict of Interest

None.

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**Cite this article:** Sadikan MZ, Abdul Nasir NA. Unravelling epidemiological trends and risk disparities in diabetic retinopathy. *J Community Health Manag.* 2022;12(2):64-69.