

Epidemiological Study of Proliferative Diabetic Retinopathy Treatments for the Vision-Threatening Complications of Diabetic Macular Edema

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Abstract

Diabetic retinopathy (DR) is a leading cause of vision-loss globally. Of an estimated 285 million people with diabetes mellitus worldwide, approximately one third have signs of DR and of these, a further one third of DR is vision-threatening DR, including diabetic macular edema (DME). The identification of established modifiable risk factors for DR such as hyperglycemia and hypertension has provided the basis for risk factor control in preventing onset and progression of DR. Additional research investigating novel risk factors has improved our understanding of multiple biological pathways involved in the pathogenesis of DR and DME, especially those involved in inflammation and oxidative stress. Variations in DR prevalence between populations have also sparked interest in genetic studies to identify loci associated with disease susceptibility.

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Keywords

Diabetic macular edema, Diabetic retinopathy, Intravitreal injection, Prevention.

Introduction

Diabetic Retinopathy (DR) is the leading cause of vision loss in adults aged 20–74 years. From 1990–2010, DR ranked as the fifth most common cause of preventable blindness and fifth most common cause of moderate to severe visual impairment. In 2010, of an estimated 285 million people worldwide with diabetes, over one-third have signs of DR, and a third of these are afflicted with vision-threatening diabetic retinopathy (VTDR), defined as severe non-proliferative DR or proliferative DR (PDR) or the presence of diabetic macular edema (DME). These estimates are expected to rise further due to the increasing prevalence of diabetes, ageing of the population and increasing of life expectancy of those with diabetes.

PDR is the most common vision-threatening lesion particularly among patients with type 1 diabetes. However, DME is responsible for most of the visual loss experienced by patients with diabetes as it remains the major cause of vision loss in the highly prevalent type 2 diabetes and is invariably present in patients with type 2 diabetes with PDR. In addition to vision loss, DR and DME have also been shown to contribute to the development of other diabetes-related complications including nephropathy, peripheral neuropathy and cardiovascular events

The most clinically important risk factors for progression to vision loss include duration of diabetes, hyperglycemia and hypertension.

Control of serum glucose and blood pressure have been shown to be effective in preventing vision loss due to DR. Prevalence and risk factors of DR have been studied widely in previous studies including regional and ethnic differences, but epidemiological data on DME are relatively scarce. A review conducted in 2012 suggested that up to 7 % of people with diabetes may have DME and risk factors of DME are largely similar to DR. Recently, new information on the epidemiology of DR and DME has been published from both developed and developing countries. In this review, we summarize the prevalence of DR and highlight regional differences in the epidemiology of DR from recent studies. We also review the incidence, progression and regression of DR and DME, as well as factors contributing to the progression or regression of DR and DME.

What retinal changes occur?

The retina is supplied by two circulatory systems: the uveal (choroidal) circulation and the retinal vasculature. Diabetes damages retinal capillaries through prolonged exposure to hyperglycaemia. This leads to loss of supporting pericyte cells and tight junctions between endothelial cells. Leakage from capillaries results in retinal oedema and capillary closure leads to ischaemia.

Proliferative diabetic retinopathy

Ischaemic retina produces growth factors including vascular endothelial growth factor (VEGF). The growth of abnormal new vessels is stimulated from the optic disc or retina.

New vessels are prone to bleeding (vitreous haemorrhage) and the accompanying fibrosis leads to tractional retinal detachment; both sight-threatening manifestations of PDR.

Diabetic Maculopathy

Retina which is oedematous or ischaemic loses function and this will reduce vision if the central retina or macular is involved. Diabetic maculopathy can be divided into two types: macular oedema and macular ischaemia which may co-exist. Macular oedema occurs due to breakdown of the inner blood-retina barrier.

Non-proliferative diabetic retinopathy

DR can be classified either non-proliferative (NPDR) or proliferative (PDR). Non-proliferative DR is characterised by microaneurysms, intraretinal haemorrhages, venous beading and intraretinal microvascular abnormalities (IRMA). NPDR is usually asymptomatic but may progress to PDR.

Statistical analysis

First, the IHS-JVN cohort was characterized by calculating frequencies, column and row percentages (to show the conditional distributions) for the social-demographics, and health summary and technology variables. Although the focus of this analysis is patients with gradable images, consistent with previous research, the analyses compared the conditional distributions of whether images were gradable or ungradable using chi-square tests. Second, to obtain overall prevalence estimates, the analyses calculated the numbers and column percentages of the IHS-JVN population for each DR, DME, and STR severity level. Third, the analyses calculated the frequencies and percentages for each level of DR, DME, and STR by social-demographics, health summary data, and technology used, and conducted chi-square tests of independence. Lastly, although not the primary focus of this study, the analyses estimated multinomial logit models with all aforementioned variables (not shown, but available upon request) to document their net effects on DR and DME. All analyses were done using SAS 9.4 (Cary, NC).

Results

Prevalence of DR

A pooled individual participant meta-analysis involving 35 studies conducted worldwide from 1980 to 2008, estimated global prevalence of any DR and PDR among patients with diabetes to be 35.4 and 7.5 % respectively. Prevalence of any DR and PDR was higher in those with type 1 diabetes, compared to those with type 2 diabetes (77.3 vs. 25.2 % for any DR, 32.4 vs. 3.0 % for PDR).

In the examined timeframe, 53,998 patients were imaged, 86.3% of which had gradable images (Table 1). Of those with gradable images, 40.3% were under age 50 and 8.8% were 70 years and older (mean age = 52.7±12.8 years). The majority of patients were female (56.0%) and lived in the Southwest (57.6%). About 31.7% of patients had a diagnosis of diabetes for more than 10 years. Most patients were on oral medications alone for their diabetes therapy (51.5%). The most recent A1c was less than 6.0% (42 mmol/mol) for 9.4% of patients, 6.0 to 7.9% (42 to 63 mmol/mol) for 35.4% of patients, and 8% (64 mmol/mol) or greater for 38.2% of patients. For the remainder of patients, 'poor glycemic control' was noted or A1c data were missing.

Compared with other age groups, a higher percentage of patients aged 60 years and older had mild NPDR (Table 3), and a higher percentage of patients less than age 60 years had moderate NPDR. A slightly higher percentage of males had moderate NPDR. With respect to geography, the highest percentage of patients with no DR was in Alaska, whereas the highest percentage of patients with PDR was in the Southwest. The percentages of people with any level of DR greater than 'no apparent' increased in expected ways when risk factors were considered; i.e., percentages were higher among patients with longer duration of diabetes and patients taking insulin alone or with oral medications.

Higher percentages of mild and moderate NPDR were found using UWFI than NMFP, but there was no difference in percentage of severe NPDR. UWFI identified PDR twice as frequently as did NMFP.

Assay

A potential limitation of this study is selection bias. First, patients with more advanced retinal conditions may already be under specialty ophthalmological care and may have chosen to defer IHS-JVN as a result. Also, patients with diabetic retinal disease may also have poor glycemic control (A1c >7%) and would be at higher risk of mortality. Both possibilities could result in some underreporting of DR and/or DME prevalence. Second, the sample may be biased in that the IHS-JVN accesses people who go to primary care clinics in facilities that participated in the teleophthalmology program. However, due to the aforementioned reach and geographic distribution of the program, and the fact that its services are offered to all known patients with diabetes receiving care at the facility, we believe risk of this type of bias is low. Indeed, unlike many previous reports of DR and DME prevalence, these patients were not recruited in specialty eye clinics, so this powerful source of selection bias was mitigated.

Another potential limitation of this study is that images for some patients were ungradable. Except for glycemic control, factors associated with the outcome of 'ungradable' paralleled those for risk of DR and DME. Thus, presence of a risk factor is more likely to result in ungradable images and referrals. But a designation of ungradable does not necessarily mean disease is visible or clinically overt. Images may be ungradable because of smaller pupil size and media opacity, both of which are more common with increasing age and duration of diabetes. To address the question of DR and DME prevalence among patients who had ungradable images in the present analysis, we extracted the diagnosis codes from the medical records for a sample of 799 unique patients whose images were ungradable for DR and/or DME in 2013 and 2014 and who got a dilated eye exam within 365 days of that original ungradable finding. Of these patients 1.5% had NPDR "not otherwise specified" (i.e., level unknown), 2.4% had mild NPDR, 2.5% had moderate NPDR, 0.6% had severe NPDR, 2.6% had PDR, and 2.9% had DME. Another 24.0% had a diagnosis code indicating 'background diabetic retinopathy' only, with no NPDR severity level specified. These percentages indicate that the rate of sight-threatening diabetic eye disease is not substantially higher among patients who had ungradable images during the period of this study, whereas levels of DR that do not (yet) threaten sight might be. Further analysis of the outcomes for people who had ungradable images is a substantial, separate undertaking to be addressed in a future project.

Metabolic Clues in Diabetic Retinopathy and Macular Edema?

Glutamate

Is being an important pathway in the development of DR and DME the function of glutamate, a molecule that is present in high levels in diabetes? Glutamate (Glu) is the most important excitatory neurotransmitter in the brain and retina.

Hyperglycemia

Hyperglycemia has been considered in recent decades as the main cause of the onset and progression of DME and DR. In this regard, two epidemiological studies, the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetic Study (UKPDS), have reported that intensive control of glycemia is linked to a lower risk of the onset and progression of DR in both type 1 diabetes and type 2 diabetes patients.

Protective Retinal Metabolites

The retina is a neural tissue which, like the brain, synthesizes a series of neurotrophic factors necessary for homeostasis. Its role is largely to neutralise the increased oxidative stress that occurs in certain circumstances; for example, the brain-derived neurotrophic factor (BDNF) is synthesized in both neurons and glial cells of the retina. Some studies have shown that it protects the retina and optic nerve from ischemia.

BDNF has been shown to stimulate glutamate uptake by Müller cells and the factor derived from the pigment epithelium-derived factor (PEDF) to protect cells from excess of glutamate [18]. DM disturbs the relationship between the neuroprotective, antiangiogenic, and proangiogenic factors.

Relationship of DR and DME with diabetes related systemic complications

Microvascular Complications

Diabetic nephropathy is closely associated to DR and DME, as many of the pathologic processes affecting microvasculature in DR are likely to be causative of diabetic nephropathy as well. In a cross-sectional study in Korea, compared to patients without DR, patients with DR had 2.11 the odds (95 % CI 1.04–4.26) of having overt diabetic nephropathy, defined as protein excretion of more than 300 mg per 24 h or albumin/creatinine ratio greater than 300 µg/mg. Ischemic diabetic retinopathy, as evidenced by capillary non-perfusion found on fundal fluorescein angiogram, was found to be associated with progression of diabetic nephropathy.

Macrovascular complications

The strength of association between DR and macrovascular complications, such as cardiovascular disease is just as strong as in nephropathy. In the Chennai Urban Rural Epidemiology Study, prevalence of coronary heart disease was higher among patients with DR as compared to those without DR. An eight-year cohort study in Japan found that patients who developed signs of mild DR were already at higher risk of coronary heart disease or stroke.

Conclusion

In patients with diabetes, regular retinal exams are essential. While laser photocoagulation is effective, if performed in time, advanced stages of diabetic retinopathy need to be treated by vitreo-retinal surgery and have limited visual prognosis. Even though new therapeutic options such as intravitreal medical therapy and sutureless pars-plana vitrectomy have improved ophthalmic care of patients with diabetes, interdisciplinary care remains essential. Good metabolic and blood pressure control is indispensable for reducing the risk of ophthalmic complications. Diabetic macular edema (DME) is the leading cause of blindness in diabetic patients. Diagnosis is easy by exploring the retina under biomicroscopy and confirming it by OCT. Due to the efficacy of current treatments, it is essential to determine which etiology of macular edema is predominant. Vasogenic changes secondary to hyperglycemia induce a rupture in the blood-retinal barrier (BRB), which begins the cascade of macular edema formation. However, the activation of a low-grade inflammation simultaneous to vasogenic changes will induce serious retinal damage and macular changes will become chronic. Currently, DME is resistant to treatment in 30% of cases. The current anti-VEGF and steroid treatments are useful, but their use should be personalised. Prior knowledge of the predominant type of DME, vasogenic or inflammatory, is essential for determining the more effective type of drug.

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