Diabetic retinopathy

Fadia T Shaya[1]
Mohammad Aljawadi[2]

[1]Center on Drugs and Public Policy, [2]University of Maryland School of Pharmacy, Pharmaceutical Health Services, Baltimore, MD, USA

Abstract: The prognosis of some of the most prevalent conditions seems to be intricately related to myriad risk factors, largely modifiable, but often leading to irreversible complications when left unmanaged. This study exemplifies the multidisciplinary approach necessary, to successfully control diabetic retinopathy, one of the leading complications of diabetes, and to discuss promising therapies. Based on a Medline Ovid database search, we present a clinical and economic review of the evidence on the epidemiology and risk factors of diabetic retinopathy, its prognosis and economic implications. Among adults aged 20–74, diabetic retinopathy (DR) is the most frequent cause of blindness. However, in both types 1 and 2 DM, improved glycemic control reduces the development and progression of DR. Risk factors of DR include duration of diabetes, pregnancy, renal disease, age, smoking, alcohol, hyperlipidemia and antioxidants. A number of drugs may play a role in DR therapy in the coming few years; eg, somatostatin agonists (sandostatin), corticosteroids (triamcinolone, dexamethasone, fluocinolone), vascular endothelial growth factor inhibitors (pegaptanib, ranibizumab), hyaluronidase and plasmin enzyme. Whether these therapies have a clinically significant impact on DR progression however, remains to be seen.

Keywords: diabetic retinopathy, diabetes mellitus, retinal vasculatures

In a most recent era in medicine history, we have moved from the thrust to treat acute conditions, to the need to prevent and manage chronic diseases, which top the list for high morbidity and mortality conditions. The prognosis of some of the most prevalent conditions seems to be intricately related to myriad risk factors, largely modifiable, but often leading to irreversible complications when left unmanaged. The study we present herein exemplifies the multidisciplinary approach, often necessary, to successfully control such conditions. We specifically focus on diabetic retinopathy, one of the leading complications of diabetes, because of its high public health impact, high morbidity, impact on quality of life, and general societal welfare. In an effort to better inform prevention and treatment, we have conducted a clinical and economic review of the evidence on the epidemiology and risk factors of diabetic retinopathy, its prognosis and economic implications.

Medline search using Ovid database was done. The search strategy was made by using "focus function" with term diabetic retinopathy combined with prevalence, incidence, risk factors, prevention, cost-effectiveness and prognosis. The results then were limited to humans and English language. In some cases where the yield was larger than 50 articles, the yield was limited to the period between 2000 and 2006.

Correspondence: Fadia T Shaya
Center on Drugs and Public Policy, University of Maryland School of Pharmacy, Pharmaceutical Health Services Research, 220 Arch Street, Baltimore, MD 21201, USA
Tel +1 410 706 5392
Fax +1 410 706 5394
Email fshaya@rx.umaryland.edu

Definition and classification

Diabetic retinopathy (DR) is one of the micro-vascular complications of diabetes mellitus (DM). It is a progressive sight threatening disease that affects retinal vasculatures (AAO 2003). One of the widely accepted classifications of DR is the American Academy of Ophthalmology's classification. According to this classification DR is

classified as: non-proliferative DR (NPDR) and proliferative DR (PDR). NPDR is the earliest stage of DR. In NPDR, retinal vasculatures are characterized by microaneurysm, intraretinal hemorrhage and cotton weed spots. NPDR is further classified as mild, moderate and severe according the degree of Severity (AAO 2003; Goldman 2004) (Table 1). As DR progresses, a gradual closure of retinal vasculatures occurs. As a result of these closures, areas supplied by the affected blood vessels become ischemic. Manifestations of retinal ischemia include venous abnormalities such as loops, beadings, intraretinal microvascular abnormalities (IRMA), increased retinal hemorrhage and exudation that lead to severe and extensive leakage (AAO 2003). Severe NPDR occurs when these signs go beyond certain defined thresholds. Patients with severe NPDR should consider scatter laser photocoagulation as a possible treatment for their case (AAO 2003). PDR is the advanced stage of DR. It is characterized by the formation of new vessels at the optic disc (NVD) or new vessels elsewhere in the retina (NVE) (AAO 2003). These new vessels are weak and can bleed easily, causing vitreous hemorrhage. Fibrosis and contraction of these new vessels may lead to complications such as vitreoretinal traction, bands, retinal tears and rhegmatogenous retinal detachment (AAO 2003). PDR progresses to the highest stage of severity when one of the following scenarios happens: new vessels on or within 1 disc diameter of the optic disc equaling or exceeding standard photograph 10A (about 1/4 to 1/3 disc area), with or without vitreous or preretinal hemorrhage; or vitreous and/or preretinal hemorrhage accompanied by new vessels either on the optic disc less than standard photograph 10A or new vessels elsewhere equaling or exceeding 1/2 disc area (AAO 2003). Predisposing risk factors for high risk PDR include increased severity of retinopathy, decreased visual acuity, higher glycosylated hemoglobin, history of diabetic neuropathy, lower hematocrit, elevated triglycerides, lower serum albumin, and, in persons with mild to moderate non-proliferative retinopathy, younger age (or type 1 diabetes) (Davis 1997). High risk PDR is the major risk factor for severe visual loss or vitrectomy (Davis 1997).

The central region of the retina is known as the macula which contains the fovea. The fovea is located at the center of the macula and is responsible for central vision. When microaneurysms or microvascular hemorrhages occur around the macula or the fovea macular lesions and exudates are developed. The term diabetic maculopathy (DM) is used to describe the macular abnormalities due to diabetes. Diabetic maculopathy can be classified to diabetic macular edema (DME) and clinically significant macular edema (CSME) (Fong 1997). DME is defined as retinal thickening within 1 disc diameter of the center of the macula and/or hard exudates (Fong 1997). CSME occurs if any of the following findings were recognized: (1) retinal thickening within 500 μm of the center of the macula; (2) hard, yellow exudates within 500 μm of the center of the macula with adjacent retinal thickening; and (3) at least 1 disc area of retinal thickening, any part of which is within 1 disc diameter of the center of the fovea (Fong 1997). CSME is a major cause for sight-threatening retinopathy and central vision loss.

Epidemiology

Among adults aged 20–74, diabetic retinopathy (DR) is the most frequent cause of blindness (ADA 2006). As a sight-threatening retinopathy, there are 12,000–24,000 new cases of blindness caused by DR each year (ADA 2006). It is estimated that more than 60% of patients with type 2 DM and nearly all patients with type 1 DM will have retinopathy by

Table 1 International clinical diabetic retinopathy disease severity scale

Proposed disease severity level	Findings observable upon dilated opthalmoscopy
No apparent retinopathy	No abnormalities
Mild nonproliferative diabetic retinopathy	Microaneurysms only
Moderate nonproliferative diabetic retinopathy	More than just microaneurysms but less than severe NPDR
Severe nonproliferative diabetic retinopathy	Any of the following: • More than 20 intraretinal hemorrhages in each of four quadrants • Define venous beading in two or more quadrants • Prominent IRMA in one or more quadrants And no signs of proliferative retinopathy
Proliferative diabetic retinopathy	One or both of the following: • Neovascularization • Vitreous/preretinal hemorrhage

Abbreviations: IRMA, intraretinal microvascular abnormalities; NPDR, nonproliferative diabetic retinopathy.

the second decade of diagnosis (Klein 1984a, 1984b; Fong 2004. The prevalence of retinopathy at diagnosis of type1 DM is 0%–3%, while in type 2 DM the prevalence of DR is 6.7%–30.2% (Williams 2004; RCO 2005). The Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR) reported 74% prevalence at 9–10 years duration and 95% at 13–14 years duration of type 1 DM (Klein 1984a). The Wisconsin Diabetes Registry Study (WDRS) studied the prevalence and severity of DR in a population-based cohort followed for 4–14 years during the period between 1990 and 2002. In this study, the investigators recruited 474 diabetic patients from the same counties of Wisconsin where patients were recruited to participate in the WESDR trial 20 years earlier. They found that the prevalence of DR increased with the duration of diabetes; from 6% in the fourth year of diagnosis to 73% in the 14th year (LeCaire 2006). The finding was consistent across all ages and highest among adults 20 years of age or older. Additionally, WDRS reported 47% prevalence at 9–10 years duration and 73% at 13–14 years duration of DM. WDRS and other studies findings indicate that the prevalence of DR decreased over the last 20 years (Younis 2002, 2003; LeCaire 2006). This finding can be explained by the huge changes in diabetes care since 1980. Within the Medicare population, one study followed 20,325 patients from 1991 to 1999. At the end of the ninth year, 10,476 patients were analyzed and investigators found that the prevalence of DR among patients with diabetes mellitus increased from 6.9% to 17.4% (Lee 2003).

In WESDR, the 4-year incidence of DR within type 2 DM patients was 59%. (Klein 1990). In patient with type 2 DM, the 4-year incidence of any DR was 34% within insulin users and 47.4% within non-insulin users. In the same study, progression of retinopathy was more frequent within type 1 DM and type 2 insulin users – 41% and 34% respectively – than within type 2 DM non-insulin users (25%). Ten percent of type 1 DM patients progressed to PDR over 4 years. In type 2 DM patients, 7% of insulin users, versus only 2% non-users, progressed to PDR over 4 years.

It is very important to interpret prevalence and incidence studies with the understanding that many factors can influence both of them. For instance, Williams and his colleagues (2004) did a systematic review on the prevalence and the incidence of DR and macular edema. They stated that the prevalence of blindness and visual impairment is declining despite the fact that the incidence of DR remains constant. The reasons behind this phenomenon are better control of glucose, blood pressure as well as lipids. In addition, the improvement in screening methods, laser treatment as well as patient's awareness of their disease contributed further to this phenomenon (Williams 2004). Therefore, while the incidence of DR remains constant over time the prevalence of DR increases due to the aforementioned reasons. In the other hand, many of the clinical trials that addressed prevalence and incidence of DR were clinic based rather than population based. Therefore, disease frequency and severity may be overestimated since patients with long standing diabetes complications may refer to specialists for eye examinations rather than receiving a community based eye examination.

Prevention of diabetic retinopathy

Prevention of DR falls into two steps. First, preventing the development of DR. However, once the patient is diagnosed with DR the goal is to slow down the progression the disease and prevent the development of sight-threatening retinopathy that eventually will lead to partial visual loss or blindness. Many risk factors are believed to play an important role in this process. While some of them can be modified others can't. Maintaining modifiable risk factors within normal ranges such as blood pressure and glycosylated hemoglobin (HbA1c) has shown to reduce the development and progression of DR. Other risk factors of DR include duration of diabetes, pregnancy, renal disease, age, smoking, alcohol, hyperlipidemia and antioxidants. In 2005, the Royal College of Ophthalmologists (RCO) published new treatment guidelines for DR. The following section discusses the suggested risk factors and the RCO observations and recommendations each one of them (RCO 2005).

Modifiable risk factors

Glycemic control and glycosylated hemoglobin

In both types 1 and 2 DM, improved glycemic control (measured by HbA1c), reduces the development and progression of DR. The advantages of improved glycemic control apply to all ages and both genders. The Diabetes Control and Complications Trial (DCCT) observational study (DCCT 1995) reported that the higher the HbA1c and the shorter the duration of diabetes at entry, the greater the benefit of intensive therapy and improved glycemic control. In the trial, a 10% lower HbA1c was associated with a 44% lower risk. In another study, patients without retinopathy at baseline (DCCT primary cohort) were assigned to either good or poor metabolic control. Among the 153 DCCT patients with "good metabolic control" (mean HbA1c = 6.87%), three-step change retinopathy developed in (9.8%), while (90%) remained free of retinopathy. On the other hand, among the 166 patients

with "poor metabolic control" (mean HbA1c = 9.49%), the complication developed in (57%) (Zhang 2001).

The United Kingdom Prospective Diabetes Study (UKPDS) is another important study that examined the effect of intensive therapy versus conventional therapy on the development of macrovascular and microvascular complications in 3867 newly diagnosed patient with type 2 DM. The intensive therapy resulted in statistically significant reduction in HbA1c comparing to conventional therapy. (7% vs 7.9). This intensive glycemic control conferred a 34% risk reduction in the development of DR. Furthermore, there was a clinically significant reduction in the need for retinal photocoagulation with intensive therapy verses conventional therapy (7.9 vs 11 events per 1000 patients – year p = 0.003). Additionally, the need for cataract extraction was significantly reduced with intensive therapy over conventional therapy (5.6 vs 7.4 events per 1000 patients – year p = 0.046) (UKPDS 1998a).

Therefore, in patients with diabetes or patients with HbA1c higher than 7%, the following recommendation should be applied: (1) patients should understand HbA1c, what it means, and how to lower it; (2) patients should be encouraged to lower their HbA1c, and be given the necessary treatment and support to allow this; (3) if retinopathy develops, HbA1c should be maintained at a level below 7% but caution should be exercised if a high risk retinopathy is present; (4) patients should understand that potential temporary worsening of retinopathy may occur with diabetes control, but long term benefits should be stressed; and finally (5) establishment of local links between ophthalmologists and physicians should be stressed, in order to smooth the progress of early referral for management of risk factors in progressive cases.

Blood pressure

In type 1 DM patients, treatment of hypertension with ACEIs resulted in a 23% reduction in the progression of DR. In addition, in type 2 DM patients, the analyses of the UKPDS trial showed that control of blood pressure reduces the progression of DR and visual acuity deterioration by 34% and 47% with tight control of blood pressure (144/82) and (152/87) respectively (UKPDS 1998b). The results from this study and other studies suggested that the beneficial effect of anti-hypertensive treatment and the deleterious effect of increased blood pressure are immediate and require regular measurement of blood pressure. Information regarding the best antihypertensive regimen was not conclusive. These observations have led to the following recommendations: (1) blood pressure measurement methodology should be correct and casual clinic measurements should be avoided; (2) even a small reduction in blood pressure, especially systolic blood pressure is considered beneficial; (3) patients should understand their blood pressure, what it means, and how to lower it; (4) patients should be counseled about the potential harm if they stop their therapy and their blood pressure increases; (5) patients should be encouraged to lower their blood pressure, and be given the necessary treatment and support to allow this; (6) regular measurement of blood pressure, to ensure continuing control is recommended; (7) if retinopathy has already developed, systolic blood pressure should be below 130 mmHg; and (8) an ACE inhibitor or angiotensin receptor antagonist antihypertensive drug may be considered since it provides additional benefit, over and above its blood pressure lowering effect.

Tobacco and alcohol use

Discontinuation of smoking is recommended for reducing the development of other complications of diabetes. However, it appears that cigarette smoking is not a risk factor for the development or progression of DR. Information regarding the role of alcohol in worsening or improving of DR is inconclusive.

Aspirin and thrombolytics

The use of thrombolytics doesn't increase the risk of retinal hemorrhage in reperfusion therapy of myocardial ischemia. Furthermore, aspirin therapy neither reduces nor increases the risk of developing retinopathy or retinal hemorrhage. Therefore, retinopathy should not be a contraindication for aspirin therapy or thrombolytic therapy for myocardial infarction.

Hypercholesterolemia

Although some studies showed a correlation between high cholesterol blood levels and risk of retinopathy, others failed to find any correlation. In addition, no randomized control trial has shown any benefit of lowering cholesterol blood level in terms of retinopathy risk reduction.

Antioxidants

One study about the efficacy of antioxidants in preventing the development of DR showed no benefit regarding their use. The study showed that vitamin E was associated with increased severity of DR among those not taking insulin. In addition, among those taking insulin, increased intake of beta-carotene was associated with a risk for severity of DR (Mayer-Davis 1998). Therefore, the role of antioxidants in developing or worsening DR has been investigated; however there is no evidence of effectiveness.

Non-modifiable

Pregnancy

Most pregnant patients with mild to moderate retinopathy will not experience any changes during pregnancy. However, a small, unpredictable group may progress to PDR and remain at risk for a year after delivery. Unfortunately, there is limited evidence that pre-gestational counseling is beneficial, in terms of deterioration of retinopathy during pregnancy. The Panel recommended that pre-pregnancy counseling should be provided to the patients; especially for improvement in glycemic control. In addition, screening should be done before conception, in each trimester and between 3 and 9 months post-natally.

Renal disease

Some studies have shown an increased risk of retinopathy worsening especially in the macula. Hemodialysis can be a better explanation for the observed worsening being a stronger associated risk factor. However, treatment of renal disease was associated with an improvement in retinopathy and a beneficial response to treatment.

Furthermore, patients with developing nephropathy – determined by the presences of microalbuminuria – have increased blood pressure that can be the cause of higher risk of retinopathy. Therefore, the panel recommended more frequent regular supervision of retinopathy in patients with established renal dysfunction. In addition, aggressive blood pressure control is essential to reducing the rate of progression of both retinopathy and nephropathy.

Age and duration of diabetes

In Both type 1 and 2 DM, duration of diabetes is associated with higher incidence and prevalence of DR. Older patients with diabetes have a greater risk of visual impairment.

Screening for diabetic retinopathy

Since the early stages of retinopathy are asymptomatic, any loss of vision can't be restored. Laser photocoagulation is effective at slowing down the progression of the disease but not at restoring lost vision (Fong 2004). Therefore, different guidelines stressed the importance of early detection of DR (AAO 2003; RCO 2005).

Medications and aggravation of diabetic retinopathy

Whether certain medications can trigger the development of DR or not, is still unclear. The evidence on the presence of a relationship between certain antidiabetic agents and diabetic retinopathy is inconclusive. One study followed up 30 patients who used either pioglitazone, rosiglitazone, or both at different times, and who had both lower extremity edema and macular edema. The discontinuation of glitazones in eleven of these patients led to a reduction of macular edema in 4 patients in <3 months and a total of 8 over two years. (Ryan 2006) In another observational study that was done to assess the association of insulin lispro with the development and progression of DR in 12 pregnant women, insulin lispro was not associated with any risk of DR. (Buchbinder 2000). The fact that these studies were observational with a very small sample size, makes the results inconclusive and hardly generalizable.

Ocular complications associated with diabetic retinopathy

Diabetic retinopathy is associated with many complications such as retinal detachment, rubeosis iridis and rubeotic glaucoma. In PDR, contraction and condensation of the vitreous gel in association with hemorrhage and fibrosis lead to tractional retinal detachment. Rubeosis iridis takes place when advanced retinal ischemia leads to the growth of new vessels on the iris. Rubeotic glaucoma occurs when the aqueous fluid drainage rout in the anterior chamber of the eye blocked by the formation of fibrotic tissues around it. Rarely, optic neuropathy may occur (RCO 2005).

Cost benefit analyses

The medical and economic effects of applying accepted methods for controlling DR among type 1 DM patients have been predicted using computer simulation models. The investigators of one model designed a model using the following published reports: Recommendations for screening of DR from the Public Health Committee of the American Academy of Ophthalmology. Treatment recommendations and treatment efficacy from the reports of the Diabetic Retinopathy Study (DRS) and the Early Treatment Diabetic Retinopathy Study (ETDRS) and costs of screening and treatment from published Medicare reimbursement data. The model predicted that over a 60 years period, 72% of type 1 patients eventually will develop PDR requiring panretinal photocoagulation and that 42% will develop macular edema. When treatments are delivered according to clinical trial recommendations, the model predicts a cost of $966 per person-year of vision saved from PDR and $1,118 per person-year of central acuity saved from macular edema. These costs are lower than the costs of one year of Social

Security Disability for those disabled by vision loss due sight – threatening retinopathy (Javitt 1989). Furthermore, the model predicts that if all patients received appropriate eye care, the predicted savings would exceed 167.0 million and 79,236 person-years-sights (Javitt 1991).

Another computer simulated model was used to evaluate the cost-effectiveness of screening and treatment for diabetic retinopathy from a societal viewpoint. Computation was performed on three subpopulations formed by patients with younger onset diabetes (age at diagnosis less than 30) of 5 years or more duration, with older onset diabetes (age at diagnosis greater than or equal to 30) who are taking insulin, and with older onset diabetes not taking insulin. The investigators found that annual examination with mydriatic fundus photography as a screening program to a cohort of 1,000 diabetics from the younger onset population who have been diagnosed at least 5 years and who are currently not receiving care might save 319 sight years over the lifetime of the cohort. The program will save 62 sight years in an older onset cohort who are taking insulin, and 21 sight years in the older onset population not taking insulin. (Dasbach 1991).

Prognosis

Prognosis of DR depends on the stage of the disease and the availability of treatment. Around 5%–10% of diabetic patients with normal retinal exam will develop diabetic retinopathy within one year. Therefore, initial dilated and comprehensive eye examinations should be done within 3–5 years after diagnosis of type 1 DM and with the diagnosis of type 2 DM. The examination helps to detect early DR where maintaining glucose level and blood pressure within the normal recommended ranges is considered the main available therapeutic modality for mild to moderate NPDR without macular edema. For instance, the DCCT showed 75% and 50% reduction in the development and progression of DR after 3 years of intensive treatment to reduce blood glucose respectively (AAO 2003).

Early Treatment Diabetic Retinopathy Study (ETDRS) recommendations are considered the main gold standard practice for the treatment of advanced stages of DR. According to ETDRS recommendations, patients with severe NPDR, non-high risk PDR, high risk PDR should be treated with scatter photocoagulation also known as panretinal photocoagulation. Early treatment of severe NPDR and non-high risk PDR before the progression to high risk PDR – the sight-threatening retinopathy – was associated with 50% reduction in the risk of blindness and vitrectomy comparing with treatment deferral until high risk PDR is developed (AAO 2003; Bhavsar 2006).

If the patient develops tractional retinal detachment or vitreous hemorrhage that hinder this procedure, then vitrectomy should be considered.

Currently a number of clinical trials are investigating drugs with different mechanism of actions for the treatment of DR. For instance, ruboxistaurin (RBX) is a new drug that inhibits the β-isoform of protein kinase C (PKC) enzyme which is believed to play an important role in the development of microvascular complications of diabetes. Animal models demonstrated that PKC mediates the increase in retinal vascular permeability and neovascularization shown in DR. Additionally, PKC has shown to mediate the changes in retinal blood flow in diabetic patients (PKC-DRS 2005). Therefore, RBX was suggested to be a good candidate for prevention of DR as well as delay the progression of already developed DR. Recently published in march 2007, a multicenter, double-blind, randomized, placebo-controlled study was investigating the effect of ruboxistaurin verses placebo in 686 patients with diabetic macular edema DME. The primary outcomes was the progression of DME and/or the application of focal/grid laser photocoagulation. After thirty months, the results didn't show any statistical significant difference in this composite primary endpoint. However, considering progression of DME alone, the daily administration of RBX 32 mg may delay progression of DME to a sight-threatening stage. In terms of side effects, RBX was well tolerated except for first-degree atrioventricular block, asthma, and dysuria. These side effects didn't appear in other 6–12 months RBX trials (PKC-DMES 2007).

It is very important to take in consideration that the inclusion criteria was very specific and included eyes with DME farther than 300 μm from the center of the macula, mild to moderately severe nonproliferative diabetic retinopathy, a visual acuity of 20/32 or better, and no prior laser photocoagulation for diabetic retinopathy or DME. Therefore, the generalizability of these results to all patients with macular edema or DR can be an issue.

Another double-masked, placebo-controlled, parallel, randomized, single-center clinical study was done to evaluate the effect of oral administration of RBX on the mean retinal circulation time (RCT) and retinal blood flow (RBF). The study included 28 patients with type 1 or 2 DM and no or very mild DR. The results showed a statistically significant reduction in the diabetes-induced increased RCT and RBF. This may suggest a potential role for RBX in early prevention of DR (Aiello 2006). However, whether this reduction

in RCT and RBF is sufficient to reduce the incidence of DR is another question that needs further investigation.

There are many other drugs that may play a role in DR therapy in coming few years such as somatostatin agonists (sandostatin), corticosteroids (triamcinolone, dexamethasone, fluocinolone), vascular endothelial growth factor inhibitors (pegaptanib, ranibizumab), hyaluronidase and plasmin enzyme (AAO 2003; Bhavsar 2006). Whether these future therapies will have a clinically significant impact on the development and/or the progression of the disease and subsequently the prognosis of the disease is unknown. This question will open a new horizon for future research.

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