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Current and future management of diabetic retinopathy: a personalized evidence-based approach

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Summary

Diabetic retinopathy (DR) is the leading cause of new-onset blindness in working-age individuals in the USA and represents a growing worldwide epidemic. Classic risk factors for onset or progression of DR include poor glycemic control, hypertension and hyperlipidemia; however, these factors account for only a small proportion of the risk of DR. New systemic risk factors are emerging, which may allow for personalized risk profiling and targeted treatment by physicians. In addition, early studies of vitreous fluid in patients with DR have resulted in a new paradigm: diabetes causes inflammation in the retina, which is mediated by multiple small signaling molecules that induce angiogenesis and vascular permeability. Future treatment of DR may involve two approaches: early vitreous analysis, followed by drug treatment targeted to the unique vitreous composition of the patient; and collaboration between ophthalmologists and primary care providers to address the unique systemic risk profile of each diabetic patient.

Importance of diabetic retinopathy

Visual complications from diabetes mellitus continue to represent a considerable source of morbidity in developing and developed countries. In the USA, 8.3% of the population or 25.8 million people are estimated to have diabetes [1]. Worldwide, there were an estimated 171 million individuals with diabetes in 2000 and the number of cases is expected to rise to 366 million by 2030 [2].

Unfortunately, many patients with diabetes will eventually develop diabetic retinopathy (DR) and visual impairment from tractional retinal detachment, vitreous hemorrhage, macular ischemia and diabetic macular edema (DME). In a cohort of patients with Type 1 diabetes followed from 1980 to 2005, 83% had progression of retinopathy and 42% developed proliferative diabetic retinopathy (PDR) [3]. A study of a multiethnic cohort with Type 2 diabetes in the USA showed a 33.2% prevalence of retinopathy and a 9.0% prevalence of DME [4].

Vision loss from diabetes results from compromised function of the neurovascular unit of the retina, which is composed of capillary endothelial cells, pericytes, glial cells and neurons [5]. Pathologic changes to the neurovascular unit are manifested clinically as retinal microaneurysms, intraretinal ('dot-blot') hemorrhages, leakage of serum lipoproteins (visible as hard exudates or retinal cysts), venular dilation and beading, and retinal nerve fiber layer disruption ('cotton wool spots') (Figure 1). Changes in visual function at preclinical and early stages manifest as reduced color vision, contrast sensitivity and abnormal visual field testing [6]. Vision is further impaired when hemorrhage, edema or ischemia affect the macula (Figure 2), or when abnormal proliferating fibrovascular membranes induce retinal detachment or vitreous hemorrhage (Figure 3). Moderate-to-severe vision loss is usually a consequence of DME or PDR.

Current treatment options are limited to controlling hyperglycemia, hyperlipidemia and hypertension. However, many patients are unable to adequately control hyperglycemia because of fear of hypoglycemia [7], so the practical options for patients who want to minimize complications are limited. Recent work shows that current standard risk factors have limited predictive value and suggest that the pathogenesis of retinopathy is more complex than previously realized. As a result of the complex nature of diabetes management and the growing diabetes epidemic, the prevention and treatment of DR will probably become a greater challenge in the future. Ophthalmologists and primary care physicians will be faced with the common challenge of finding better ways to preserve vision in a growing population with diabetes-related visual impairment. We propose that this challenge is best addressed by implementing evidence-based medicine to modify currently known risk factors and a systems biology approach to identify new risk factors. Development of more detailed metabolic and inflammatory profiles in people with diabetes will be imperative to deliver patient-specific predictive treatments. This is consistent with the 'P4' approach proposed by Hood *et al.* [8], which advocates medicine that is predictive, preventive, personalized and participatory.

Prevention of diabetic retinopathy incidence & progression

Risk factor identification

The 'classic' risk factors for onset or progression of DR have been demonstrated in early studies and have received significant attention; these include poor glycemic control, hypertension and hyperlipidemia. The DCCT demonstrated that, in Type 1 diabetes, intensive control of blood glucose versus conventional therapy significantly reduced diabetic retinopathy onset (by 76%) and progression (by 54%) [9]. Elevated HbA1c is also associated with increased risk of diabetic retinopathy progression in Type 1 diabetes [3,10]. The UKPDS showed similar reductions in DR progression with strict metabolic control in Type 2 diabetics [11]. The importance of tight blood pressure control in preventing vision loss and progression of retinopathy was demonstrated in a later report of the UKPDS [12] and has been confirmed by additional studies [13]. In addition, elevated total cholesterol and LDL have been shown separately to increase the risk of diabetic retinopathy [13,14]. The benefit of lipid control was evaluated by the ACCORD study group; in this study, treatment with fenofibrate was found to significantly reduce progression of DR (by 40%) [15].

Risk factor modification

Although blood glucose, lipids and blood pressure have been clearly identified as risk factors, it is challenging to apply this knowledge to achieve target values and to optimally reduce the risk of complications. Data from the recent National Health and Nutrition Examination Surveys (NHANES) indicates that 52% of diabetics reached the target HbA1c, 51% reached the target blood pressure and 56% reached the target LDL cholesterol levels, but only 19% of people met all three goals [16]. This is similar to data in Type 2 diabetes, where only 7% of patients meet goals for all three risk factors [17]. These figures are an indication of the difficulty in achieving evidence-based treatment goals. The reasons for this failure are multiple, and include inadequate access to care, medications and diabetes education.

Nevertheless, the long-term importance of risk factor modification was recently highlighted in a longitudinal report of the DCCT cohort after 30 years of follow-up. It showed significantly lower cumulative incidence of PDR in the intensive therapy group versus historical cohorts of patients who developed diabetes between the 1950s and 1970s [18]. Similar trends have also been observed in Scandinavia [19,20]. The reduced rates of diabetic complications demonstrated here are probably the result of intensive glycemic control, in addition to improved treatment of hypertension and hyperlipidemia.

Emerging risk factors

Physicians often consider persons with diabetes, whether Type 1 or 2, to be relatively homogeneous from a metabolic standpoint, and, therefore, treat a limited number of systemic parameters, notably HbA1c, blood pressure and cholesterol levels. Standard treatment guidelines, however beneficial, reflect this tendency to group patients. However, recent research has highlighted additional risk factors in the development of DR and other complications. It is now clear that the development of DR is a more complex, multifactorial process than originally thought. Moreover, the severity of expression of retinopathy can be highly variable from one individual to another and the limited predictive ability of HbA1c has become increasingly evident. A model of DR progression indicated an approximate progression rate of 2% per year in Type 1 diabetic patients that had achieved the target HbA1c of 7.0 [9]. Quantification of the contributions of different factors in the development of DR has further demonstrated the limitations of HbA1c. A reappraisal of the DCCT data showed that HbA1c was responsible for only 11% of the risk of developing DR [21]. Similarly, in the WESDR, the combination of lipids, blood pressure and blood glucose were responsible for 10% of the risk of DR [22]. This finding supports the notion that a variety of other risk factors exist and contribute to the development and progression of DR, even when the classic risk factors are appropriately modified.

Recent studies using multivariate regression models have elucidated new independent risk factors for retinopathy that account for a significant relative contribution to the overall risk (Table 1). These risk factors involve multiple systemic organs and tissues, and demographic factors, including male gender [3,23], Hispanic and African-American ethnicity [23], and longer duration of diabetes (Figure 4) [4].

The presence of coexisting nephropathy and neuropathy increase the risk of diabetic eye complications. Multiple cross-sectional and cohort studies have demonstrated that factors related to renal insufficiency impact the likelihood of DR, including vitamin D and magnesium deficiency [24,25], proteinuria [26] and nephropathy [27]. Neuropathy can lead to non-healing extremity ulcers and amputations, and a well-known connection has been established between peripheral neuropathy and DR [28,29]. Hamalainen and colleagues demonstrated a correlation between lower limb amputations and retinopathy in a case-control study of 733 diabetic patients [30]. In addition, a fivefold greater risk for nonproliferative diabetic retinopathy and 21-fold greater risk for PDR were demonstrated in a study of Pima Indians who had undergone lower-extremity amputations [31].

Other organ dysfunction, including pulmonary and hepatic disease, increases the risk of progression of retinopathy. Obstructive sleep apnea was shown to be an independent predictor of DR in a cohort of 118 men with Type 2 diabetes [32]. Other investigators have demonstrated higher rates of sleep-disordered breathing in patients with DME [33] and PDR [34], when compared with peers with less severe DR. Nonalcoholic fatty liver disease also appears to predict a risk of DR. Nonalcoholic fatty liver disease was found to be independently associated with a threefold increased risk of retinopathy incidence in a multivariate regression analysis of Type 1 diabetic patients [35] and nearly a twofold increased risk in Type 2 diabetes [36].

In addition, obesity and other metabolic factors have also been linked to the risk of worsening DR. An elevated BMI (hazard ratio [HR]: 1.16) [3], visceral fat accumulation (HR: 4.8) [37] and metabolic syndrome (HR: 3.7) [38] all increase the risk of retinopathy. Specific diabetes-related endocrine abnormalities are also linked to increased rates of retinopathy, including low C-peptide levels [39,40] and insulin resistance [23,37]. Abnormalities in levels of several components in the serum have been implicated with development of DR, including adiponectin [41], prolactin [42], plasmin- α 2 antiplasmin [43] and homocysteine [43].

The above risk factors may not solely represent markers for poor glycemic control, but systemic factors (i.e., amputations and nonhealing ulcers) may also contribute to the progression of PDR through inflammatory pathways. A recent multivariate analysis of a large cohort of patients with newly diagnosed nonproliferative diabetic retinopathy found that the risk of progression to PDR increased by 54% in patients with non-healing ulcers after adjustment for confounders [27]. In the same study, each one-point increase in HbA1c increased the risk of retinopathy progression by 14%; therefore, a nonhealing ulcer conferred the same risk as a 3% increase in HbA1c. One explanation for this finding may be that nonhealing ulcers upregulate the systemic inflammatory response, worsening inflammation in the retina. This argument is strengthened by the observation that diabetic wounds have elevated levels of cytokines, including TNF- α , IL-8 and MCP-1 [44].

The key role of inflammation in the pathogenesis of systemic diabetic microvascular complications, including retinopathy, has become increasingly clear [45]. Inflammation may mediate the link between many of the systemic risk factors connected to the progression of DR. Patients with DR have elevated cytokine levels locally in the retina and vitreous [46],

which may be secondary to systemic inflammation. For example, increased serum cytokine levels, including VEGF and MCP-1 [47], IL-1 and TNF- α [48], and NO and IL-8 [49], have been correlated with the severity of DR. This evidence suggests that, in people with diabetes, a variety of systemic conditions elevate circulating inflammatory factors, leading to retinal inflammation, angiogenesis and vascular permeability. For example, periodontal disease causes higher circulating levels of lipopolysaccharide and inflammatory cytokines, and is associated with a higher risk of PDR [50].

Treatment of diabetic retinopathy

Vision loss secondary to DME

Currently, patients diagnosed with DME may undergo focal laser photocoagulation or intravitreal injections of corticosteroid or anti-VEGF medication. Focal laser photocoagulation targets microaneurysms in the macula and reduces leakage of plasma responsible for macular thickening. Focal laser photocoagulation reduced the risk of moderate vision loss by 50–70% in patients with macular edema in the ETDRS trial [51]. Anti-VEGF medications target retinal vascular permeability and improve visual acuity and macular thickness in patients with DME. This effect was demonstrated in the READ-2 and RESOLVE trials [52,53] and further validated in the RISE and RIDE trials [54]. Intravitreal triamcinolone is occasionally utilized for treatment of DME, but it is inferior to a focal macular laser at long-term follow-up and is associated with a higher incidence of glaucoma and cataracts [55].

Current therapies have a significant effect on patients with DME, but response to treatment is both variable and limited; more than half of patients do not achieve visual improvements with treatment [56]. In addition, the treatment burden of frequent (often monthly) injections of anti-VEGF antibodies is substantial, and most patients require the assistance of a family member to safely drive to their appointment. There is also a small but real risk of complications, including severe intraocular infection (0.03%) [57].

One approach to minimize risk and maximize treatment response is to identify biomarkers predictive of response to treatment. Recent identification of cytokines, growth factors and proteins in the vitreous that are altered in patients with DME suggest that this goal may be feasible. Unfortunately, most studies to date have focused on targeted quantification of specific proteins and cytokines, and have failed to incorporate substantial phenotypic information.

Vision loss secondary to PDR

Persons with PDR are treated with pan-retinal photocoagulation and may require vitrectomy if vitreous hemorrhage and/or retinal detachment ensues. Pan-retinal photocoagulation obliterates ischemic peripheral retinal tissues, which are the source of VEGF and other molecules that lead to abnormal vascular proliferation. Early vitrectomy improves the odds of obtaining good vision in patients with severe PDR who develop vitreous hemorrhage [58–60].

Beyond VEGF

It is well established that VEGF has a role in DR, but it is likely that retinopathy results from a multi factorial process involving additional cytokines and growth factors. In 2012, Zechmeister-Koss and colleagues concluded that, while anti-VEGF therapies are superior to alternative treatments for DME, 60–85% of patients did not achieve a clinically relevant improvement in visual acuity [56]. A Cochrane review reached similar conclusions; anti-VEGF treatments for DME produce a small-to-moderate improvement in vision at 1 year, but five to ten patients must be treated to gain benefit in one person [61].

The multifactorial etiology of DME is also supported by the observation that low VEGF levels in the eye do not always correspond with clinical improvement. Funk and colleagues demonstrated that aqueous fluid in patients with DME differs from that in control patients with respect to multiple cytokines, including IL-8 and MCP-1 [62]. In addition, treatment with anti-VEGF therapy reduced aqueous VEGF below physiologic levels, but there was no correlation between VEGF concentration and visual acuity or macula thickness. While there are a variety of explanations for this finding, including that aqueous concentrations of cytokines are not reflective or relevant to retinal physiology, another possibility is that VEGF only represents one of many factors responsible for DME. In the future, additional characterization of small signaling molecules will probably lead to new therapeutic agents, biomarkers of response to therapy and improved visual outcomes.

Recent studies have revealed many differentially expressed cytokines in the vitreous of patients with retinal pathology. Enzyme-linked immunosorbent assays have been used to compare vitreous quantities of a few select (two to five) cytokines in patients with DME or central retinal vein occlusion (CRVO), and have demonstrated increased levels of IL-6 and MCP-1 compared with controls [63–65]. Recent development of cytometric bead assays has allowed for analysis of a greater number of signaling molecules. Yoshimura *et al.* utilized a 20-plex assay to compare vitreous cytokine content in DME, CRVO and control patients, and found that IL-6, IL-8 and MCP-1 levels were elevated compared with controls [66]. A similar study with a 27-plex assay identified IL-10 and -13 as key contributors to macular edema in patients with CRVO and PDR [67].

Vitreous analysis

A new paradigm for the etiology of diabetic retinopathy is emerging. DR is a multifactorial process involving low-level inflammation mediated by multiple small signaling molecules favoring angiogenesis and vascular permeability [68,69]. Treatment with anti-VEGF drugs does not fully address the pathophysiology. By contrast, vitreous sampling allows for identification of the molecular signature of the retina that reflects the underlying disease state (Figure 5).

Vitreous sampling and analysis may become a useful means to define patient-specific disease mechanisms and treatments. A study of 578 in-office vitreous aspiration procedures demonstrated that this technique is safe and reproducible with a high yield of successful samples (95%) [70]. Vitreous sampling does not expose the patient to additional office visits or setup, and it can be performed prior to intravitreal injection. Vitreous analysis led to the

breakthrough that identified the role of VEGF in DR [71], and further analyses will probably be valuable in understanding the pathophysiology of DR, developing new drug targets and predicting response to treatment.

Despite optimism about the future of vitreous analysis, biomarker research can be subject to several pitfalls and limitations. To date, biomarker research has seldom been translated into tools that guide routine clinical decisionmaking [72]. In addition, investigations of new biomarkers can be subject to publication bias and over estimations of effect [73,74]. In order to avoid these pitfalls, future research will require randomized clinical trials that incorporate well-designed biobanks [75]. In the future, multiple treatment options will be available for DME. The challenge will be deciding which medication to use for each patient. At present, the approach is to empirically administer different agents until the desired outcome is achieved. We propose that a molecular diagnosis of altered treatment targets will offer personalized and optimized treatment options. In this model, the ophthalmologist will obtain a vitreous biopsy, analyze the biopsy at the molecular level with standardized commercial assays and administer targeted treatment combinations to the patient. We believe that this will reduce the treatment burden, result in better visual outcomes and reduce the cost of care.

Evidence-based medicine & risk profiles

As noted above, achieving evidence-based treatment targets is a formidable challenge for patients and clinicians. We propose that this complexity is best addressed by use of an individual, comprehensive risk profile for each patient. Such a profile would facilitate collaboration between ophthalmologists and primary care providers, and allow for treatment and prevention to be tailored to each patient's unique clinical situation.

One can imagine several further benefits of personalized risk profiles. Ophthalmologists could communicate unambiguously with the patient and primary care provider about the concrete risk of vision loss. For example, the ophthalmologist might advise that there is a 50% chance of moderate vision loss in the next 5 years if improved glucose control is not achieved. A risk profile could indicate which systemic factors deserve urgent attention, such as loss of excess abdominal fat or treatment of obstructive sleep apnea. In addition, healthcare resources could be allocated more efficiently for deciding when to initiate treatment or to schedule follow-up.

Risk models have been published by several authors, but will require further validation and incorporation of additional factors. Nwanyanwu and associates created a model demonstrating that the presence of nonhealing ulcers confers a similar risk for retinopathy progression as a 3–4% increase in HbA1c [27]. In addition, Aspelund and colleagues created a risk calculator to generate individualized recommendations for the frequency of screening visits for diabetic retinopathy [76]. This model incorporated duration and type of diabetes, HbA1c, blood pressure and severity of retinopathy. Based on the model, patients with a higher risk of retinopathy required shorter screening intervals, and those with a low risk could extend the duration between screening visits. While current recommendations indicate the need for annual screening visits for diabetic patients, the Aspelund model advised follow-ups ranging from 6 to 60 months, resulting in 59% fewer visits overall. As the impact of additional risk factors for retinopathy is elucidated, more accurate models might

automatically determine the most appropriate time to initiate treatment or schedule follow-up.

Conclusion

Our article identifies many risk factors for DR. Some of these, such as peripheral neuropathy and nephropathy, may merely serve as markers for poor glycemic control or may be the result of multivariate regression models that failed to account for a confounding variable. However, some risk factors identified in large studies were associated with high hazard ratios and are probably important in understanding DR. The factors that appear to present a major hazard for the development or progression of diabetic retinopathy include HbA1c >8.0, duration of diabetes >10 years, an amputated or nonhealing ulcer, metabolic syndrome or excess abdominal fat, and African–American or Hispanic ethnicity (Table 2).

Considering these major risk factors for DR and the need for open collaboration between ophthalmologists and primary care providers, we created a shared primary care/ophthalmology model for tracking major modifiable and unmodifiable risk factors [77]. Using data from a patient in our retina clinic with Type 2 diabetes and DR, we have demonstrated how the model can be used (Table 3). This model is useful to the ophthalmologist in estimating the risk of DR and can be used by the primary care physician to track treatment goals and identify areas needing urgent attention.

Future perspective

In 5–10 years, the treatment of DR will probably have become increasingly individualized and targeted, with an expanded number of intravitreal drugs available for combined injection. As inflammatory and metabolic factors involved in the pathophysiology of DR are further elucidated, other drugs will become available to the ophthalmologist. Future treatment will probably involve early vitreous sampling followed by an injection of multiple combined medications tailored to the individual's vitreous signature. Use of risk profiles will facilitate improvements in risk factor control, reduce incidence and progression of DR, and reduce costs. In addition, manipulation of pharmacokinetic drug properties may allow for a longer intravitreal half-life and less need for frequent injections. As the duration and efficacy of intravitreal drugs improve, the use of treatment modalities that destroy retinal tissue, such as focal laser photocoagulation or pan-retinal photocoagulation, may no longer be necessary.

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Practice Points

- In the USA, 8.3% of the population (25.8 million people) are estimated to have diabetes, many of whom will eventually develop visual impairment from diabetic retinopathy (DR). DR is a complex condition that is best addressed by systems biology and evidence-based medicine. Development of patient-specific treatments will require analysis of individual metabolic and inflammatory profiles.
- The classic risk factors for onset or progression of DR include poor glycemic control, hypertension and hyperlipidemia, and only 19% of patients meet the targets for all three factors. As well as HbA1c levels, additional factors are important in the development of diabetic retinopathy; HbA1c is estimated to be responsible for only 11% of the risk of retinopathy.
- Emerging nonmodifiable risk factors for DR include longer duration of diabetes, male gender, Hispanic or African–American ethnicity, and nephropathy. Emerging modifiable risk factors for DR include nonhealing ulcers, obstructive sleep apnea and metabolic syndrome.
- In people with diabetes, a variety of systemic conditions elevate circulating inflammatory factors, which leads to retinal inflammation, angiogenesis and vascular permeability.
- While anti-VEGF therapies are superior to alternative treatments for diabetic macular edema, 60–85% of patients did not achieve a clinically relevant improvement in visual acuity. VEGF represents one of many factors responsible for DR; it is likely that retinopathy results from a multifactorial process involving additional cytokines and growth factors. Multiple cytokine levels are elevated in the vitreous of patients with diabetic retinopathy compared with controls, including MCP-1, IL-6, -8, -10 and -13.
- Vitreous sampling will be used to create individual vitreous profiles that help us to improve our understanding of the DR pathophysiology, develop new drug targets and predict response to treatment.
- A personalized approach to diabetic retinopathy will involve increased collaboration between ophthalmologists and primary care providers, and the use of risk factor models to tailor treatment and prevention to each patient's unique risk profile.

Figure 1. Fundus photo of a patient with nonproliferative diabetic retinopathy, demonstrating cotton wool spots, dot–blot hemorrhages and venous beading

Figure 2. Optical coherence tomography image of the retina of a patient with diabetic macular edema

Figure 3. Fundus photos of a 39-year-old patient with proliferative diabetic retinopathy in both eyes

(A) Right eye: proliferating fibrovascular membranes and preretinal hemorrhage overlying the macula. (B) Left eye: abnormal blood vessels and hard exudates in the macula.

Figure 4. Systemic and demographic risk factors for diabetic retinopathy

Figure courtesy of David Murrell (Kellogg Eye Center, MI, USA).

Figure 5. Cytokines and growth factors from the retina diffusing into the vitreous can be collected for analysis

Figure courtesy of David Murrell (Kellogg Eye Center, MI, USA).

Table 1

Published risk factors for diabetic retinopathy

Risk factor	Study (year)	Type of study	Methods	Patients (n)	Duration (years)	Findings	Ref.
Demographic							
Male gender	Klein <i>et al.</i> (2008)	Population based	Type 1 DM patients followed for progression of DR	955	25	HR = 1.33; p = 0.002	[3]
Male gender	Zhang <i>et al.</i> (2010)	Cross-sectional	Type 1 and 2 DM patients evaluated for the presence of DR	1006	–	HR = 1.79	[23]
Hispanic ethnicity	Zhang <i>et al.</i> (2010)	–	–	–	–	HR = 3.63	[23]
African– American ethnicity	Zhang <i>et al.</i> (2010)	–	–	–	–	HR = 3.77	[23]
Duration of diabetes	Wong <i>et al.</i> (2006)	Cross-sectional	Type 1 and 2 DM patients evaluated for the presence of DR	778	–	DM for 3–10 years: HR = 2.63; p < 0.001 DM for >10 years: HR = 9.09; p < 0.001	[4]
Hepatic							
Hepatic steatosis	Targher <i>et al.</i> (2008)	Cross-sectional	Type 2 DM patients evaluated for kidney disease, hepatic steatosis and the presence of DR	2103	–	HR = 1.75; p = 0.03	[36]
Hepatic steatosis	Targher <i>et al.</i> (2010)	Cross-sectional	Type 1 DM patients evaluated for kidney disease, hepatic steatosis and the presence of DR	202	–	HR = 3.31; p = 0.05	[35]
Renal							
Vitamin D deficiency	Patrick <i>et al.</i> (2012)	Cross-sectional	Serum 25-hydroxy vitamin D compared in patients with Type 1 and 2 DM with and without DR	1790	–	More severe DR associated with higher likelihood of vitamin D deficiency (p = 0.07)	[25]
Low serum magnesium	Kundu <i>et al.</i> (2013)	Cross-sectional	Serum magnesium compared in Type 2 DM patients with and without DR	120	–	Lower serum magnesium levels in patients with DR (1.38 ± 0.39 mg/dl) vs patients without DR (2.02 ± 0.29 mg/dl)	[24]

Risk factor	Study (year)	Type of study	Methods	Patients (n)	Duration (years)	Findings	Ref.
Proteinuria	de Boer <i>et al.</i> (2011)	Observational cohort	Type 1 DM patients with microalbuminuria followed for long-term health outcomes	325	–	Higher likelihood of developing macroalbuminuria in patients with retinopathy: HR = 3.15; p = 0.03	[26]
Nephropathy	Nwanyanwu <i>et al.</i> (2013)	Retrospective cohort	Database study of Type 1 and 2 DM patients with NPDR followed for progression to PDR	4617	–	HR = 1.29 (95% CI: 0.99–1.67)	[27]
Pulmonary							
Obstructive sleep apnea	West <i>et al.</i> (2010)	Retrospective case-control	Type 2 DM patients evaluated for OSA; multivariate regression performed	240	–	OSA accounted for partial risk of maculopathy (30%; p < 0.0001) and microaneurysm (21%; p = 0.004)	[32]
Sleep-disordered breathing	Shiba <i>et al.</i> (2010)	Case-control	Type 2 DM patients with NPDR or PDR evaluated for oxygen desaturation during sleep	166	–	Higher rate of sleep-disordered breathing in patients with PDR (47.5%) vs NPDR (29.2%; p = 0.03)	[34]
Cardiovascular							
Hypertension	UKPDS 38 (1998)	Randomized controlled trial	Tight blood pressure control in patients with Type 2 DM and hypertension	1148	9	RR of DR progression reduced by 34% (p = 0.0004); RR of loss of three lines of acuity reduced by 47% (p = 0.004)	[12]
Hypertension	Cohen <i>et al.</i> (1999)	Prospective cohort	Type 1 DM patients followed for progression of DR	485	41 months	HR = 1.8; p = 0.04	[13]
Elevated total cholesterol	Cohen <i>et al.</i> (1999)	–	–	–	–	HR = 1.9 in highest total cholesterol quartile (p = 0.03)	[13]
Elevated total cholesterol	Chew <i>et al.</i> (1996)	Case-control	Type 1 and 2 DM patients examined for the presence of hard exudates and serum lipid levels	2709	–	HR = 2.00 (95% CI: 1.35–2.95)	[14]
Elevated LDL	Chew <i>et al.</i> (1996)	–	–	–	–	HR = 1.97 (95% CI: 1.31–2.96)	[14]
Obesity							

Risk factor	Study (year)	Type of study	Methods	Patients (n)	Duration (years)	Findings	Ref.
Elevated BMI	Klein <i>et al.</i> (2008)	Population based	Type 1 DM patients followed for progression of DR	955	25	HR = 1.16; $p < 0.001$	[3]
Visceral fat accumulation	Anan <i>et al.</i> (2010)	Cross-sectional	Analysis for insulin resistance and visceral fat (by CT of abdomen) in Type 2 DM patients with and without DR	427		HR = 4.8; $p = 0.002$	[37]
Endocrine							
Pancreatic β -cell failure (low C-peptide)	Bo <i>et al.</i> (2012)	Retrospective cohort	Analysis of C-peptide levels in Type 2 DM patients	2113	–	Higher serum C-peptide associated with lower risk for DR; OR = 0.33 (95% CI: 0.23–0.47) in highest tertile of C-peptide	[39]
Insulin resistance	Anan <i>et al.</i> (2010)	Cross-sectional	Analysis for insulin resistance and visceral fat (by CT of abdomen) in Type 2 DM patients with and without DR	102	–	HR = 6.4; $p < 0.001$	[37]
Metabolic syndrome	McGill <i>et al.</i> (2008)	Cross-sectional	Type 1 DM patients evaluated for metabolic syndrome and presence of DR	427	–	HR = 3.7 for severe DR; $p = 0.01$	[38]
Elevated HbA1c	Sabanayagam <i>et al.</i> (2009)	Population based	Type 1 and 2 DM patients' HbA1c levels correlated with the presence of retinopathy	3190	–	HR = 12.0; $p < 0.001$	[10]
Elevated HbA1c	Klein <i>et al.</i> (2008)	Population based	Type 1 DM patients followed for progression of DR	955	25	HR = 1.32; $p < 0.001$	[3]
Neuropathy							
Amputation	Hämäläinen <i>et al.</i> (1999)	Case-control	Analysis of Type 1 and 2 DM patients with and without retinopathy and need for amputation	733	–	HR = 6.1; $p = 0.002$ for amputation in presence of DR	[30]
Amputation	Mayfield <i>et al.</i> (1996)	Case-control	Analysis of Pima Indians with Type 2 DM, and PDR or NPDR, and control nondiabetics	244	–	HR = 21.0 (95% CI: 5.8–80) for amputation with PDR HR = 5.6 (95% CI: 2.1–15) for amputation with NPDR	[31]
Nonhealing extremity ulcer	Nwanyanwu <i>et al.</i> (2013)	Retrospective cohort	Database study of Type 1 and 2 DM patients with NPDR	4617	–	HR = 1.54 (95% CI: 1.1–2.07)	[27]

Risk factor	Study (year)	Type of study	Methods	Patients (n)	Duration (years)	Findings	Ref.
Hypothalamic–pituitary axis							
Low serum prolactin	Arnold <i>et al.</i> (2010)	Case–control	Measurement of serum prolactin levels in Type 1 and 2 DM patients with PDR and no retinopathy	221	–	Prolactin level significantly reduced in PDR (26.7 ng/ml) vs no retinopathy (34.1 ng/ml; p = 0.05)	[42]

CT: Computerized tomography; DM: Diabetes mellitus; DR: Diabetic retinopathy; HR: Hazard ratio; NPDR: Nonproliferative diabetic retinopathy; OR: Odds ratio; OSA: Obstructive sleep apnea; PDR: Proliferative diabetic retinopathy; RR: Risk ratio.

Table 2
Major risk factors for diabetic retinopathy; hazard ratios cited from individual studies in the text

Risk factors	Hazard ratio
HbA1c >8.0	12
Diabetes duration >10 years	9.1
Amputated/extremity ulcer	6.1
African–American/Hispanic ethnicity	3.6
Metabolic syndrome/excess visceral fat	3.7

Table 3
Example of the shared ophthalmology/primary care model for tracking major modifiable and unmodifiable risk factors for diabetic retinopathy

Risk factor	Attention needed/present	Notes
Modifiable		
HbA1c >8.0 [†]	Attention needed	Last HbA1c reading: 10.9
Metabolic syndrome/abdominal fat [†]	Attention needed	BMI: 35
Amputation/extremity ulcer [†]	No	Last foot examination in July 2013
Dyslipidemia	No	Lipids at goal in July 2012; on atorvastatin
Hypertension	No	Controlled on lisinopril
Sleep apnea	Attention needed	Snoring/daytime drowsiness; recommend testing
Unmodifiable		
Diabetes duration >10 years [†]	Yes	Since 1998
African–American/Hispanic ethnicity [†]	No	Caucasian
Male gender	Yes	
Renal insufficiency	No	Normal creatinine; positive microalbuminuria

[†] Major risk factor.