Diabetic Retinopathy in the Context of Patients with Diabetes

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Keywords

Diabetic retinopathy · Genetic heritability · Glycemic variability · Micro- and macrovascular complications · Cognitive impairment · Neurodegeneration

Abstract

Diabetic retinopathy (DR) is the most frequent complication of diabetes. The main risk factors are disease duration, a poor glycemic control, and the presence of hypertension. However, there is an important variation in risk which indicates that other factors, such as genetic heritability or glycemic variability, play an important role in accounting for the susceptibility to DR development. Another important concept is that DR is an independent predictor of both microvascular and macrovascular complications. Thus, the presence of DR should be taken into account when evaluating the cardiovascular risk of a diabetic subject. Moreover, the evaluation of retinal neurodegeneration could help to identify those diabetic subjects at risk of cognitive impairment, an emerging complication of the type 2 diabetic population. When evaluating a diabetic subject, the awareness of the presence of DR has also therapeutic implications. In this regard, a worsening of DR could occur after a rapid improvement of blood glucose. In summary, a critical review on the importance of the presence of DR in the general management of subjects with diabetes is provided.

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The Magnitude of the Problem

Diabetic retinopathy (DR) is the most frequent complication of diabetes and remains the leading cause of preventable blindness in the working-age population in developed countries [1–3]. DR has long been considered a microvascular complication of diabetes; however, growing evidence suggests that neurodegeneration is an early event in its pathogenesis [4, 5]. In fact, abnormalities in retinal function can be detected in patients without any evidence of microvascular abnormalities, and the American Diabetes Association (ADA) has recently defined DR as a highly specific neurovascular complication [6].

The presence and progression of DR is associated with significant increases in health costs [7]. Since DR is the most common complication of diabetes and is expected to increase from 415 million in 2015 to 642 million by 2040, DR will become an even more serious problem in the future [8].

Current treatments target late stages of DR when vision has already been significantly affected. A better understanding of the pathogenesis of DR would permit the development of novel and more efficient preventive/interventional strategies for early stages of DR [9, 10]. In this article, a critical review of the state of the art regarding the bidirectional influence of DR on diabetes and its complications is provided.

Risk Factors for Developing DR

The most relevant risk factors for the development of DR are disease duration, a poor glycemic control (high HbA1c levels), and the presence of hypertension. Other risk factors for DR include higher body mass index, puberty and pregnancy, as well as cataract surgery [3].

There is robust evidence regarding the relationship between blood glucose levels and the development and progression of DR. Intensive versus conventional glycemic management was associated with a 39% reduction in the risk of laser photocoagulation in the type 2 diabetic population of the UKPDS [11]. Tight versus less tight glycemic control in the type 1 diabetic population of the Diabetes Control and Complications Trial (DCCT) reduced the risk of new retinopathy by 76% and of the progression of existing retinopathy by 54% [12]. Recently, it has been reported that keeping the HbA1c level below 7.6% (60 mmol/mol) as a treatment target seems to prevent proliferative DR for up to 20 years in type 1 diabetic patients [13]. Serum lipids seem to have less influence in the development of proliferative DR or diabetic macular edema (DME) [14, 15]. However, increasing evidence supports the idea that nontraditional lipid measures (for example, apolipoproteins A and B) are stronger risk markers of DR than total cholesterol and triglyceride levels [16, 17].

The relationship between hypertension and DR is also well established. The UKPDS showed that after 9 years of follow-up, the group assigned to tight blood pressure control had a 34% reduction in risk in the proportion of patients with deterioration of retinopathy by two steps ($p = 0.0004$) and a 47% reduced risk ($p = 0.004$) of deterioration in visual acuity by three lines of the ETDRS chart [11]. A recent cross-sectional population-based study (13,473 subjects) showed that hypertension was an independent risk factor for both mild-to-moderate DR and sight-threatening DR [18]. Control of blood pressure to a level of <140/90 mm Hg is recommended under the Joint National Committee 8 regulations [19]. Best current evidence from the ophthalmology literature does not suggest any benefit to altering this recommendation for patients with confirmed DR.

Circulating cytokines, which are increased in type 2 diabetic patients, could also increase the vascular leakage but their contribution to the DR and DME development remains uncertain. In this regard, it should be noted that the local synthesis by the retina, mainly retinal pigment epithelium and glial cells, is the main source of proinflammatory cytokines. For this reason, intraocular rather

than systemic anti-inflammatory agents, such as corticosteroids, are effective in the treatment of DME [9, 20].

Despite of the influence in the development and progression of the abovementioned risk factors, clinical studies on diabetic patients reveal a substantial variation in the onset and severity of DR that is not fully explained by the known risk factors, and all clinicians are aware that a subset of patients with poor control of glycemia and/or uncontrolled blood pressure do not develop DR. On the other hand, there are patients with very good control of blood glucose levels and without hypertension that will develop DR. In fact, the DCCT/EDIC Research Group showed that HbA1c values explained up to 11% of the risk of DR and that the unexplained 89% of variation in risk is due to elements of the diabetic milieu not captured by the mean HbA1c value [21].

These data suggest that other factors play an essential role in accounting for the susceptibility to the development of this late diabetic complication. In this regard, heritability estimates ranging from 25 to 50% have been reported for proliferative DR [22, 23]. Indeed, the study of identical twins found a concordance for DR (68% in type 1 and 95% in type 2 diabetes) [24]. In the DCCT cohort, the odds ratio for severe retinopathy when a relative had retinopathy was 3.1 [25]. Similar findings have been replicated in other familial risk studies [26–28].

Plasma glucose variability is also a reason accounting for the weaknesses of the HbA1c level in predicting the development and progression of DR. The introduction of continuous glucose monitoring (CGM), which captures the glucose profile over a number of days, has provided an opportunity to develop metrics of glycemic control that deliver valuable information beyond that furnished by the HbA1c level. Among the metrics generated from CGM, time in range (TIR) refers to the time an individual spends within their target glucose range (usually 3.9–10.0 mmol/L), which provides valuable information about whether the frequency and duration of hypoglycemia or hyperglycemia improve over time. In a recent study, TIR was found to be associated with all stages of DR after controlling for age, sex, BMI, diabetes duration, blood pressure, lipid profile, and the HbA1c level [29]. In addition, a systematic review and a meta-analysis have shown that fasting plasma glucose variability was strongly associated with the risk of retinopathy [30].

Finally, changes in the epigenome may be a key mechanism underlying the phenomenon of “metabolic memory” which could explain the long-term effects of metabolic status obtained for a period of time several years ago [31].

DR – The Pandora Box of Diabetic Complications

The presence of DR means that the microcirculation has already been damaged by the diabetic milieu and, therefore, it can be considered a reliable biomarker of the deleterious effects of diabetes in a specific individual. In fact, this is one of the most important indicators for planning a personalized medicine. A recent systematic analysis has provided clear evidence supporting relationships between DR and complications of diabetes, including micro- and macrovascular conditions and events [32]. Although many of these associations have been identified in cross-sectional and retrospective studies, several have been confirmed in prospective investigations based on multivariate analyses that controlled for the influence of traditional or other known risk factors.

DR increases the likelihood of nephropathy [33–35] and is a significant and independent predictor of progression to micro- or macroalbuminuria [33]. DR correlates with a declining in the glomerular filtration rate [36, 37]. Therefore, a close monitoring of individuals with DR for the presence of albuminuria and impaired glomerular function may help prevent progression to more serious kidney disease.

DR was found to be associated with two neuropathies: diabetic peripheral neuropathy [38, 39] and cardiac autonomic neuropathy (CAN) [40, 41]. At present, it is unknown whether retinal neurodegeneration is related to peripheral neuropathy. However, a recent study performed in 27 type 1 diabetic subjects has shown a correlation between inner retinal loss in SD-OCT and diminished autonomic regulation [42].

In addition to the microvascular complications, the presence of DR has also been associated with the development of macrovascular complications of diabetes, specifically, cerebrovascular complications (stroke, cerebral infarction/hemorrhage), cardiovascular complications (atherosclerosis, cardiovascular events, and coronary heart disease), and peripheral complications (foot ulcers, lower extremity amputations, and peripheral arterial disease) [32]. It should be noted that DR as well as microalbuminuria and peripheral neuropathy are much better predictors of cardiovascular diseases than the classical risk factors such as cholesterol and hypertension [43].

As both CAN and DR have been identified as predictors of cardiovascular morbidity and mortality in several prospective studies of individuals with diabetes, it may be interesting to investigate whether both conditions in conjunction are associated with a greater risk of cardiovascular complications compared with the presence of either

complication alone. If this were the case, screening for CAN in patients who have diabetes with DR could help identify high-risk groups for monitoring and early detection of clinical progression to cardiovascular disease.

The Importance of DR in the Design of Clinical Trials Aimed at Evaluating Cardiovascular Disease

In 2008, following the withdrawal of rosiglitazone from the market due to its apparent association with increased cardiovascular risk, there was somewhat of a turning point. As part of the regulatory process, the Food and Drug Administration (FDA) published a guide for the sponsors about how to demonstrate that a new antidiabetic therapy to treat type 2 diabetes was not associated with an unacceptable increase in cardiovascular risk [44]. This FDA recommendation led the pharmaceutical companies to design studies addressed to the testing of the cardiovascular safety of new antidiabetic drugs.

Since then, several multicenter prospective randomized control trials assessing the cardiovascular safety of drugs used in the treatment of type 2 diabetes have been published, and they have had a significant impact on the last position statement of the ADA and the European Association for the Study of Diabetes (EASD) for the treatment of type 2 diabetes [45]. Since SGLT-2 inhibitors and GLP-1R agonists have been shown to be superior to placebo in reducing cardiovascular morbidity and mortality, these drugs have a preeminent role in the therapeutic guidelines. In all these studies, the presence and degree of DR has not been taken into account for randomization. This is a serious scientific gap that should be considered in future clinical trials on this issue.

DR as a Predictor of Cognitive Impairment and Dementia

The results of longitudinal studies show that the speed of cognitive decline in type 2 diabetic patients is up to twice as fast as that of normal aging, and diabetic patients have an increased risk of mild cognitive impairment (MCI) [46], which consists of cognitive impairment, as determined on standard tests but with no impact on activities of daily living, and represents a transitional state between normal cognitive function and dementia. In addition, type 2 diabetic patients had an almost two-fold higher risk of developing Alzheimer's disease than age-matched nondiabetic subjects [47]. This increased risk was maintained even after

adjusting for vascular risk factors. The annual conversion rate from MCI to dementia ranges between 10 and 30% in the general population, but this is even higher in the type 2 diabetic population [48]. In addition, the number of type 2 diabetic patients with cognitive impairment or dementia is expected to increase because of the diabetes pandemic and the concomitant rise in aging populations worldwide. In this regard, severe cognitive impairment can be envisaged as a “new” long-term diabetic complication with dramatic consequences for the affected subjects and their families and with a significant impact on healthcare systems [49]. Therefore, strategies aimed at identifying diabetic patients at risk of dementia are urgently needed. In fact, the ADA recommends individualizing diabetes treatment taking into account the cognitive capacity of patients [50]. However, in clinical practice, there are no reported phenotypic indicators or reliable examinations to identify type 2 diabetic patients with MCI.

The diagnosis of MCI is based on complex neuropsychological tests which makes their incorporation into current standards of care for the type 2 diabetic population unfeasible. Recently, retinal sensitivity [51] and gaze fixation [52] assessed by microperimetry have been reported as a useful biomarker for identifying type 2 diabetic patients at risk of developing Alzheimer’s disease. These findings open up new feasible clinical management procedures addressed to testing cognitive status, which could easily be added to the routine ophthalmologic examination for the screening of DR.

Influence of DR in the Management of Diabetes

Although there is no doubt regarding the relationship between glycemic control and the long-term development and progression of DR, initial worsening of DR has been reported as a consequence of rapid improvement of hyperglycemia. An early worsening was observed in 13.1% of 711 type 1 diabetic patients assigned to intensive treatment in the Diabetes Control and Complications Trial (DCCT) at 6 and/or 12 months in comparison with 7.6% of 728 patients assigned to conventional treatment (odds ratio, 2.06; $p < 0.001$) [53]. The most important risk factors for early worsening were a higher HbA1c level, a large ($>2\%$) and rapid reduction of the HbA1c level, and the severity of DR at baseline [53–55]. A similar phenomenon was reported in type 2 diabetic patients after a rapid improvement of blood glucose levels when they were switched from oral agents or diet alone to insulin therapy [56, 57], and more recently after bariatric surgery [58].

Interestingly, the initial worsening of DR observed in the early period of intensive glycemic control is manifested by the increase of soft exudates, a typical feature of the ischemic retina. Hypoglycemia exacerbates ischemic retinal injury [59] and, therefore, antidiabetic drugs with very low capacity if any to provoke hypoglycemia, such as GLP-1RA or SGLT-2 inhibitors, might theoretically be more appropriate for initiating intensive treatment in those patients with DR.

The strong relationship between the reduction of the HbA1c level and the beneficial effects on DR has obscured the necessity of performing clinical trials addressed to investigate the specific effect of hypoglycemic drugs on DR per se, independently of their effectiveness in lowering blood glucose levels. The reported pleiotropic actions of GLP-1RA in experimental models of DR, apart from their capacity in lowering blood glucose levels, confer on these drugs a potential extra value in preventing the development or arresting the progression of DR [60]. The results obtained in the SUSTAIN-6 study are one exception to this statement. In this study, semaglutide (a long-acting GLP-1R agonist) showed an unexpected higher rate of severe DR complications (i.e., vitreous hemorrhage, blindness, or conditions requiring treatment with an intravitreal agent or photocoagulation) [61]. Although this was observed in a very small percentage of patients, this was really a surprising finding because, as mentioned above, beneficial rather than deleterious effects on the development of DR were reported in preclinical studies by using GLP-1RA [60]. The main reason accounting for this deleterious effect was the rapid decrease in HbA1c levels and the lack of grading of DR at study entry [60, 62]. However, a specific clinical trial (FOCUS study) addressed to further clarify this issue will be initiated very soon.

Concluding Remarks and Future Perspectives

Despite the improvements in the management of diabetes, DR remains a leading cause of visual acuity impairment and blindness in the working-age population in the developed countries. Blindness and visual loss is the major fear of most patients with diabetes and leads to emotional distress and reduces functionality in daily life [63]. In addition, in very early stages of DR when only neurodegeneration exists, an alteration of the quality of life has also been reported [64]. Therefore, the decades-old grading schemes of DR, based solely on nonquantitative assessment of microvascular abnormalities, should be re-

placed by robust quantitative readouts that are reflective of progressive dysfunction in the retinal neurovascular unit. In addition, more interventional studies targeting pathogenic pathways that impact the retinal neurovascular unit and that offer both vaso- and neuroprotection are needed. This will be crucial, not only for increasing our understanding of DR, but also to implement a timely and efficient personalized medicine approach for the treatment of this disease.

An important concept is that DR is not only associated with other diabetic microangiopathic diseases such as nephropathy or neuropathy but also with cardiovascular disease. This is a well-established concept that should be taken into account not only in clinical practice but also in the design of any study addressed to evaluate the cardiovascular outcome in the diabetic population.

DR has also been associated with dementia [49], but even more interesting is the recent evidence that the study of retinal neurodysfunction could identify type 2 diabetic patients in a prodromal state of dementia (i.e., MCI). This is clinically relevant because the early identification of cognitive impairment should adapt the goals and the treatment of the patients in order to avoid hypoglycemias,

hospital admissions, and the acceleration of dementia. In addition, it should be noted that interventions that delay the clinical onset of dementia by 1 year would reduce the prevalence by 9 million cases in 2050 [65].

In summary, the presence of DR in a diabetic subject not only means that a “vision problem” does exist but that this patient presents a high risk of developing other micro- and macrovascular diseases, as well as dementia. Hence, the presence of DR is often a forgotten hallmark for implementing a personalized medicine in diabetic patients. In addition, the retina could be a useful window to indirectly explore the brain, thus permitting us to identify patients with cognitive impairment and, consequently, at risk of dementia. A coordinated activity among diabetologists, ophthalmologists, basic researchers, pharmaceutical companies, and healthcare providers will be essential for ameliorating the devastating consequences of this still highly prevalent complication of diabetes.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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