

Prevention of diabetic eye disease: the commonest cause of blindness in individuals younger than 65 years

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Abstract: There has been a considerable advancement in the treatment of diabetes and understanding of the biochemical mechanisms underlying diabetic complications in the last 20 years. However, this advancement has not translated into a consistent reduction in diabetic retinopathy, one of the most frightening complications of diabetes mellitus. It is probable that greater attention to preventive intervention will help reduce the damage load in the next future, and that several drugs for the treatment of more advanced stages of diabetic retinopathy will become available. Competent strategies targeting prevention based on screening programs should be proposed to reduce the burden and to improve the clinical outcome of this devastating diabetes complication.

Keywords: blindness, diabetes, eye disease, prevention

Epidemiology

Although there have been advancements in the treatment of diabetes in recent years, diabetic retinopathy (DR) remains the most common cause of blindness among adults. According to the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), 3.6% of type 1 diabetes patients and 1.6% of type 2 diabetes patients were legally blind.¹ The time of disease onset is evident in type 1 diabetes patients, therefore we know with certainty that the development of DR is unusual before the fifth year of disease onset and reaches a prevalence of more than 95% 15 years after disease onset. On the contrary, up to 20% of type 2 diabetes mellitus patients, in whom the exact time of onset of the disease is less evident, may have signs of retinopathy at the time of diagnosis, which in most cases is preceded by a long unrecognized latency period. The prevalence of DR 15 years after disease onset in type 2 diabetes mellitus patients may reach 60%.² The UK Prospective Diabetes Study (UKPDS), a 10-year study of newly diagnosed type 2 diabetes patients, indicates that the presence of even a single aneurysm in these patients is evidence of DR, with the prevalence of this condition at diagnosis being 38%.² Although the percentage is higher among type 1 diabetes patients, the much greater absolute number of type 2 diabetes patients with this disease indicates DR to be a devastating complication in this category.³

However, the prevalence of progressive sight-threatening retinopathy is limited to 10%,⁴ which is still relatively high. The prevalence of DR of any severity in the diabetic population as a whole is approximately 30%.⁵ Furthermore, we cannot accurately predict when severe DR will progress to blindness, although hyperglycemia and hypertension are risk factors. The actual prevalence of blindness is approximately 5% (range 3%–7%) and may be as high as 8%.⁴

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Although there are no comparative studies, it is highly probable that the incidence of diabetes mellitus in all its forms may vary according to the local resources and standards of care. There is abundant literature demonstrating that screening programs have been highly effective in reducing the incidence and the progression of DR.⁶

Etiology and pathogenesis

Diabetic retinopathy tends to follow a progressive course from minor lesions to the most serious sight-threatening patterns, but there is frequently considerable overlapping. The earliest manifestations are mild and characterized by increased vascular permeability, followed by moderate to severe changes with intravascular clotting, defined as non-proliferative DR. A more advanced phase is the proliferation of new vessels, defined as proliferative DR (PDR), with impending risk of hemorrhage. An ominous manifestation is significant macular edema (clinically significant diabetic macular edema [CSDME]) caused by retinal thickening due to leaky blood vessels, which should be distinguished from mild thickness of the retina that does not have the same serious prognosis. This sight-threatening complication may supervene at any stage of the DR.

The earliest changes are a loss of retinal neurons (neurodegeneration) and disruption of the vascular structure, which is essential to the survival of the retina.⁷ Interruption of the integrity of retinal capillary bed, which allows the exchange of nutrients with the retina, leads to protein leakage and the appearance of exudates, which are among the early signs of DR. It is highly probable that the hyperglycemia in diabetes leads to an array of metabolic changes, many of which may be directed toward limitation or repair of the damage. Unfortunately this hypothesis has not yet been accepted. All the above factors and possibly some other unknown factors interact to cause DR, and it is not known yet which factor may be the primary cause.

The most well known structural components of retinal capillaries are the basement membrane and pericytes, which are cells that have both structural and regulatory functions.⁸ The disarrangement of these structures leads to weakening of the capillaries, aneurism, and protein leakage. Loss of retinal pericytes is an early feature of DR and correlates with microaneurysm.⁹ Other common features of early DR are the thickening of the capillary basement membrane and the increased deposition of extracellular matrix components, leading to the development of abnormal retinal hemodynamics.¹⁰ A subsequent intervention of blood cells that clog the capillaries and lead to occlusion is probably

the body's misguided attempt at damage limitation.¹¹ There is extensive clot formation in the capillaries as the disease progresses, which interrupts blood flow and causes ischemia. In more advanced stages, there is an inordinate proliferation of blood vessels in an attempt to restore oxygen and nutrient supply to the ischemic territory. Pathogenesis of PDR is essentially due to ischemia, and pathogenesis of CSDME is due to the fluid leakage from retinal blood vessels into the area of the macula, which is rich in cones that are critical for color and daytime vision. This study mainly reviews prevention in the initial stages of the disease when medical intervention may be effective. Proliferation may be mediated by vascular endothelial growth factor (VEGF), which will be discussed later.

The etiology of DR is complex and predisposing factors are as follows: 1) duration of diabetes,¹² 2) poor glucose control,¹³ 3) hypertension,^{14,15} 4) pregnancy,^{16,17} 5) puberty,¹⁸ 6) renal disease¹⁹ (the relation between kidney and retina is so relevant that the diagnosis of diabetic nephropathy should always be questioned in the absence of a DR), and 7) hyperlipidemia²⁰ (believed to play a role in this complication, although this hypothesis has not been confirmed).²¹ These factors will be discussed in detail.

The pathogenesis of DR includes both systemic and local factors, but we still do not know the exact influence of and role played by each in the different stages of the disease.

Duration of diabetes

The duration of diabetes is probably the strongest predictor of progression to DR,⁶ but is not clinically helpful in most cases of type 2 diabetes because diagnosis is delayed and the time of onset of the disease is unknown. The WESDR showed that incidence of retinopathy increased progressively from 8% 5 years after disease onset to 80% after 15 years.²² The recognition of the role of disease duration is one more argument in favor of those interventions that may delay the onset of diabetes. After disease onset nothing can be done to reduce this risk factor.

Hyperglycemia

The role of hyperglycemia was proven by two landmark studies. The Diabetes Control and Complications Trial (DCCT), a study of 1441 type 1 diabetes patients randomly assigned to intensive and conventional treatment groups with different glycosylated hemoglobin (HbA_{1c}) levels, conclusively demonstrated that good control plays a critical role in the prevention of DR. In the intensively treated group, there was a reduction of 76% in the risk of progression.

The patients were assigned to a primary prevention group (those with no signs of retinopathy) and a secondary prevention group (those with retinopathy) according to the status of their retina. Those in the primary prevention cohort had a similar cumulative incidence of retinopathy progression in the conventional and intensive arms until 36 months, and then intensive treatment reduced the risk of retinopathy by 76%. The intensive group in the secondary intervention cohort fared worse than the nonintensive group during the first 18 months; a phenomenon largely offset by a much greater long-term improvement with a reduced risk of 54% by 36 months.¹³ The results of the Epidemiology of Diabetes Interventions and Complications study, a follow-up study to the DCCT, are interesting from a theoretical perspective because there was no further attempt to use intensive treatment and the HbA_{1c} levels of the two groups were nearly the same. Even after 5 years, outcome of the intensive therapy was favorable.²³ This phenomenon is termed a 'legacy effect'. The data were deemed so relevant that, subsequently, the level of fasting blood glucose at which retinopathy appeared was included in the current criteria for the diagnosis of diabetes mellitus. In a recent study on the association of glycated HbA_{1c} and fasting plasma glucose (FPG) with the diagnosis of diabetes mellitus, the authors found that the highest increase in the prevalence of retinopathy occurs among individuals with HbA_{1c} \geq 5.5 and FPG \geq 5.8 mmol/L, and that, based on the areas under the receiver operating characteristic curves, HbA_{1c} was found to be a strong discriminator of retinopathy.²⁴

With a protocol similar to that of the DCCT, the UKPDS randomly assigned 3867 newly diagnosed type 2 diabetes patients to an intensive or conventional treatment group and found a statistically significant 25% reduction in microvascular complications including the need for photocoagulation of the retina. This is a much more crude result than in the DCCT because the impact on each complication was not clearly determined and favored lowering blood glucose levels. An epidemiological analysis of the UKPDS data demonstrated the existence of a continuous relationship between the risk of microvascular complications and blood glucose level; for each percentage point decrease in HbA_{1c}, the relative risk of microvascular complication was reduced by 35%.²⁵ A follow-up of the UKPDS subjects, analogous to that of the DCCT, demonstrated the existence of the legacy effect, with a 24% reduction in the risk of microvascular complications.²⁶

The Veterans Affairs Diabetes Trial (VADT) that followed a different population of 1791 older diabetic veterans, mostly men, for a median of 5.6 years did not find

any effect from intensive glucose control on retinopathy (progression to proliferative disease, macular edema, increase in severity of disease, and new onset of disease; all P = not specified [NS]).²⁷ Similar results were obtained for the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicon MR Controlled Evaluation) study in which there were no changes in the rate of severe retinopathy.²⁸ Taken together, these observations suggest that the effect of good glycemic control is most evident at disease onset when harmful microvascular complications can set in. Any later intervention is likely to have only modest beneficial effect. This is confirmed by the UKPDS observation that a favorable legacy effect of glucose control was found in newly diagnosed subjects which lasted until follow-up.²⁶ However, the VADT and ADVANCE studies in a longstanding diabetic population did not find any significant effect.

The exact mechanisms that cause persistent hyperglycemia to become DR are still partially unknown, however, the polyol pathway has been found to play a prominent role.²⁸ The polyol pathway is dependent on the glucose overload to the noninsulin-dependent cells such as cells of the eye.²⁹ This pathway leads to the intracellular accumulation of sorbitol and fructose.³⁰ It has been demonstrated that the increase in aldose reductase activity within the retinal cells contributes to oxidative stress and overexpression of VEGF protein.³¹ Furthermore, an increased frequency of the Z-2 allele of the aldose reductase gene in diabetes patients with DR vs those without DR (39.1% vs 26.5%; $\chi^2 = 6.9$) has been demonstrated, which partially explains the role of genetics in this complication.^{31,32} Modest results were obtained in therapeutic trials with aldose reductase inhibitors that reduce the efficiency of the polyol pathway, and one of these substances purported to be beneficial for diabetic neuropathy has now been withdrawn from the market for proven negative cost-to-benefit ratio.^{33,34} Furthermore, these drugs have frequent and potential dangerous side effects (liver and kidney damage).

Increased oxidative stress causes a characteristic endothelial dysfunction, which has been observed in diabetes patients and normal subjects.^{35,36} Brownlee and colleagues demonstrated that damage can be reversed by suppression of intracellular free radicals with manganese superoxide dismutase, which has an antioxidant effect.³⁷ Another important and still not totally explored aspect is that oxygen-free radicals can activate nuclear factor κ B and in turn many genes related to vascular stress response.³⁸ One disappointing aspect is that clinical trials with vitamin E, a potent antioxidant, failed to demonstrate beneficial effects.³⁹ This failure

could be explained by the fact that since vitamin E only acts by scavenging already formed oxidants in this antioxidant therapy, this therapy may be a more “symptomatic” rather than causal treatment for vascular oxidative stress.⁴⁰

The formation of advanced glycation end products (AGEs) may also have a role. These compounds result from the nonenzymatic binding of glucose to protein side chains.⁴¹ Accumulation of these protein side chains in the capillaries of the retina leads to loss of pericytes, causing blood–retinal barrier dysfunction, increasing synthesis of VEGF in the retina,⁴² and increasing monocyte adhesion to the retinal endothelial cells through an increase in the expression of intercellular adhesion molecule 1.⁴³ Aminoguanidine, an inhibitor of AGE formation, appears to reduce the early histological changes in the retina. However, the drug causes anemia in humans.⁴⁴

Another mechanism of damage is the activation of the protein kinase C (PKC) family pathway.⁴⁵ This pathway is a consequence of hyperglycemia and has a role in the pathogenesis of DR.⁴⁶ The main isoform implicated is PKC- β_2 , which causes hyperexpression of endothelin, increased vascular permeability, alterations in renal blood flow, and in vitro stimulations of VEGF secretion.⁴⁷ Two drugs with inhibitory effect have been developed, ruboxistaurin (Eli Lilly, Indianapolis, IN) and midostaurin, but their effectiveness is still uncertain.⁴⁸ Brownlee recently put forth a unifying theory according to which glucose overload flowing through the glycolytic pathway could cause a kind of “collateral damage” consisting of superoxide production in endothelial cells at the mitochondrial level. The superoxide could cause DNA damage in turn, and the consequent attempt to repair the damage could start the aforementioned dangerous cascades involved in diabetes complications.⁴⁹ The existence of all these pathways leading to diabetic complications led to the search for antioxidant compounds that are still in the pipeline or in early experimental stages. Among the available compounds, lipoic acid is purported to have the ability to restore endothelial function in diabetes.⁵⁰ As will be dealt with later, other commonly used drugs such as thiazolidinediones, statins, angiotensin-converting enzyme inhibitors (ACEI), and angiotensin type 1 (AT1) receptor blockers may also have potent antioxidant effects, although there are no evident conclusive results for the protection of the retina.

An increase in VEGF, a family of proteins mitogenic for vascular endothelial cells that increase vascular permeability, has been demonstrated in DR.⁵¹ The knowledge of the role of these substances led to extensive research on its antagonists. The systemic administration of these antagonists might

cause serious damage by blocking angiogenesis, impairing the response to ischemic events, worsening peripheral ischemia, increasing proteinuria, and impairing wound healing process,⁵² and hence the use of these agents is restricted to intravitreal administration. However, a backflow is possible from the vitreal chamber to the systemic circulation.⁵³ It has yet to be proven that these agents for intravitreal administration are preferred over triamcinolone acetonide.

Other growth factors of interest are growth hormone (GH) and insulin-like growth factor-1 (IGF-1). Hypophysectomy was performed in advanced DR in the past,⁵⁴ with a good rate of regression. Further evidence for the role of GH or IGF-I comes from the observation of the increased rate of appearance and progression of the DR in puberty and pregnancy, which are stages of increased GH secretion.⁵⁵ The GH antagonist, pegvisomant, has been used to induce regression of neovascularization, with a negative outcome.⁵⁶ Octreotide, a somatostatin analog, decreases the need for photocoagulation.⁵⁷

Although the literature on the pathogenetic mechanisms that lead to DR is abundant, exploiting the mechanisms did not yield fruitful results. Control of hyperglycemia proved to be the mainstay of prevention of DR and progression of the disease was able to be reversed to a certain point. In the intensive treatment of diabetes, the physicians should make any effort to avoid the risk of hypoglycemia as it is a risk factor for progression to DR. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) eye study,⁵⁸ a subset of the ACCORD trial, was designed primarily to study the effects of intensive glycemic control on cardiovascular events in type 2 diabetes subjects. The primary outcome of 2,856 subjects was a 3-step change on a 17-step retinopathy scale (from retinal photographs) or development of PDR. After 4 years of follow-up, intensive treatment to lower the blood glucose to normal levels significantly reduced the incidence of progressive DR compared with conventional treatment that resulted in a higher HbA_{1c} levels (7.3% vs 10.2%), but not vision loss (16.3% vs 16.7%). However, the drawbacks of this study were the excess mortality and the absence of positive effects on adverse cardiovascular events in the intensive arm. Although the exact cause of the increased mortality is not known, there is general agreement that the intensive intervention to reduce the blood glucose level should be individually weighed against the risk.

We observed an unexpected improvement in the most initial forms of retinopathy while using a combination of arginine, glutamine, and hydroxy- β -butyrate coupled with an increased percentage of dietary protein for the treatment

of diabetic foot ulcers over 14 months. This combination treatment can increase the formation of collagen fibers. The treated patients presented a reduction in the number of microaneurysms after 6 months (20%; $P = 0.012$) and 12 months (39%; $P = 0.006$), and retinal exudates were reduced 38.6% ($P = 0.000$) at 6 months and 52% at 12 months ($P = 0.003$). We hypothesize that protein loss in diabetes patients through neoglycogenesis and proteinuria may cause a disarrangement of the basement membrane of the retinal capillaries, a phenomenon that was reversed by diet and the combination of drugs.

Blood pressure

There is sufficient data to validate high blood pressure as a risk factor for DR and the positive effect of blood pressure reduction on the progression of the disease.⁵⁹ The UKPDS showed that intensive blood pressure control in type 2 diabetes was effective in reducing the microvascular complication associated with diabetes. Analogous to the results of blood glucose control, the initial study results released in 1997 demonstrated that an effective blood pressure control could induce a relative risk reduction of 37%.⁶⁰

However, contrary to the blood glucose results, there was no legacy effect for blood pressure and the UKPDS follow-up study in 2007, 10 years after the intensive treatment had been interrupted, reported only 16% relative risk reduction in the intensive group ($P = \text{NS}$). Thus, it appears that good blood pressure control must be continued to control disease progression.⁶¹

The ACCORD eye study group published the results of the effects at 4 years of either intensive or standard treatment for diabetes and dyslipidemia or for systolic blood pressure control on 2856 diabetes subjects.⁵⁸ In 4 years, the rate of progression was 10.4% with intensive blood pressure lowering treatment vs 8.8% with standard therapy ($P = \text{NS}$). According to the authors, intensive glycemic control and intensive combination treatment of dyslipidemia, but not intensive pressure control, reduced the rate of progression of DR.

There have been many studies on ACEI and angiotensin receptor blockers (ARBs) to investigate the existence of direct effects not mediated by blood pressure reduction. The basis for these studies is the discovery of the renin–angiotensin system in the eye⁶² and the in vitro binding of angiotensin II to the AT1 receptors, which causes a series of negative effects such as inflammation, oxidative stress, neoangiogenesis, and fibrosis.⁶³ However, the in vivo studies did not confirm these observations completely. The UKPDS did not find any significant differences among patients treated with

atenolol, a beta blocker, and those treated with captopril, an ACEI. However, captopril is a very old drug with a short half-life. The EUCLID study did not consider DR as a primary end-point and demonstrated that normoalbuminuric and microalbuminuric lisinopril could significantly reduce the progression of DR in normotensive diabetes patients but with no decrease in incidence.⁶³ However, in this study, statistical significance almost disappeared after adjusting for the mean HbA_{1c} of the control group. Furthermore, the follow-up period was only 2 years. Thus, this study can be considered only suggestive and not conclusive. In another highly sophisticated study, the Direct Protect, in which both type 1 and 2 diabetes patients were studied for prevention and progression of DR with the ARB candesartan, the only clearly significant outcome not specified as a primary end-point was a 34% regression ($P = 0.009$) mostly in subjects with mild disease.⁶⁴ Overall, one can surmise that the benefits attributable to the current ACEI/ARB blockers are marginal or absent.

The current recommendations for control of blood glucose and hypertension are $\text{HbA}_{1c} < 7\%$ ($< 6.5\%$ according to the European Association for the Study of Diabetes) and blood pressure $\leq 130/80$ mm Hg.⁶⁵

Dyslipidemia

Among the known risk factors, hyperlipidemia is associated with the presence of hard exudates in the retina,⁶⁶ which has been confirmed by recent studies. Nathan and colleagues found a significant association of total to high-density lipoprotein (HDL) cholesterol ratio and triglycerides only on significant macular edema and hard exudates, which in itself is not proof of cause–effect.⁶⁷ The Fenofibrate Intervention and Event Lowering in Diabetes study was designed to answer these questions. Fenofibrate is a peroxisome proliferator receptor (PPR)- α agonist that lowers triglycerides, reduces total and low-density lipoprotein (LDL) cholesterol, increases HDL cholesterol, and decreases small LDL particles and apolipoprotein B.⁶⁷ Fenofibrate reduced the need for laser treatment and less consistently the progression of retinopathy.⁶⁸ The effects of fenofibrate are independent of lipid levels, as demonstrated by the observation that PPR- α may reduce the expression of VEGF receptor 2.⁶⁹

Although the aim of this review is limited to the pharmacological treatment of DR, it is worth mentioning that most of the effective treatments of DR now involve surgical or laser procedures. Vitrectomy laser treatments have effectively revolutionized prognosis, although there are still drawbacks.

The correct therapeutic approach to DR can be summarized as follows: blood glucose control; fundus examination (ophthalmoscopy, retinal fluoroangiography, indocyanine green angiography, and optical coherence tomography); evaluation of the stage of progression if any; retinal laser therapy to prevent the proliferation of neovessels; or surgical therapy in growth of neovessels into the vitreous, in vitreous hemorrhage, or in fibrous tissue proliferation on the retinal surface or on the optical disc. In these cases, vitrectomy is the only methodology available to interrupt the progression of the disease, through the suction of hematic vitreous, that, if left untreated, is an obstacle to vision and supports the growth of neovessels.

Furthermore, the intravitreal injection of anti-VEGF drugs (ranibizumab, pegaptanib, bevacizumab, etc) improved the prognosis of retinal neovessels and exudative disorders.

All these observations are complicated because DR is probably not a single disease, and the dependency on different causative factors may vary according to the different stages of the disease. Clinicians may be disappointed by divergent and often conflicting study results if the studies do not consider this aspect of the disease. Furthermore, some drugs used to reduce the blood glucose may damage the retina. One example is the use of rosiglitazone, suspected of causing macular edema under certain circumstances,⁶⁹ although we did not find any effect in a retrospective series.⁷⁰

Conclusion

Current medical interventions may be useful if carried out early, and the effect is limited to the rate of appearance and the minor manifestations of the disease. When the disease progresses, the best treatment option is laser therapy or surgery, and is not the recommended medical treatment at present.

Disclosure

The authors report no conflicts of interest in this work.

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