Diabetic retinopathy: Pathogenesis

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INTRODUCTION

Diabetic retinopathy (DR) is one of the largest causes of vision loss worldwide and is the principal cause of impaired vision in patients between 25 and 74 years of age [1-3]. In the United States, it is estimated that 9.6 million adults have DR and 1.84 million have vision-threatening DR [4]. Visual loss from DR results from progression of the disease and may be secondary to macular edema (retinal thickening and edema involving the macula), development of hemorrhage from new vessels, retinal detachment, or neovascular glaucoma.

The pathogenesis of DR is reviewed here. Issues related to screening and treatment are discussed separately. (See "Diabetic retinopathy: Screening" and "Diabetic retinopathy: Classification and clinical features" and "Diabetic retinopathy: Prevention and treatment".)

GENERAL PRINCIPLES

The development and progression of DR is primarily caused by the tissue-damaging effects of chronic hyperglycemia that results in a complex interplay of multiple mechanisms (figure 1), which cause two basic changes within the retinal vessels, namely: abnormal permeability, and occlusion with ischemia and subsequent neovascularization. The relative contributions of different mechanisms vary in importance at different stages of retinopathy and may vary among individuals.

- Biochemical pathways (glycation, protein kinase C, and polyol pathways) and changes in neuronal function and retinal blood flow are particularly important during early disease,

even before the development of microaneurysms or other clinically visible findings.

- Angiogenesis factors such as vascular endothelial growth factor (VEGF) and insulin-like growth factor 1 (IGF-1) are more likely to be important later in the course of the disease, immediately prior to and during the development of proliferative DR or diabetic macular edema.

Differences in genetic susceptibility to the effects of hyperglycemia in the retina may exist among people at different stages of diabetic disease. This could result in inter- and intra-individual variations in biochemical or physiologic responses to hyperglycemia and may exist among people at different stages of diabetic disease. This variability may explain why a few patients with diabetes have minimal retinopathy despite years of severe hyperglycemia, whereas in others, severe retinopathy develops in a short period despite relatively good glycemic control.

CHRONIC HYPERGLYCEMIA

Both the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) established that chronic hyperglycemia is the initiating major cause of diabetic tissue damage in the retina [5,6]. In the DCCT, intensive insulin therapy in patients with type 1 diabetes, achieving a mean glycated hemoglobin (A1C) of 7.0 percent, reduced the incidence of new cases of retinopathy by as much as 76 percent compared with conventional therapy [5]. The reduction was directly related to glycemia as estimated from A1C values (mean A1C with conventional therapy was approximately 9.0 percent); progressive retinopathy was uncommon in patients with A1C values below 7.0 percent (figure 2). (See "Glycemic management and vascular complications in type 1 diabetes mellitus".)

The UKPDS found similar results in patients with type 2 diabetes; each 1 percent point reduction in A1C was associated with a 37 percent reduction in development of retinopathy [6]. (See "Glycemic management and vascular complications in type 2 diabetes mellitus".)

This state of chronic hyperglycemia results in structural, functional, and biochemical changes that alter cellular metabolism, retinal blood flow, and retinal capillary competency. The data supporting these mechanisms primarily refer to the induction of retinal injury. More advanced retinal disease, including proliferative vascular changes and neovascularization in the setting of retinal ischemia, may be mediated by other mechanisms such as the action of insulin-like growth factor 1 (IGF-1) and vascular endothelial growth factor (VEGF) [7,8] (see 'Growth factors' below). Furthermore, this process has been shown to be influenced by both genetic

determinants of individual susceptibility and by independent accelerating factors such as hypertension.

Structural anatomic retinal changes — Classic diabetes-related structural changes in the retina include the loss of retinal pericytes, capillary basement membrane thickening [9,10], and capillary walls outpouchings called microaneurysms [11]. These anatomic changes may lead to closure of retinal capillaries and arterioles resulting in retinal ischemia and disruption of the blood retinal barrier, increasing vascular permeability, and, subsequently, retinal edema. Later in the disease, due to the progressive development of retinal ischemia, there is proliferation of new vessels, growth of fibrous tissue, and contraction of vitreous and fibrous proliferation leading to subsequent retinal traction and detachment.

Retinal microthrombosis — The occurrence of retinal microthrombosis leads to the occlusion of retinal capillaries and capillary leakage. Increased adhesion of leukocytes to retinal vascular endothelium is one of the earliest changes observed in the retina before the onset of clinically detectable DR and may be involved in increased vascular permeability [12]. A loss of endothelial integrity leads to retinal ischemia, with subsequent release of growth factors such as IGF-1, platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and VEGF.

Altered retinal blood flow — Chronic hyperglycemia may increase retinal blood flow. Retinal blood flow is autoregulated and remains constant until the mean arterial pressure is raised approximately 40 percent above baseline. In the presence of chronic hyperglycemia, this autoregulatory mechanism becomes impaired [13]. The ensuing increase in retinal blood flow due to hyperglycemia and loss of the autoregulatory mechanisms causes increased shear stress on the retinal blood vessels, which may be a stimulus for the production of vasoactive substances, vascular leakage, and increased fluid accumulation in the outer layers of the retina, resulting in macular edema.

Retinal neurovascular alterations — The proper functioning of the retina relies on a complex interaction of photoreceptors and neurons transferring the electrochemical signal to the brain with support by glia and vascular tissue. This neuronal function depends on a complex interplay of retinal cells that includes the formation of a blood-retinal barrier [14]. The clinical diagnosis of DR is typically characterized by retinal vascular abnormalities, but neural deficits have been shown to occur early in the disease. Neurosensory changes have been detected before the onset of observable retinopathy by electroretinography (ERG) [15]. Early diabetes-related ERG findings include decreased b-wave amplitudes and alterations in the oscillatory potential that include reduced amplitudes and delays in the times to peak. The electrophysiologic changes occur early in diabetes and may potentially predict proliferative disease that leads to degenerative changes and significant visual impairment [16].

Sorbitol — Glucose that enters cells is metabolized in part to sorbitol via the enzyme aldose reductase; sorbitol is then metabolized to fructose, a process that is relatively slow (figure 3). The role of sorbitol production and accumulation in the pathogenesis of DR is uncertain. The observation that a polymorphism near the transcription site of the aldose reductase gene is associated with the early onset of retinopathy in some patients with type 2 diabetes is compatible with a potential pathogenetic role for this pathway [17].

Utilization of NADPH during sorbitol production can lead to a change in NADPH-to-NADP levels and oxidative stress [18], and subsequent sorbitol accumulation can result in altered Na/K-ATPase activity, impaired phosphatidylinositol metabolism, increased prostaglandin production, and alterations in the activity of protein kinase C isoforms. Protein kinase C is important in the pathogenesis of retinopathy because it may mediate the activity of VEGF as well as regulate vascular permeability, and it may cause the further accumulation of sorbitol [19].

Sorbitol accumulation within the cells of the lens is more pronounced with chronic hyperglycemia. It leads to a rise in intracellular osmolality (which causes movement of water into the cells and cell swelling) and to a decrease in intracellular myoinositol, both of which can interfere with cell metabolism. Sorbitol accumulation may also be important in cataract formation induced by hyperglycemia because swelling of lens fiber cells can lead to their rupture [20].

Advanced glycation end products — In chronic hyperglycemia, some of the excess glucose combines with free amino acids or serum or tissue proteins. This nonenzymatic process initially forms reversible early glycation products and later irreversible advanced glycation end products (AGEs) via an Amadori rearrangement (figure 4) [21]. Serum AGE concentrations are high in patients with diabetes, a change that can lead to tissue accumulation of AGEs, which may cross link with collagen, thereby initiating microvascular complications. AGE accumulation has also been implicated in cataract formation.

In addition, the interaction between AGEs and their receptor (RAGE) generates reactive oxygen species and, subsequently, vascular inflammation. Reactive oxygen species have been shown to be elevated in the vitreous fluid of patients with proliferative diabetic retinopathy (PDR), with a correlation between increasing levels of reactive oxygen species and more advanced PDR [22]. There is also evidence that inhibition of the renin-angiotensin system with an angiotensin II receptor blocker (ARB) in vitro can inhibit AGE-evoked inflammatory reactions in endothelial cells by suppressing reactive oxygen species generation [23].

GROWTH FACTORS

Growth factors promote the growth of new blood vessels from adjacent vessels in an abortive attempt to revascularize the diseased tissue. Studies in experimental models of retinopathy have shown that neovascularization is mediated in part by the interaction between insulin-like growth factor 1 (IGF-1) and vascular endothelial growth factor (VEGF). In one animal model of retinopathy, as an example, an IGF-1 receptor antagonist reduced the degree of retinal revascularization [24]. The possible role of IGF-1 is supported by the clinical observations that retinopathy often worsens in the first year after the onset of intensive insulin therapy (figure 5) [5,25], which may increase serum IGF-1 concentrations, and that advanced retinal disease can be reversed by pituitary injury or hypophysectomy, which lowers serum IGF-1 concentrations [26].

VEGF is produced by many retinal cell types in response to hypoxia. In retinas from patients with diabetes, the intensity of immunostaining for VEGF is proportional to the severity of the retinopathy and vitreous fluid VEGF concentrations are increased [27,28]. VEGF promotes growth of new blood vessels and may increase vascular permeability.

Erythropoietin has also been identified as a likely factor promoting retinal angiogenesis in DR [29-31]. Concentrations of erythropoietin and VEGF were elevated in the vitreous fluid of 73 patients with PDR compared with 71 patients without diabetes (erythropoietin concentration 464.0 versus 36.5 mIU per mL, respectively). Erythropoietin was more strongly correlated with retinopathy than VEGF. Blockade of erythropoietin inhibited endothelial cell proliferation in vitro and inhibited retinal neovascularization in vivo in a mouse model. Elevated erythropoietin levels have also been identified in patients with diabetic macular edema who did not have retinal ischemia or proliferative retinopathy [32].

Although VEGF appears to be the primary direct causative angiogenic factor in PDR, the complex mechanisms regulating in vivo angiogenesis likely involve factors in addition to VEGF. Other angiogenic pathways such as the angiopoietin 1 (ANGPT1) and Tie2 system modulate the effect of VEGF and directly affect retinal pericytes and endothelial cells, which are the principal cell types thought to be involved in the pathologic processes of PDR and diabetic macular edema [33]. Similarly, other growth factors may contribute to progression of retinal disease, including basic fibroblast growth factor and hepatocyte growth factor [28,34].

GENETIC FACTORS

Genetic influences affect the severity of retinopathy. In 372 patients in the Diabetes Control and Complications Trial (DCCT; who had 467 first-degree relatives with diabetes), severe retinopathy

was three times more frequent among the relatives of the retinopathy-positive patients than the retinopathy-negative patients [35].

How genetic factors might affect the development of retinopathy is not well understood. One possibility is polymorphisms in the platelet membrane glycoprotein Ia/IIa (alpha-2, beta-1 integrin) receptor for collagen (see "Overview of hemostasis"). In a case-control study, patients with type 2 diabetes who were homozygous for the Bgl II polymorphism had a significantly increased risk of retinopathy (odds ratio [OR] 3.4) as compared with those lacking this polymorphism [36]. Platelets with this polymorphism may interact with glycated collagen more easily than those lacking it, leading to more rapid retinal vascular injury.

Genetic susceptibility to retinopathy is also suggested by the finding in some studies of a greater prevalence of retinopathy among certain ethnic groups. As examples:

- In a study of 105 patients with type 2 diabetes who were followed for four years, retinopathy occurred more often among Black patients than White patients (50 versus 19 percent); the difference could not be explained by other factors such as A1C values, systolic blood pressure, or sex [37].

- In the Veterans Affairs Diabetes Trial (VADT), the prevalence of moderate to severe DR was found to be higher for Hispanic and African American persons than for non-Hispanic White persons (36, 29, and 22 percent, respectively) [38]. The differences were not accounted for by other factors (age, duration of diabetes, A1C, blood pressure).

However, race or ethnicity did not explain the difference in prevalence of retinopathy in a cross-sectional study of 778 patients with diabetes aged 45 to 85 years [39]. Although there was a higher prevalence of retinopathy, as well as macular edema in Black persons (36.7 and 11.1 percent, respectively) and Hispanic persons (37.4 and 10.7 percent) compared with White persons (24.8 and 2.7 percent), race/ethnicity was not an independent predictor of retinopathy; longer duration of diabetes, higher fasting glucose, greater waist-to-hip ratio, and use of insulin or oral hypoglycemic medications were independent predictors of diabetic eye disease.

PROTECTIVE FACTORS

Given sufficient time, the development of some degree of retinopathy is nearly universal; however, the development of proliferative diabetic retinopathy (PDR) plateaus at 60 percent even after more than 50 years of diabetes [40]. This observation, in a patient population that did not historically benefit from intensive glycemic control or current-day blood pressure control, has generated significant research interest as it suggests that there may be protective

mechanisms that may delay or prevent the progression to PDR. Hyperglycemia reduces platelet-derived growth factor (PDGF) survival-promoting activity, thus leading to pericyte apoptosis and diabetic vasculopathy. This mechanism is driven by hyperglycemia-induced activation of protein kinase C-delta (PKC-delta), which leads to increased expression of a protein tyrosine phosphatase called Src homology-2 domain-containing phosphatase 1 (SHP-1) [41]. SHP-1 activation, in turn, mediates resistance to PDGF, resulting in loss of cellular survival mechanisms and increased pericyte apoptosis. Inhibition of SHP-1 is being investigated as a possible protective mechanism against initial retinal changes that underlie subsequent development of PDR. Antiangiogenic mediators such as pigment epithelium-derived factor are reportedly lower in patients with diabetes and in patients with active PDR compared with other retinopathies [41].

Proteomic and protein expression analysis identified elevated concentrations of photoreceptor-secreted retinol binding protein 3 (RBP3) in the retina and vitreous of patients protected from advanced DR despite diabetes durations of over 50 years [42]. Early work on retinal cell-based assays and rodent models has shown that elevation of RBP3 can prevent or stop neural and capillary changes induced by diabetes. Mechanistically, RBP3 may have a role in the protection against the progression of DR by decreasing the expression of inflammatory cytokines and VEGF and inhibiting glucose uptake into retinal cells via glucose transporter 1 (GLUT1), thereby mitigating the effects of chronic hyperglycemia [41].

It is likely that an interplay between both angiogenic and antiangiogenic pathways may be important at various stages of retinopathy.

OTHER

Carbonic anhydrase — Carbonic anhydrase concentrations were elevated in the vitreous from individuals with proliferative diabetic retinopathy (PDR) compared with patients with diabetes but without retinopathy and patients without diabetes [43]. In addition, intravitreal carbonic anhydrase injections increased retinal vascular permeability with equal potency to vascular endothelial growth factor (VEGF), through a pH-mediated activation of bradykinin, a vasoactive substance. Furthermore, injection of both carbonic anhydrase and VEGF produced additive increases in vascular permeability in rat models. Thus, carbonic anhydrase may play a role in retinal vascular permeability in PDR and may be a target for future therapies.

Medications — Some studies have reported an association between the use of thiazolidinediones and an increased incidence of diabetic macular edema, but the complication is relatively rare [44,45]. Patients who are at risk for fluid retention or who have heart or renal

insufficiency appear to be at greatest risk. These data are reviewed in more detail elsewhere. (See "Thiazolidinediones in the treatment of type 2 diabetes mellitus", section on 'Macular edema'.)

In one trial, semaglutide (a glucagon-like peptide-1 receptor agonist) was associated with an increase in diabetic retinopathy complications, particularly among patients with existing retinopathy [46]. This trial is reviewed in more detail separately. (See "Glucagon-like peptide 1-based therapies for the treatment of type 2 diabetes mellitus", section on 'Microvascular outcomes'.)

Relation to nephropathy — There is an association between the development of DR and nephropathy, independent of the degree of hyperglycemia and the duration of diabetes. One study evaluated the correlation between albuminuria and retinopathy in 815 patients with type 2 diabetes (144 Hispanic and 671 White patients) [47]. The presence of albuminuria, defined as urinary albumin excretion >200 mcg/min, was a significant predictor for retinopathy (as detected via stereoscopic retinal fundus photographs) among the Hispanic (odds ratio [OR] 11.1) but not the White patients. Common pathogenetic factors may underlie the development of retinopathy and nephropathy. (See "Diabetic kidney disease: Pathogenesis and epidemiology", section on 'Pathogenesis'.)

SUMMARY AND RECOMMENDATIONS

- **General principles** – Diabetic retinopathy (DR) is a major cause of morbidity in patients with type 1 and type 2 diabetes. The development of DR is complex and is the result of many interrelated factors, which cause two basic changes within the retinal vessels, namely: abnormal permeability, and occlusion with ischemia and subsequent neovascularization (figure 1). (See 'General principles' above.)

- **Chronic hyperglycemia** – Chronic hyperglycemia is thought to be the primary cause of DR. Both the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) have found that better glycemic management reduces the incidence of new cases of retinopathy. (See 'Chronic hyperglycemia' above and "Diabetic retinopathy: Prevention and treatment", section on 'Prevention'.)

  Hyperglycemia can cause retinal injury through several possible mechanisms, including altered retinal blood flow, accumulation of sorbitol within retinal cells, and accumulation of advanced glycation end products (AGEs) in the extracellular fluid. (See 'Altered retinal blood flow' above and 'Sorbitol' above and 'Advanced glycation end products' above.)

- **Growth factors** – More advanced retinal disease, including proliferative vascular changes and neovascularization in the setting of retinal ischemia, may be mediated by other mechanisms such as the action of insulin-like growth factor 1 (IGF-1) and vascular endothelial growth factor (VEGF). (See 'Growth factors' above.)

- **Genetic factors** – In addition, inter- and intra-individual variations in biochemical or physiologic responses to hyperglycemia (perhaps as a result of differences in genetic susceptibility) may exist among people at different stages of diabetic disease. This variability may explain why a few patients with diabetes have minimal retinopathy despite years of severe hyperglycemia, whereas in others, severe retinopathy develops in a short period despite relatively good glycemic management. (See 'Genetic factors' above.)

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