

Diabetic retinopathy: from pathophysiology to treatment

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Abstract

There are inter-individual variations in the severity of diabetic retinopathy despite similar glycemic control. This review discusses the pathophysiology of diabetic retinopathy that may explain these variations and different treatment options.

Key words: Diabetic retinopathy; Pathophysiology; Treatment outcome

Introduction

Diabetic retinopathy (DR) is a debilitating complication of diabetes mellitus. In Hong Kong, its prevalence in patients with type 2 diabetes is estimated to be 39%, of whom 25% have sight-threatening diabetic retinopathy.¹ According to the United Kingdom Prospective Diabetes Study (UKPDS)² and the Action to Correct Cardiovascular Risk in Diabetes (ACCORD) Eye Study,³ the rate of DR is associated with glycemic control. Nonetheless, it is not uncommon to observe inter-individual variations in the severity of DR despite similar glycemic control. This review discusses the pathophysiology of DR that may explain these variations and different treatment options.

Pathophysiology

Several pathways have been implicated in the development and progression of DR, namely the increased polyol pathway, accelerated formation of advanced glycation endproducts (AGEs), activation of protein kinase C (PKC), hemodynamic changes, activation of the renin-angiotensin-aldosterone system (RAAS), inflammation and capillary occlusion and increased expression of growth factors such as vascular endothelial growth factor (VEGF) and insulin-like growth factor 1.⁴

Increased polyol pathway / aldose-reductase-sorbitol pathway

The increased polyol pathway is also known as the aldose-reductase-sorbitol pathway. In the setting of a high intracellular glucose concentration in the retina, aldose reductase, which normally functions to reduce toxic aldehydes in cells to inactive alcohols, reduces glucose to sorbitol. The latter process consumes nicotinamide adenine dinucleotide phosphate, which is an important intracellular antioxidant that plays a role in the reduction of glutathione. Decrease in glutathione reduction leads to increased cellular susceptibility to oxidative stress and damage.⁵ In addition, the strongly hydrophilic sorbitol does not diffuse readily through cell membranes, thereby accumulating intracellularly and leading to possible osmotic consequences, such as damage to retinal cells or formation of cataracts.^{6,7} Indeed, the association of genetic variants of the aldose reductase gene with susceptibility to DR has been demonstrated.⁶ Sorbitol is slowly metabolized to fructose, which in turn is phosphorylated to fructose-3-phosphate and degraded to 3-deoxyglucosone. Both of these molecules are strong glycating agents that can result in the production of AGEs, causing further damage.⁸

Accelerated formation of advanced glycation end products

AGEs are a heterogeneous group of molecules formed through non-enzymatic reactions of reducing sugars with free amino groups of proteins, lipids and nucleic acids. AGEs are normally formed in the body at a constant but slow rate and accumulate over time. Their formation is accelerated in diabetes due to the increased availability of glucose.⁹ AGEs have been implicated as a pathogenic mediator in DR. They are found in retinal vessels of patients with diabetes and their level correlates with DR severity.¹⁰ AGEs interact with specific cell surface receptors (including receptor for AGEs [RAGE], galectin-3, CD36, and the macrophage scavenger receptor) in the course of the development of DR.¹⁰

Activation of Protein Kinase C

Hyperglycemia induces the activation of PKC,¹¹ which is associated with vascular alterations (such as increased permeability, contractility, extracellular matrix synthesis, cell growth and apoptosis, angiogenesis, leukocyte adhesion, and cytokine activation and inhibition) that cumulate in tissue damage.¹² Inhibition of PKC- β isoform by ruboxistaurin (Arxxant; Eli-Lilly) has been shown in phase III clinical trials to reduce the progression of diabetic macular edema.¹³

Hemodynamic changes

Increased blood pressure in individuals with diabetes damages the retinal capillary endothelial cells by way of increased blood flow.¹⁴ The UKPDS reported a 2.8-fold increased risk of DR in individuals with systolic blood pressure ≥ 140 mm Hg, compared with those with systolic blood pressure < 125 mm Hg.¹⁵ In a UKPDS interventional trial involving the use of a β blocker or angiotensin-converting enzyme inhibitor (ACEI) and additional medications including a loop diuretic, a calcium channel blocker and a vasodilator, tight blood pressure control was associated with a 35% reduction in retinal photocoagulation, a 34% reduction in progression of retinopathy by ≥ 2 steps using the modified Early Treatment Diabetic Retinopathy Study (ETDRS) severity scale, and a 47% reduction in the incidence of deterioration of visual acuity by ≥ 3 lines using the ETDRS charts, over 7.5 years of follow up.¹⁶

Activation of the renin-angiotensin-aldosterone system

According to the EURODIAB Controlled Trial of Lisinopril in Insulin Dependent Diabetes Mellitus Study, administration of lisinopril reduced progression to proliferative diabetic retinopathy by 82% in largely normotensive younger patients with diabetes.¹⁷ As such, the renin-angiotensin-aldosterone system might have effects on DR that are independent of blood pressure. Possible mechanisms by which an ACEI acts to counter DR development and progression include beneficial hemodynamic effects, enhancement of nitric oxide resulting in a reduction of endothelial dysfunction, blockage of induction of VEGF receptors, and reduction of metalloproteinase activity improving the blood-retinal barrier.¹⁸

Inflammation and capillary occlusion

Hyperglycemia, oxidative stress, AGE formation, and hypertension all contribute to inflammation. This is further propagated by the inflammatory response itself, which involves the production of cytokines, adhesion molecules, VEGF signaling, enhanced RAGE expression, changes in nitric oxide regulation, and nuclear factor κ B signaling.⁴ Interactions between several proinflammatory factors will also lead to leukostasis, which leads to capillary-occlusion, reactive oxidative species mediated cell death and further inflammatory response.⁴

Increased expression of growth factors

The above-mentioned changes in the retina result in ischemia, which is a strong trigger for the secretion of growth factors that act to stimulate the proliferation of

residual vessels. Growth factor proteins (mainly VEGF, platelet-derived growth factor, and basic fibroblast growth factor), their receptors and/or mRNA have been demonstrated histologically in pre-retinal membranes afflicted with proliferative DR.¹⁹ Elevated vitreal levels of insulin-like growth factor 1 and VEGF have been found in individuals with neovascular activities.¹⁹

Treatment

Depending on the severity of DR, treatment should aim to prevent progression, promote regression and minimise loss of vision.

Intensive glycemic control (with HbA1c controlled to $< 6.4\%$ vs. 7.5% in the standard therapy group at 1-year follow-up) has been shown to reduce progression of DR by 33% after 4 years of follow-up.³ The benefit of intensive blood pressure control is less well-defined. Despite the early positive results from the UKPDS trial, later studies including the Appropriate Blood Pressure Control in Diabetes trial²⁰ and ACCORD Eye study³ failed to find any significant difference in DR progression between intensive treatment (mean blood pressure, 132/78 mmHg; median systolic blood pressure, 117 mmHg) and standard treatment (mean blood pressure, 138/86 mmHg; median systolic blood pressure, 133 mmHg).

Despite a lack of evidence for the benefits of intensive blood pressure control in DR, inhibition of the RAAS by ACEI has been shown to reduce DR progression and possibly cause DR regression. In a meta-analysis of 21 randomized clinical trials with 13,823 participants, a 21% reduction in the risk of DR progression and a 43% increase in the chance of DR regression was reported in normotensive patients treated with any renin-angiotensin system inhibitor.²¹ There was no benefit observed for patients who remained hypertensive despite RAAS inhibition. ACEI seemed to confer additional benefits over ARB in both reducing DR progression (OR [95% CI], 0.84 [0.75-0.94] vs. 0.92 [0.80-1.06]) and increasing DR regression (OR [95% CI], 1.50 [1.20-1.86] vs. 1.32 [1.07-1.61]).²¹ The association of antihypertensive drugs with the risk of DR progression was lowest for ACEI, followed by ARBs, β blockers, calcium channel blockers, and placebo in rank order. The association of antihypertensive drugs with a possibility of DR regression was highest for ACEI, followed by ARBs, placebo, and calcium channel blockers in rank order. These suggest that blood pressure control is an integral part of DR management and is best achieved using ACEI, followed by the addition of β blockers and calcium channel blockers if control is suboptimal. ARBs can be used as an alternative to ACEI if necessary.

According to the ACCORD Eye Study, fenofibrate might be beneficial in reducing DR progression (adjusted OR is 0.6 at 4 years compared with placebo).³ The putative mechanisms implicated in the mode of action of fenofibrate involve lipid and non-lipid pathways, including beneficial effects on apoptosis, oxidative stress, inflammation, blood-retinal barrier breakdown, and neuroprotection.

For severe DR, local treatment is necessary to prevent loss of vision. In addition to laser photocoagulation therapy, intravitreal anti-VEGF agents (e.g. bevacizumab and ranibizumab) are an important treatment for proliferative DR and can be considered in patients with center-involved macular edema.^{22,23} Aspirin therapy for cardioprotection is not contraindicated in DR as there is no increased risk of retinal hemorrhage. For patients with proliferative DR or severe non-proliferative DR, vigorous-intensity aerobic or resistance exercise may be contraindicated because of the risk of triggering vitreous hemorrhage or retinal detachment.²³

Screening

DR is usually asymptomatic in the early stages. Early detection of DR is useful in guiding management. Screening for DR is the standard of care for those with diabetes mellitus.²³ Although retinal photography is a useful DR screening tool for non-ophthalmologists, it is not a substitute for a dilated and comprehensive eye examination, which should be performed by an ophthalmologist.²³ In the absence of retinopathy, re-examination every 2 years may be considered. If any level of DR is detected, subsequent dilated retinal examinations

for patients with type 1 or type 2 diabetes should be repeated at least annually by an ophthalmologist. If retinopathy is progressing or sight-threatening, more frequent examinations are warranted. For pregnant patients, eye examination should be performed before pregnancy or in the first trimester and the patient should be monitored every trimester and/or 1 year post-partum depending on the severity of retinopathy.

Conclusion

DR is a debilitating condition with multiple pathophysiological pathways that have differential contributions to DR. Effective treatment should target all pathways by adequate glycemic and blood pressure control, reducing oxidative stress and reducing neovascularization. The intensity of glycemic and blood pressure control should be balanced against the risk of deleterious effects of hypoglycemia, hypotension or hyperkalemia (in the case of RAAS blockade).

Declaration

All authors have disclosed no conflicts of interest.

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