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Future Opportunities in Diabetic Retinopathy Research

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Abstract

Purpose of review—The risk of vision loss from diabetic retinopathy has fallen dramatically over the past 3 decades with improvements in diabetes and blood pressure treatments, and with advances in laser surgery and intraocular drug delivery. Nevertheless, diabetes remains to be a major cause of blindness. This paper summarizes the state of the art in diabetic retinopathy research and provides a perspective on opportunities for future investigations.

Recent findings—New insights into the pathophysiology of diabetes and diabetic retinopathy will improve metabolic control. Structure—function analyses are revealing new details of diabetic retinopathy. Intraocular drug therapy provides improved visual outcomes. Together these steps will yield better means to detect and quantify vision loss, and to develop patient-specific treatments to preserve vision for persons with diabetes.

Summary—Retinopathy is one of the most successfully treated complications of diabetes and will continue to be an important area of research for patients and their families.

Keywords

diabetic retinopathy; metabolism; neurodegeneration; intraocular drug delivery

I. Introduction

Diabetic retinopathy remains a major cause of visual impairment and blindness, just as diabetic nephropathy is a major cause of renal failure, owing to the growing burden of type 2 diabetes. Over one-third of the world's 285 million people with diabetes are estimated to have diabetic retinopathy, and one-third of these (approximately 3.2 million) have vision-threatening retinopathy¹. Therefore, there is still substantial need to: 1) better define the risk factors and underlying pathophysiology of diabetic retinopathy; 2) improve the means to quantify retinal dysfunction; and 3) determine how to intervene *prior* to vision impairment.

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Microaneurysms, hemorrhages and cotton wool spots define non-proliferative retinopathy; swelling of the macula characterizes diabetic macular edema; and retinal or iris neovascularization defines proliferative diabetic retinopathy. These features are observed by ophthalmoscopy or fundus photography and are graded in clinical terms as mild, moderate, and severe diabetic retinopathy, and in a semi-quantitative fashion (Early Treatment Diabetic Retinopathy Research Study grading) for research purposes. Approximately 50% of persons with diabetes have retinopathy by these criteria, so persons who have no visible vascular lesions are said to have no retinopathy, but these classifications do not include subtle changes in retinal function. Mild, moderate and severe retinopathy grades are analogous to the insidious progression from asymptomatic nephropathy with microalbuminuria and preserved creatinine clearance through progressive decline of creatinine clearance and the attendant consequences of hypertension and intravascular fluid overload that typify overt renal failure. The ability to identify early functional endpoints of renal insufficiency in terms of albuminuria and impaired creatinine clearance provides quantitative means by which to detect and intervene with pharmacologic agents such as antihypertensive and renin-angiotensin system inhibitors. Similar functional endpoints are not currently available for retinopathy.

II. Pathophysiology of diabetic retinopathy

Systemic pathophysiology

From 1980 to 2007, the estimated annual incidence of proliferative diabetic retinopathy decreased by 77% and vision impairment decreased by 57% among persons with type 1 diabetes ². These profound improvements resulted from the Diabetes Control and Complications Trial (DCCT) and United Kingdom Prospective Diabetes Study (UKPDS) which showed that intensive metabolic control reduced the risk of new onset retinopathy, nephropathy and peripheral neuropathy, and slowed the progression of existing mild complications in persons with type 1 diabetes, and hypertension in type 2 diabetes ³⁻⁵. The Wisconsin Epidemiologic Study of Diabetic Retinopathy also showed each one percent increase in hemoglobin A_{1c} was associated with a 30% increase in retinopathy, whereas each one percent improvement in hemoglobin A_{1c} translated into approximately 18% improvement of retinopathy ⁶. After 18 years of the Epidemiology of Diabetes Interventions and Complications (EDIC) study, patients who were in the intensive therapy group continued to have lower rates of diabetic macular edema and proliferative diabetic retinopathy or to require treatment for these states when compared to those who were in the conventional treatment group ⁷. Intensive metabolic control also reduces the need for laser photocoagulation for diabetic macular edema and for ocular surgery in general ⁸. However, there was no overall difference in the risk of vision loss between the two groups because therapies for reducing visual acuity loss in diabetic retinopathy are highly effective.

The general interpretation of these findings is that glycemia, as reflected by hemoglobin A_{1c}, is the primary determinant of the risk of retinopathy. Despite a close association of hemoglobin A_{1c} with all complications, the intensively treated group was associated with greater stimulated C-peptide levels (0.10 to 0.15 nmol/L) at study entry, lower hemoglobin A_{1c} levels, and a 25% reduction in the rate of retinopathy ⁹. Thus, intensive therapy

preserves β cell function. Other investigators have also found that C-peptide levels are inversely associated with the development of retinopathy in type 1 and type 2 diabetes^{10, 11}. These results strongly suggest that small amounts of residual insulin production continue to have beneficial effects on overall health and that there is a direct effect of insulin receptor activity at a systemic level. Conclusive clinical trials of C-peptide therapy have not been conducted¹² but it is possible that C-peptide directly contributes to the salutary effects of intensive therapy. Nevertheless, the biological effects of intensive control are more complex than simply reducing hyperglycemia.

The extensive analysis of DCCT/EDIC data continues to guide the principles of diabetes care. However, the results have been reported primarily as group means and the investigators have not yet reported findings of outliers whose retinopathy progressed in spite of intensive control or who did not develop retinopathy in spite of conventional control. Moreover, glycemic control estimates are steady state measures whereas blood glucose concentrations often fluctuate widely in patients. Emerging evidence suggests that excess glycemic variability influences the risk of cardiac autonomic neuropathy and mild retinopathy^{13, 14}.

The DCCT/EDIC has been invaluable but the results may not apply to all current patients with type 1 diabetes. The mean body mass index in the DCCT subjects was 23 – 24 kg/mg²¹⁵. However, current patients with type 1 diabetes are much heavier, and therefore more insulin resistant. Notably, 46% of 1894 adults with type 1 diabetes in the T1D Exchange clinic registry are overweight or obese¹⁶. These differences suggest additional factors may contribute to retinopathy and may require treatment in current diabetes patients. The role of other parameters beyond hemoglobin A_{1c} levels has been raised with the possibility of tailoring care for individuals^{17, 18}. However, as yet a comprehensive assessment of the impact of variables such as body mass index, nonalcoholic fatty liver disease or genetic traits has not been defined. A recent review concluded that no genetic loci are clearly associated with the risk of retinopathy¹⁹.

Thus, multiple factors must be included in the consideration of the pathophysiology and treatment of diabetic retinopathy. Of note, control of elevated blood pressure reduces the incidence of retinopathy²⁰ and the American Diabetes Association recommends blood pressure less than 140/90 mm Hg in patients with diabetes²¹. The effects of hypertension on the retina include activation of the renin-angiotensin system and direct hemodynamic effects on the blood-barrier that result in impaired autoregulation. To date, little attention has been given to the role of lipid classes other than triglycerides and cholesterol, or to other metabolites such as amino acids in the determination of risk factors. Indeed, the statistical association of hemoglobin A_{1c} and complications does not establish a causal relationship between glucose *per se* and the pathophysiology of diabetes complications.

The role of systemic inflammation in diabetic retinopathy has been investigated for more many years, and recent evidence suggests that chronic systemic inflammation such as due to non-healing ulcers is associated with a higher risk of progression of non-proliferative to proliferative retinopathy²². The mechanisms by which systemic inflammation might aggravate existing retinopathy are uncertain but may include both humoral and cellular factors. Elevated serum cytokines; *e.g.*, CCL5 and stromal cell derived factor, levels are

associated with more severe retinopathy²³, and high levels of soluble E-selectin and plasminogen activating inhibitor are associated with retinopathy in persons with type 1 diabetes^{24, 25}. Likewise, soluble tumor necrosis factors 1 and 2 are predictors of macroalbuminuria in patients with type 1 diabetes²⁶. A potential mechanism that may regulate the inflammatory mechanism is via hyper-acetylation of histone proteins in monocytes. Patients from the conventional group of DCCT with retinopathy exhibited higher acetylation of the promoter regions of inflammatory genes such as nuclear factor- κ B than did subjects from the intensive treatment group without retinopathy²⁷. However, as of yet, no systematic approach to the definition of inflammation in diabetes has been developed, but this is major potential opportunity.

Ocular pathophysiology

In a broad sense the clinical studies show the retina is sensitive to the ongoing metabolic status of the patient and has the ability to adapt. Institution of intensive insulin therapy in patients with type 1 diabetes restores impaired rod photoreceptor function as assessed by the electroretinogram²⁸. Efforts to understand the pathophysiology of the retina are constrained by the inability to biopsy the retina as can be done for studies of peripheral nerves and kidneys, so animal studies provide important insights. The retina is one of the most energetically demanding tissues in the body, yet has a relative paucity of blood vessels so it can provide clear vision^{29, 30}. Techniques that could non-invasively assess retinal metabolism³¹ would be very useful.

A prominent physiologic consequence of early diabetes on the retina is impairment of autoregulation in response to hyperoxia and flickering light^{32, 33}, reflecting reduced responsiveness of the neurovascular unit³⁴. Impaired autoregulation is detectable in patients with no detectable retinopathy, revealing rapid loss of the coupling between neuroglial cell activity and blood flow³⁵. Further impairment of autoregulation is evident as venous dilation in patients with diabetes who have no microaneurysms or hemorrhages, and venous dilation is associated with increased risk of retinopathy and mortality³⁶. The ultimate loss of autoregulation is seen as the development of macular edema or retinal neovascularization. That is, the adaptive mechanisms that maintain the blood-retinal barrier have failed. In that sense, these vision-threatening stages of diabetic retinopathy represent “retinal failure”, equivalent to renal failure³⁷. Further progress in preventing vision loss in persons with diabetes will benefit from understanding the interactions of systemic and ocular pathophysiologic mechanisms that compromise the neurovascular unit.

The treatment for diabetic retinopathy has improved dramatically over the last several decades with the improved metabolic and blood pressure control of patients, and the development of laser treatments and vitrectomy surgery. The advent of intraocular drug delivery of steroids and anti-vascular endothelial growth factor (VEGF) inhibitors over the past decade has established the principle of direct pharmacotherapy for diabetic retinopathy. Additional pathways, including plasma kallikrein signaling³⁸, loss of neurotrophic support^{39, 40}, and deficient angiopoietin 1 signaling⁴¹ may be targets for future therapy. Direct ocular drug administration will continue to be a major route of diabetic retinopathy treatment with sustained delivery methods now in clinical testing⁴².

II. New diagnostic approaches to diabetic retinopathy

The standard diagnostic approaches for diabetic retinopathy are based on visible vascular lesions with ophthalmoscopy and photographs. Optical coherence tomography (OCT) provides near cellular level detail such as thickening of the macula, and gives quantitative data on the response of intraocular anti-VEGF agents or steroids. OCT also reveals vitreous traction on the retina and areas of retinal atrophy. These anatomic features are informative but do not reveal the status of the neurosensory retina and visual function. Multiple studies have shown that the electrical activity and visual function are impaired within a few years of the onset of diabetes, but to date these findings have not influenced clinical practice, largely because the tests are time-consuming. Recent studies have shown that visual field tests reveal reduced retinal sensitivity in patients with minimal retinopathy^{43,44}. Specifically, Jackson⁴⁴ found that a 5 minute long frequency doubling perimetry test has 83% sensitivity to the presence of mild non-proliferative retinopathy. The current state of knowledge is that diabetes impairs the function and structure of the entire retina and that these changes can be detected by clinically practical tests⁴⁵⁻⁴⁷. The ability to detect and predict vision loss in patients with glaucoma and retinal degenerations has been established in prospective, longitudinal studies⁴⁸⁻⁵⁰. Similar well-planned, multi-site studies that reflect disease pathophysiology and that respond to therapeutic intervention are now needed for diabetic retinopathy⁵¹, as discussed at a workshop sponsored by the National Eye Institute and the Food and Drug Administration in June, 2015.

III. Therapy of diabetic retinopathy

Systemic therapies

The role of systemic therapies is crucial for reducing both the development and progression of diabetic retinopathy, as demonstrated in persons with type 1 diabetes (DCCT/EDIC). Intensive glycemic control reduced the progression of diabetic retinopathy in type 2 diabetes in the United Kingdom Prospective Diabetes Study (UKPDS)⁵² and the Actions to Control Cardiovascular Risks in Diabetes (ACCORD).⁵³ In addition, intensive blood pressure control (140 mm Hg vs. 180 mm Hg) reduced the progression of diabetic retinopathy in the UKPDS⁵⁴. However, in the ACCORD Eye Study⁵³, the goal of achieving blood pressure of 120 mm Hg in the intensive group did not result in any effects on diabetic retinopathy. In ACCORD, fenofibrate (160 mg daily) plus simvastatin reduced the risk of progression of diabetic retinopathy.

Achieving and maintaining intensive glycemic control is not feasible for many patients. As in DCCT/EDIC and ACCORD follow-up study (ACCORDION), the intensive glycemic group began to have an increase in their hemoglobin A_{1c} that is almost equivalent to that of the standard therapy group. A study headed by DRCR.net ophthalmologists⁵⁵ to influence the participants ability to control glycemia and blood pressure in a randomized trial of educational materials showed no benefit at one year. By contrast, Stem et al⁵⁶ found that patients with suboptimally controlled diabetes (hemoglobin A_{1c} > 7.0%) who received a diagnosis of a complication (retinopathy, nephropathy or neuropathy) exhibited a clinically significant reduction in average hemoglobin A_{1c} at 15 months of follow up. This study also found that 71% of the persons who were diagnosed with a complication did not fill their

prescriptions. Clearly there is a need for better approaches to educate and motivate patients with diabetes.⁵⁷

Ocular Therapies for Diabetic Retinopathy

Specific ocular therapies have evolved from destructive therapy using laser photocoagulation to the targeting of the vascular changes with antibodies against the vascular endothelial growth factor (VEGF). The two main causes of visual impairment include the presence of edema in the macula or diabetic macular edema (DME) or proliferative diabetic retinopathy. For 3 decades laser photocoagulation was the mainstay of therapy until the introduction of intraocular injections of anti-VEGF therapies including bevacizumab (Avastin, Genentech), ranibizumab (Lucentis, Genentech) and aflibercept (Eylea, Regeneron). These therapies have been tested in comparative studies that show subtle differences but demonstrate visual acuity gains superior to those treated with laser photocoagulation^{58–62}. VEGF inhibition yields a higher likelihood of 3-line visual acuity improvement than laser treatment^{58, 63}. There is a remarkably low rate of adverse effects, so this approach has become the first-line of treatment. Laser photocoagulation was tested against intravitreal injections of anti-VEGF agents for the treatment of proliferative diabetic retinopathy, providing another alternative to the traditional laser photocoagulation for the treatment of proliferative diabetic retinopathy⁶⁴. Vitrectomies are still required to treat the more severe stage of diabetic retinopathy with vitreous hemorrhage and tractional retinal detachment.

Current therapies for diabetic retinopathy attack vision-threatening disease that is assumed to be due to VEGF. Future work may use the power of vitreous proteomics to reveal molecular targets for therapy,⁶⁵ and yield personalized treatment based on the complexity of systemic and local pathophysiologic mechanisms in individual patients.⁶⁶

IV. Conclusion

Improvements in diabetes and diabetic retinopathy treatments have resulted from better understanding of pathophysiology and clinical trials that show the benefits of aggressive approaches. Future improvements will build on these successes to further reduce the risk of vision loss and will lead to early diagnosis and less invasive treatments.

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Abbreviations

DCCT	Diabetes Control and Complications Trial
UKPDS	United Kingdom Prospective Diabetes Study
EDIC	Epidemiology of Diabetes Interventions and Complications
CCL5	Chemokine C-C motif ligand 5
VEGF	Vascular endothelial growth factor

OCT	Optical coherence tomography
UKPDS	United Kingdom Prospective Diabetes Study
ACCORD	Actions to Control Cardiovascular Risks in Diabetes

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Key points

1. The systemic and ocular pathophysiology of diabetic retinopathy extends beyond hyperglycemia.
2. Structure—function analyses reveal that diabetes impacts the entire retina and will lead to more sensitive and pathophysiology-based diagnosis.
3. Combined ocular and systemic treatments have reduced the risk of vision loss in persons with diabetes and next steps will provide the opportunity for personalized care.