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Diabetic Retinopathy and Diabetic Macular Edema

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Abstract

Diabetic retinopathy and diabetic macular edema result from chronic damage to the neurovascular structures of the retina. The pathophysiology of retinal damage remains uncertain but includes metabolic and neuroinflammatory insults. These mechanisms are addressed by intensive metabolic control of the systemic disease and by the use of ocular anti-inflammatory agents, including vascular endothelial growth factor inhibitors and corticosteroids. Improved understanding of the ocular and systemic mechanisms that underlie diabetic retinopathy will lead to improved means to diagnose and treat retinopathy and better maintain vision.

This chapter summarizes the pathogenesis, risk factors, diagnosis, signs and symptoms, and treatment options for diabetic retinopathy (DR) and diabetic macular edema (DME). The complex nature of DR has led to a variety of therapies, but treatments for DR and DME are still challenging, particularly in the stages when retinopathy is mild and patients retain good vision.

Diabetic Retinopathy Prevalence

DR is one of the major complications of diabetes and is a leading cause of blindness and vision impairment. Approximately 75% of persons suffering from type 1 diabetes develop retinopathy, while approximately 50% of persons with type 2 diabetes may develop retinopathy [1], and approximately 25% of persons with diabetes may develop macular edema. During the next two decades, over 360 million people worldwide are projected to have diabetes and its complications [2]. Fortunately, the prevalence of severe retinopathy and nephropathy in patients with type 1 diabetes has diminished over the past 35 years due to improved medical care [3], but the recent epidemic of type 2 diabetes requires a new understanding of the biology of DR and our approach to its prevention and treatment. Approximately 500,000 persons in the United States have clinically significant DME, with an annual incidence of 75,000, and approximately 700,000 have proliferative DR, with an annual incidence of 65,000 [4].

Risk Factors

The clinical risk factors for DR have long been recognized to include diabetes severity and duration, hypertension, presence of other complications, anemia, hyperlipidemia, insulin resistance and deficiency, and a family history of DR (reviewed by Antonetti et al. [5] and

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Girach and Vignati [6]). While the benefits of decreasing HbA_{1c} or blood pressure levels have been demonstrated in large clinical trials [7, 8], there is presently no integrated index of the risk of DR and other complications that include these known variables. Such an integrated index would greatly facilitate the identification of patients who are at increased risk of complications and who merit aggressive systemic and ocular therapy. A study to identify risk factors associated with the progression to proliferative DR (PDR) identified HbA_{1c}, diabetic nephropathy, and nonhealing foot ulcers as three risk factors that can help predict progression to PDR. From this, the authors derived a risk score [9]. However, most of the risk for retinopathy is not accounted for by traditional clinical indices [10].

Indeed, much work remains to be done to determine the potential contribution of genetic factors and the impact of systemic inflammation. A single nucleotide polymorphism in the promoter region of the erythropoietin gene confers a twofold increased risk of PDR and end-stage renal disease versus patients without this mutation [11]. This finding was the result of large-scale genomic screening in three population groups and demonstrates the power of interdisciplinary collaborative studies. However, genetic studies have yet to yield major insights into DR, partly related to the complexity of the disease and the small size of most studies [12].

Several studies have demonstrated a relationship between plasma levels of inflammatory markers and DR [13–16], but it remains unclear if these inflammatory molecules contribute directly to the retinal damage in diabetes or simply reflect the systemic inflammatory state, and if they predict progression of disease or can be employed as markers of treatment response.

Etiology and Pathogenesis

The etiology and pathogenesis of DR and DME have been the subject of much research and debate for the past three decades. At present, the understanding of these processes is undergoing a dramatic shift from a strictly vascular focus to a more comprehensive view of the disease.

The vascular lesions of DR have been emphasized from the first case report of DR in 1855, reviewed by Wolfensberger and Hamilton [17], through the development of fluorescein angiography and trypsin digest studies of retinal blood vessels in the early 1960s, and in the classification of DR for the laser treatment trials in the 1970s and 1980s. The microvascular disease approach led to successful development of laser photocoagulation for proliferative retinopathy and DME. Expanded research into molecular pathways and chemical mediators has now led to the use of pharmacologic treatments for DR and DME in addition to laser therapy.

Concurrent with the development of fluorescein angiography and trypsin digest studies, two studies of postmortem human eyes in patients with DR [18, 19] emphasized the degeneration of the retinal neuropil even in regions remote from sites of vascular lesions. Electroretinographic studies subsequently confirmed the impairment in neural retinal function in patients with DR [20–23], indicating the presence of Müller cell defects and predicting the risk of progression from severe nonproliferative to high-risk proliferative

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retinopathy. However, a lack of appreciation of the biology of the transparent neurosensory retina by clinicians may have limited the clinical application of these findings.

Over the past decade, numerous studies of animals and humans have confirmed that all retinal cell types are damaged by diabetes, including loss of inner retinal neurons and their projections [24, 25], dysfunction of Müller cells [26–28] and astrocytes [26, 29], activation of microglia, resident immune cells of the nervous system [30, 31], and degeneration of the pigment epithelium [32]. Thus, the current biological definition of DR includes all functional and structural changes in the retina due to diabetes, and the term ‘microvascular disease’ does not fully describe the retinal features of diabetes and is misleading in its limited scope.

The interrelationships between these retinal cell changes remain to be resolved. Do the vascular changes cause neuronal or glial cell defects, or vice versa, or are all the changes part of a coordinated sequential process? This question remains difficult to resolve.

Neuroretinal cell changes have not been well appreciated because they are invisible to clinical examination by ophthalmoscopy, fluorescein angiography, and standard optical coherence tomography (OCT). Therefore, new diagnostic methods based on changes in retinal neural cells are now being developed, as discussed below. In eyes with cystoid macular edema, the clinical appearance of cysts and corresponding leakage of fluorescein dye suggest that leakage of the perifoveal capillaries likely accounts for macular thickening. However, histologic studies show loss of retinal neurons in addition to foveal cysts; a reduction in macular edema may not result in visual improvement if retinal neurons are nonfunctional. Hence, recognizing both the clinical and biological aspects of retinal changes in DME and DR are essential to understanding the mechanisms of vision loss and designing appropriate treatments.

The cell biology of DR and DME is now becoming better understood, but the pathophysiologic processes that lead to the cellular lesions remain highly controversial. Hence, there is currently no well-established unifying hypothesis that accounts for the full range of vascular and neural changes, and impairment in visual function. The major concepts are summarized as follows.

First, the basic pathophysiology of diabetes itself deserves emphasis. Diabetes mellitus refers to ‘honey urine’ and reflects the emphasis on glucose accumulation. Clinicians diagnose diabetes based on elevated blood glucose levels because blood glucose concentration correlates closely with clinical manifestations and is readily measured. However, both type 1 and type 2 diabetes results from impaired insulin action, which secondarily leads to hyperglycemia, hyperlipidemia, and elevated serum branched-chain amino acids, with catabolic degradation of tissues such as skeletal muscle and adipose tissues.

The role of excess glucose in DR has received extensive investigation as part of the aldose reductase (polyol) pathway, nonenzymatic glycation and advanced glycation end product receptor activation, protein kinase Cβ activation, and oxidative and nitrative stress. Most of these changes have been investigated in rodent models of diabetes, where they seem to have

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a close connection with vascular changes. However, the promise of aldose reductase inhibitors in diabetic rats was not borne out in diabetic dogs or humans [33]. Likewise, advanced glycation end product blockers did not demonstrate beneficial effects on diabetic complications in humans and were toxic. The only successful treatment based on a glucose-activated pathway has been the protein kinase Cβ inhibitor, ruboxistaurin, which has been shown to reduce vision loss in DR [34–36]. However, this medication failed to achieve Food and Drug Administration approval and did not achieve statistical significance in the most recent studies [37].

Inflammation is an early and intrinsic feature of systemic insulin resistance and diabetes that involves the release of cytokines from adipose tissue that impairs insulin action, and affects patients with both type 1 and type 2 diabetes [38, 39]. Interestingly, DR was formerly termed ‘diabetic retinitis’ [40] before the inflammatory component was understood. The clinical picture of DR provides numerous clues to the presence of chronic inflammation, including diffuse vascular dilation, tortuosity, leakage and neovascularization, atrophy of the retinal neural parenchyma, edema of the macula, and eventual fibrosis. Cellular studies reveal activation of microglia [29–31] and leukostasis [41]. Together, these clinical and laboratory-based studies leave little doubt as to the presence of inflammation in DR, even though it is much more insidious than the uveitis associated with other systemic conditions such as sarcoidosis or multiple sclerosis.

The relationship of systemic inflammation to DR is currently unclear. Inflammatory responses are part of the intrinsic immune system reaction to multiple stresses, such as injury, ischemia, and infection, and inflammation is designed to limit the stress. Unrelenting stress and inflammation, however, lead to the clinical features associated with tissue damage that we recognize as ‘disease’. If the intrinsic immune response in diabetes is similar to that in other tissues, its activation in diabetes may be designed to maintain cell viability in the presence of metabolic stress. The retina may respond with increased production of growth factors such as vascular endothelial growth factor (VEGF) and erythropoietin, cytokines, complement, and microglial cell activation as a physiologic compensatory response. If the metabolic stress is relieved, the inflammation may subside, but prolonged metabolic stress may lead to a maladaptive response in which inflammation would damage tissue because of tissue edema, invasion of circulating immune cells, and fibrosis. Thus, the inflammatory response is probably a double-edged sword with both beneficial and detrimental aspects. At present, it is not clear which components of the inflammatory response are critical or which may serve as useful therapeutic targets.

Impaired insulin action is the sine qua non of diabetes and, along with glucagon excess, accounts for numerous tissue changes, including atrophy of skeletal muscles and adipose tissue. Until recently, there was very little information on the role of the insulin receptor signaling system in the retina. Biochemical studies show that the receptor is structurally similar to that in the liver, is expressed in all retinal cells, forms heterodimers with the insulin-like growth factor 1 receptor, and has high basal activity relative to other tissues such as the liver [42, 43]. In diabetic rodents, the basal activity decreases progressively with time, and systemic insulin treatment restores the activity [44]. The impaired activity may predispose the retina to additional metabolic insults from systemic inflammation and

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hypertension, which also incite inflammation via the retinal renin-angiotensin system [45]. This dynamically regulated insulin receptor system likely maintains the activity and viability of postmitotic retinal cells, but full understanding of this process is currently lacking.

In summary, the etiology of DR is tied closely with the fundamental processes of diabetes itself, but the precise mechanisms that initiate or perpetuate retinal damage and lead to vision impairment remain to be clarified.

Diagnosis and Ancillary Testing/Differential Diagnosis

DR is diagnosed clinically on the basis of visible hemorrhages, microaneurysms, cotton wool spots, lipid exudates, and neovascularization. Fundus photography and fluorescein angiography have greater sensitivity than ophthalmoscopy because of superior optics, the enhanced contrast of fluorescein angiography, confirmation of vascular leakage, and the ability of the observer to review magnified images without the interference of patients moving or blinking.

Prevention of vision loss requires better understanding of the fundamental processes that impair vision and improved diagnostic tests to provide parameters to gauge the response to pharmacologic interventions. Retinal dysfunction in diabetes has long been known to begin before the onset of microvascular lesions. Changes in color vision, contrast sensitivity, visual fields, and electroretinography responses have been documented thoroughly [23] over the past three decades. Technological advances have allowed newer imaging modalities to be applied to retinal diseases, both in clinical practice and research. Most prominent has been the increasing utilization of OCT for the detection and quantification of DME. Macular thickness maps and OCT images provide guidance for treatment response to anti-VEGF therapy and macular laser therapy, and have been extensively utilized in large clinical trials [46]. The high resolution available with spectral-domain OCT allows for close study of the retinal layers and cells in clinical disease [47]. Ultra-wide-field imaging is currently used for the screening and detection of DR as is ultra-wide-field angiography [48, 49]. Adaptive optics is being applied to in vivo retinal imaging, allowing visualization of individual retinal cells and microvasculature that may help clarify the structure and function of the retina in diabetes and its response to treatment [50, 51]. Other functional tests have been investigated to detect early visual dysfunction in DR, such as the use of frequency doubling perimetry, which indicates inner retinal impairment as a significant contributor to visual dysfunction in DR [52]. However, no test of retinal function other than visual acuity has been shown conclusively to predict the onset or progression of retinopathy or vision loss, or to be a useful endpoint for clinical trials. Thus, the understanding of the biology of DR continues to evolve and provides new opportunities to move the timeline of diagnosis and treatment much earlier in the course of diabetes [53]. The process of translating the results of laboratory findings into clinical utility is complex, expensive, slow, and requires new ways of studying DR [54], but investments in the process should pay substantial dividends in the future.

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Signs and Symptoms

DR is unusual among retinal diseases in that the symptoms vary widely and may be out of proportion to the severity of retinal pathology. For example, eyes with mild DME involving the fovea of one eye can have symptomatically decreased vision whereas eyes with severe proliferative retinopathy may have 20/20 acuity and no symptoms until they begin to develop vitreous hemorrhage. This variability and discrepancy between structure and function are the rationale for programs that screen populations at risk to identify and treat asymptomatic patients to reduce the risk of vision loss [55].

Treatment Options

The key to preventing and controlling ocular complications from diabetes is strict glycemic control and control of blood pressure. The importance of controlling the underlying disease process should be stressed to patients and has been proven in several large clinical trials [7, 56, 57]. Once the patient presents with PDR, panretinal photocoagulation remains the standard treatment at present and significantly reduces the risk of vision loss [58, 59]. Strong evidence also exists for use of focal macular laser photocoagulation in the prevention of vision loss secondary to DME [58, 60, 61]. For many years, these were the only interventions for which strong clinical evidence existed. With the use of anti-VEGF agents expanding beyond macular degeneration, more options have become available in preventing and even reversing vision loss secondary to DR and DME.

VEGF plays a critical role in DR and DME. Diabetes increases the production of VEGF, leading to increased vascular permeability and angiogenesis [62]. As a result, blockage of the VEGF-A molecule has been the recent focus of pharmacologic therapy aimed at treating these diseases [63]. In 2012, intravitreal ranibizumab received FDA approval for the treatment of DME based on the results of several large clinical trials [64–69]. These studies demonstrated that intravitreal ranibizumab significantly reduces macular edema and results in improved visual acuity for patients with DME. In some studies, ranibizumab was more effective than focal laser therapy at reducing DME, with laser therapy providing no additional benefit. The DRCR.net (Diabetic Retinopathy Clinical Research Network) Protocol I study evaluated ranibizumab with prompt or deferred focal/grid macular laser therapy for center-involving DME and demonstrated a clear benefit of using ranibizumab when initiating treatment. Longer-term results of this study also showed that adding macular laser therapy at the initiation of ranibizumab was no better, and may in fact be worse, compared with delaying laser therapy to >24 weeks [65, 66, 68]. READ-2 compared ranibizumab alone to laser alone or ranibizumab plus laser, and found mean best-corrected visual acuity (BCVA) to be better with ranibizumab monotherapy, with sustained efficacy [67]. RESTORE (Ranibizumab plus Macular Laser Photocoagulation) also demonstrated superiority of ranibizumab monotherapy over macular laser photocoagulation, and found no additional benefit of ranibizumab therapy combined with macular laser therapy [69]. The RISE and RIDE studies have provided additional evidence that ranibizumab monotherapy provides rapid and sustained results in improving macular edema and BCVA. In addition, a delay in the initiation of ranibizumab therapy resulted in limited improvement in BCVA in the 36-month results [64]. Bevacizumab is frequently used off-label to treat DME as well

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and has demonstrated efficacy in several clinical trials [70, 71]. BOLT (Bevacizumab or Laser Therapy) compared intravitreal bevacizumab to laser therapy alone and found mean BCVA to be significantly better in the bevacizumab group versus laser therapy alone [70]. Another anti-VEGF agent, aflibercept, received FDA approval in 2014 for the treatment of DME and has the potential to decrease the frequency of required injections [72]. The DRCR.net Protocol T study evaluated the relative efficacy and safety of aflibercept, bevacizumab, and ranibizumab for the treatment of center-involving DME [73]. The 1-year results concluded that all three agents improved vision in eyes with DME. In eyes with better baseline visual acuity (Snellen 20/40 or better), there was no statistically significant difference among the three agents. In eyes with worse baseline visual acuity (Snellen 20/50 or worse), aflibercept achieved greater average gains in visual acuity compared to bevacizumab and ranibizumab, and this difference was statistically significant [73].

The use of anti-VEGF agents has allowed for a tremendous improvement in the clinician's ability to treat DME. However, the use of focal/grid macular laser therapy still plays a critical role in the treatment of this disease process and can help individualize treatments for patients who may not respond to or tolerate treatment with frequent anti-VEGF medications.

Panretinal photocoagulation remains the standard for treatment of PDR. However, given the prominent role of VEGF as a driving mediator in angiogenesis, studies are exploring the effects of intravitreal anti-VEGF therapy on DR and its possible role in treatment. In these studies, ranibizumab has been shown to reduce the probability of retinopathy progression in eyes with and without PDR [74]. Studies are ongoing in determining the utility of using anti-VEGF agents to delay panretinal photocoagulation for PDR (NCT01489189). Bevacizumab has also been incorporated pre- and postoperatively for use in vitrectomy for PDR. Studies have examined its effects on intraoperative maneuvers and intraoperative bleeding, as well as rates of postoperative vitreous hemorrhage [75]. However, high-quality evidence is still lacking in demonstrating a clear benefit.

Given that inflammation plays a critical role in DR and DME, various corticosteroids have been used in the treatment of DME. In addition to anti-inflammatory effects of corticosteroids, they also inhibit VEGF and increase tight junctions between capillary endothelial cells [76]. Corticosteroids are effective in various forms and delivery systems when used in combination with macular laser therapy. Intravitreal triamcinolone combined with prompt focal/grid laser therapy has demonstrated equal efficacy in comparison to ranibizumab monotherapy in pseudophakic patients [65, 68]. However, intravitreal triamcinolone as a monotherapy was less effective when compared to macular laser photocoagulation [77]. Evidence also exists that intravitreal triamcinolone may reduce the progression of PDR [74]. Other corticosteroids that have been used for DME in combination include sustained drug delivery implants for dexamethasone (Ozurdex) and fluocinolone acetonide (Retisert and Iluvien). These treatments are not without significant ocular side effects, which include an increased incidence of glaucoma and a high rate of cataract formation requiring cataract surgery [78, 79].

Surgery with vitrectomy remains an indispensable treatment option for patients with complications from DR including nonclearing vitreous hemorrhage and tractional retinal

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detachments. In addition, vitrectomy with induction of posterior vitreous detachment can be used for the treatment of DME with a tractional component [80, 81]. This treatment option has led to interest in the use of enzymatic vitreolysis to treat DME [82], which may become more of a possibility given FDA approval of ocriplasmin for use in symptomatic vitreomacular adhesions [83]. Research is ongoing for additional pharmacotherapies that can modulate molecules other than VEGF that contribute to inflammation and vascular permeability, resulting in macular edema and angiogenesis [84].

Treatment Outcomes and Prognosis

All treatments for the established vascular lesions of DR reduce the risk of blindness and vision loss but seldom restore normal vision [85, 86]. The continued impact of diabetes, hypertension, and other systemic insults continues to reduce vision. Long-term follow-up of patients treated with panretinal photocoagulation in the Diabetic Retinopathy Study retained useful vision that gradually declined over time [87]. With results of the clinical trials involving intravitreal anti-VEGF for DME, the treatment paradigm has shifted from preventing vision loss to actually improving vision in patients with DME [62]. Although these results are encouraging, treating the long-term effects of metabolic dysfunction on neuroretinal cells presents a challenge. Early disease detection and prevention through intensive blood glucose control remains essential in delaying the onset and progression of DR [88].

Conclusion and Key Points

Retinopathy continues to be a frightening and devastating consequence of diabetes for patients and their families. The prognosis for patients with diabetes and the ensuing complications improves with overall enhancements in diabetes management, but the ocular complications are still diagnosed and treated late in terms of the biological processes. Fundamentally different approaches to the problem must be taken as the number of persons with diabetes doubles over the next 25 years to prevent a global epidemic of preventable blindness. Intravitreal agents have added an invaluable management option in addition to laser photocoagulation and vitrectomy. However, given the high disease burden, the practicality of delivering this care in a timely and effective fashion remains a challenge, particularly in developing nations. This further stresses the importance of early disease detection and treatment through large-scale screening and patient education. Utilizing developments in technology and telemedicine will likely play a key role in achieving this goal.

On a more molecular level, research is needed to treat the metabolic pathway upstream, as opposed to treating the downstream consequences. Better information is needed on the mechanism of the effects of intensive insulin therapy and how to design and deliver agents to achieve the effect without inducing hypoglycemia or other adverse events. Viewing DR as a specific consequence of the metabolic derangement of diabetes provides promise that pharmacotherapy should have a dramatic impact on the risk of vision loss in persons with diabetes.

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