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MINI REVIEW

Diabetic Retinopathy - Brief Overview

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Abstract

Diabetic retinopathy (DR) is a major complication of diabetes, which affects over 90 million people worldwide. Lifetime occurrence of DR is over 90% and 50-60% for Type I diabetes mellitus (T1DM) and T2DM, respectively. Such a high prevalence makes DR a leading cause of blindness in working aged people and a major public health issue in developed countries. In the inaugural issue, this editorial provides a brief overview of the salient features of DR, including risk factors, diagnosis, pathobiology, molecular and cellular mechanisms, and therapeutics. Aspects of DR that are critically important, but not commonly known, will also be discussed.

Key Words: *Diabetic retinopathy; Hyperglycemia; Diabetes*

Introduction

Diabetic retinopathy (DR) is a major complication of diabetes, which affects over 90 million people worldwide. Lifetime occurrence of DR is over 90% and 50-60% for Type I diabetes mellitus (T1DM) and T2DM, respectively [1,2]. Such a high prevalence makes DR a leading cause of blindness in working aged people and a major public health threat in developed countries. It is therefore worthwhile to have a brief overview on the salient features of DR in this inaugural issue, including risk factors, diagnosis, pathobiology, molecular and cellular mechanisms, and therapeutics. Discussion will also be provided for those critically important, but not commonly known, aspects of DR, such as the retinal pigment epithelium (RPE) barrier function and neuropathy.

Risk factors for DR

Long-term epidemiological studies indicate that chronic hyperglycemia is the primary risk factor for DM and DR, which is measured by glycosylated hemoglobin (HbA1c). HbA1c below 6.5% is recommended by the International Diabetes Federation and the American College of Endocrinology [3]. Hyperglycemia or high retinal glucose is the likely inducer for some secondary risk factors, such as oxidative stress, cytokine, chemokine, and growth

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factor upregulation, and inflammation, which eventually lead to blood-retina barrier (BRB) breakdown in DR [4-8]. Other major risk factors for DR include hypoxia, hypertension, and dyslipidemia (Figure 1) [9-12]. Pregnancy is often associated with hypertension and proteinuria. Increases in these pathological conditions promote an abrupt onset or progression of DR [13]. Therefore, pregnant women with potential DM and DR risks require frequent eye examinations, according to American Academy of Ophthalmology. As DM and DR are multifactorial disorders, it is difficult to pin-point the role of specific gene(s) in the development of the diseases. With the advancement in genetic methodology, such as genome-wide association studies and sequencing technologies that permit genetic analysis on large biodata banks and aggregation of diabetes cohorts, at least 44 single-nucleotide polymorphisms for DM and its complications have been identified [14], including one specifically for DR in both T1DM or T2DM [15].

Pathobiology and mechanisms of diabetic complication in the eye

BRB abnormalities and diagnosis

Traditionally, DR is regarded as a retinal microvascular disorder, as diabetes-induced key microvascular abnormalities can be diagnosed with fundus imaging and fluorescent angiography. These procedures permit the detection of microaneurysms, retinal hemorrhages, cotton wool spots, lipid exudates, capillary occlusion, and retinal neovascularization. The development of optical coherence tomography (OCT) and OCT angiography made it possible to diagnose diabetic macular edema (DME), epiretinal membrane formation, retinal thinning, non-perfusion, vitreomacular adhesion, intraretinal cysts, and foveal avascular zone enlargement [16]. The imaging modalities discussed above are diagnostic tools for BRB pathological characteristics in DR patients, which are commonly used as to classify non-proliferative DR (NPDR), DME, proliferative DR (PDR), major subclasses of DR associated with abnormal BRBs. Figure 1 is a simplified summary for pathogenic mechanisms of BRB breakdown in DR. Of note, the traditional description of DR as a disorder of (only) retinal microvasculature, which appears in most professional publications currently, is very misleading for the following reason. The endothelial and RPE barriers (also called outer BRB) constitute BRBs. It is important to point out that approximately 80% of retinal blood circulation is achieved through the RPE barrier. A critical observation for RPE barrier breakdown in diabetes was demonstrated 40 years ago [17], which was confirmed in our hands [18,19]. RPE barrier breakdown can now be readily observed in humans with OCT technology [20]. In summary, diabetes-induced changes in the RPE is a significant contributing factor to NDPR, DME, and retinal fibrosis in PDR. Developing new methodologies for the advancement of RPE barrier research is an urgent task for the DR field.

Alteration of retinal neuronal viability and function

The developments in basic and clinical research and imaging technology for the past few decades have led to the gradual recognition of DR as a disorder of retinal neurons, in additional to BRB abnormalities, which is also referred to as diabetic neuropathy. It has been shown that alterations in retinal neuronal viability and function precede BRB alterations in diabetic animals and patients [21-25]. It is now widely

accepted that diabetes impairs retinal neuronal function, including color discrimination [23,24,26]. In experimental animal models of DR, increase in apoptosis and thinning of all retinal layers can be detected [21,25,27], suggesting the degeneration of all types of retinal neurons. These observations have established a clear consensus that DR induces functional alteration and degeneration of retinal neurons (Figure 1). However, the mechanisms by which DR-induced alteration of neuronal functions are largely uninvestigated.

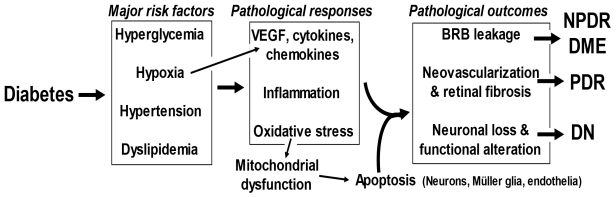

Figure 1) *Simplified pathogenic mechanisms of DR. NPDR: non-proliferative DR; DME: diabetic macular edema; PDR: proliferative DR; DN: diabetic neuropathy.*

Other diabetic complications in the eye

Although not the subject matter in this editorial, it is worth mention that cataract and diabetic glaucoma, two major diabetic complications in the eye (outside the retina), are also leading causes of vision loss. Diabetes-induced cloudiness in lens is the major cause of vision loss in cataract. The biochemical mechanisms of diabetes-induced cataract are similar to that in DR [28]. Diabetic glaucoma, which is defined by elevated ocular pressures, is caused by diabetes-induced iris neovascularization. The risk factors, pathogenic mechanisms, and therapeutic strategies for iris neovascularization are similar to that in retinal neovascularization during the development of DR [29].

Pathogenic mechanisms of DR

Hyperglycemia or high retinal glucose will elevate oxidative stress which causes mitochondrial dysfunction, advanced lipoxidation and glycation end-product accumulation, cytokine and chemokine upregulation, cellular apoptosis, and inflammation (Figure 1) [4-8,30-32]. Eventually, the retina becomes hypoxic that leads to BRB lesions and leakages, neovascularization, and fibrosis [7,8,33]. At present, the mechanisms of diabetes-induced alteration of retinal neuronal functions remain largely unknown, such events occur early and independent from major vascular lesions. Diabetes-induced apoptosis is likely a major cause of retinal neuronal degeneration (Figure 1) [27]. Among the critical molecular and cellular mechanisms, it is worth mention that retinal Müller glia (MG), major retinal supporting cells for retinal homeostasis and pathological responses, are a key cellular entity to coordinate DR responses. MG are a major producer for vascular endothelial growth factor (VEGF), a cardinal pathogenic factor for retinal inflammation, neovascularization, and BRB lesions and leakage in the development of DR [7,8]. MG are also the site for regulating water-balance in the retina [34], a potential diabetes-induced physiological or pathological response that leads to DME. Our recently work suggests that VEGF receptor-2-mediated AKT survival pathway in MG plays a critical role in neuroprotection through MG viability and through the production and action of MG-derived neurotrophins [27,35], such as brain-derived neurotrophic factor (BDNF). BDNF exerts additional MG viability via AKT and ERK, classical survival and proliferation mediators. Moreover, MG-derived VEGF and neurotrophin(s) may work in a synergistic fashion to regulate MG viability in DR and hypoxic retinal disorders [36], which in turn, makes MG healthier and leads to an elevated production of trophic factors for neuroprotection.

Treatment of DR

Treatments of BRB breakdown

Patients with intensive glycemic control has shown a 70-80% reduction in the progression of DR in clinical trials, compared those under normal care [3,37]. Prospective studies suggest that intensive blood pressure control will reduce the risk of DR by 30% [9,10]. Inflammation-reducing steroid hormones and dyslipidemia-controlling fibrates also demonstrate efficacies in reducing DR-induced BRB leakage and breakdown [38,39]. These strategies are effective in treating BRB pathology in DR. For patients not responding to pharmacological interventions for BRB breakdown in DR, the traditional laser photocoagulation can seal specific leaking blood vessels and reduce neovascularization in the retina [40]. In addition, vitreoretinal surgery to remove the jelly-like substance in the vitreous at early stage of PDR is effective in restoring vision [40]. Finally, combinational approaches are not uncommon for treating BRB breakdown in DR.

Anti-VEGF strategy for BRB breakdown

A major accomplishment in the quest for effective treatment of BRB breakdown and neovascularization in DR and other hypoxic retinal vascular disorders is the development of VEGF blockade agents. In general, ocular injected anti-VEGF drugs are effective in reducing BRB pathology and improving visual acuity in DR and neovascular age-related macular degeneration (nAMD) patients [40-42]. Owing to its relatively simple delivery procedure and effectiveness, anti-VEGF treatment has been suggested as a primary therapeutic strategy for a wide range of DR pathologies. However, a significant portion of DME patients does not respond to anti-VEGF therapies [40]. The treatment of BRB breakdown in these patients may rely on alternative therapies discussed above.

Neural degeneration and protection in DR

While treatment of DME with anti-VEGF strategy demonstrates an improvement in best-corrected visual acuity (BCVA) initially, such an improvement is not sustained after long-term therapies [43,44]. The reduced BCVA may be relevant to the loss of retinal and choroidal integrity, as the choroids and retina are significantly thin in some patients [45,46]. A substantial portion of nAMD patients with long-term anti-VEGF therapies appears to have similar morphological changes [47,48]. These clinical studies, along with the observations of anti-VEGF approaches in animal models of DR and hypoxia [49,50], suggest that VEGF plays a protective role in the retina and adjacent tissues in DR and hypoxic ocular disorders. Theoretically, VEGF could be used as a neuroprotectant to treat retinal neuronal degeneration in DR, as discussed earlier [21,25,27]. However, VEGF is a cardinal pathogenic factor and a major therapeutic target for DR and hypoxic retinal vascular disorders. Our work that demonstrates VEGF-mediated MG viability and neuroprotection through the upregulation of BDNF production in MG offers a new avenue for neuroprotection and for safer anti-VEGF therapies in DR [27,35]. As BDNF has been used in clinical trials for neuroprotection in various non-DR-related retinal degenerations [51-53], its safety profile is undisputable. BDNF has also been shown to be effectively in protecting retinal ganglion cells in glaucoma [54,55]. The use of BDNF in conjunction with other neurotrophins or growth factors may be feasible for neuroprotection in DR or during anti-VEGF treatment [36]. As neuroprotection in DR has

not been explored in depth, significant amount of efforts in identifying the therapeutic potential of neuroprotectant singly or in combination may be necessary.

Conclusion

While the prevalence of diabetes and DR has been increased significantly for recent decades, it is encouraging that the number of severe vison loss resulted from DR is actually decreasing due to education, preventive measures, and new diagnostic technologies and therapies. At present, managing DR remains a major challenge. Significant progress is needed in education, patient care, and in research for the genetics and molecular and cellular mechanisms, as well as for the development of new diagnosis and more effective and safer therapeutics. The ultimately goal is to prevent vision loss in DR, a major complication of diabetes.

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Conflicts of Interest

Author declare no conflicts of interest.

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