Review Article

Diabetic Retinopathy: A Comprehensive Literature Review

Rakesh Kumar Gupta [1] Amit Kumar Patel [2] Niranjan Shah [3] Arun Kumar Chaudhary [4] Ajay Narayan Sharma [5]
Uday Chandra Yadav [6] Uday Kant Jha [7] Chutra Bahadur KC [8] Uttam Pakuwal [9]

[1, 3, 4]Department of Biochemistry, National Medical College, Birgunj, Nepal, [2]Department of Pathology and Incharge, Department of Blood Bank, National Medical College, Birgunj, Nepal, [5]Centre for Molecular Dynamics, Kathmandu, Nepal, [6] Kathmandu National Medical College, Kathmandu, Nepal, [7]Department of Pathology, Shri Mithila Ayurveda Medical College and Research, Janakpur, Nepal, [8]Department of Orthopaedics, Delhi Orthopaedic Clinic and Portea Vista Health Care, New Delhi, India
[9]Manmohan Memorial Eastern Regional Hospital, Jhapa, Nepal

Abstract

Diabetes increases the risk for many serious health problems. Diabetic retinopathy is a vision-threatening disease and has long been regarded as a vascular disorder, which is staged clinically according to the proliferative status of the retinal vasculature. The vascular disruptions in diabetic retinopathy are characterized by abnormal auto regulation of retinal blood flow caused by the loss of the pericytes that normally regulate vessel calibre, breakdown of the inner blood-retinal barrier, thickening of the capillary basement membrane and damage, and proliferation of endothelial cells. Among the major factors responsible for the onset and progession of diabetic retinopathy are longer duration of Diabetes, poorer control of blood glucose, and elevated blood pressure. Diabetic retinopathy remains the leading cause of blindness and visual impairment in the working age population. The pathophysiology of diabetic retinopathy has been extensively studied and many contributing biochemical pathways have been identified. In this review, we highlight and discuss Diabetic Retinopathy, its complications, classifications, characteristics, epidemiology, and various risk factors associated with it. At last, we emphasized on Pathophysiology of DR and various biomarkers associated with it.

Keywords: Diabetic Retinopathy - Early Treatment of Diabetic Retinopathy Study - Proliferative Diabetic Retinopathy – Epidemiology – Risk Factors – Pathophysiology – Biomarkers

Introduction

Diabetes Mellitus is the most frequent endocrine disease in developed countries estimated to have affected 366 million people worldwide and is expected to nearly double by 2030 owing to an increase in obesity, life span extension, and better detection of the disease. This global increase has a significant impact on the prevalence of diabetic complications among which diabetic retinopathy (DR) takes an important place.

Diabetic Retinopathy

Diabetic retinopathy (DR), one of the most common eye disease faced by diabetic patients, is a slow progressing vision-threatening disease and has long been regarded as a vascular disorder, which is staged clinically according to the proliferative status of the retinal vasculature.

Classification of Diabetic Retinopathy

A.Modified Airlie House Classification

The first standardized classification of DR was developed in 1987 (Goldberg and Jampol, 1987), which was modified and used in the Diabetic Retinopathy Study (DRS). This same classification was modified for use in the Early Treatment of Diabetic Retinopathy Study (ETDRS). It became the gold standard for many years. The modified Airlie House Classification of DR is based on grading of stereo photographs of 7 fields and classifies DR into 13 complex levels ranging from level 10 (absence of retinopathy) to level 85 (severe vitreous hemorrhage or retinal detachment involving the macula) (Early

Address for correspondence
Mr. Rakesh Kumar Gupta, Assistant Professor of Biochemistry,
National Medical College, Birgunj, Nepal.
E-mail: rakeshkg_biochemistry@yahoo.com

Treatment of Diabetic Retinopathy Study Report Number 10, 1991). It is an excellent tool in the research setting but its clinical applicability is limited due to its complexity. Most ophthalmologists do not use this classification in their daily clinical work.

B. International Clinical Disease Severity Scale for Diabetic Retinopathy

In an attempt to simplify the classification of DR, a number of experts met and created the International Clinical Disease Severity Scale for DR, which is based upon the findings of the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) and the ETDRS (Wilkinson et al., 2003). There are five stages that are recognized. The first is "no apparent retinopathy". As the name implies, there are no diabetic fundus changes. The second stage, "mild non-proliferative retinopathy (NPDR)", is characterized by the presence of a few micro aneurysms. The third stage, "moderate NPDR", is characterized by the presence of micro aneurysms, intraretinal hemorrhages or venous beading that does not reach the severity of the "Severe NPDR", the fourth stage, which is the key level to identify. The final stage is "proliferative diabetic retinopathy (PDR)". PDR is characterized by neovascularization of the disc, neovascularization of the retina, neovascularization of the iris, neovascularization of the angle, vitreous hemorrhage or tractional retinal detachment. With regards to macular edema, it should be noted if macular edema is present or absent. If it is present then it can be further classified as mild, moderate and severe depending on the distance of the exudates and thickening from the center of the fovea.

C.Fluorescein Angiographic Classification

The investigators from the ETDRS recognized that some diabetic features could be assessed better with fluorescein angiograms (FA) than clinical fundus photographs. Thus the ETDRS also classified DR from FA. This fluorescein angiographic classification scheme is time consuming, complex, and ideal for the research setting but not for regular clinical use (Early Treatment of Diabetic Retinopathy Study Report Number 11, 1991). Of the three classification of DR as mentioned above, The International Clinical Disease Severity Scale is simple to use, easy to remember, and based on scientific evidence. It does not require specialized examinations such as Optical coherence tomography (OCT) or FA. It is based on clinical examination and applying the ETDRS 4:2:1 rule. Its use should be encouraged. As new technologies for the evaluation of DR become available, current classification systems may be substituted or enhanced but the basis of DR staging established by landmark clinical trials such as the ETDRS and DRS will most likely remain the same.

Characteristics of Diabetic Retinopathy (DR)

The vascular disruptions in DR are characterized by abnormal auto regulation of retinal blood flow caused by the loss of the pericytes that normally regulate vessel calibre, breakdown of the inner blood-retinal barrier, thickening of the capillary basement membrane, and proliferation of endothelial cells. Another lesion characteristic of DR is capillary occlusion (nonperfusion with retinal ischemia), which may lead to the proliferation of new vessels (neovascularization), seeking out new routes to irrigate the ischemic area. These new vessels are often surrounded by fibrous tissue, and this fibrovascular complex may adhere to the posterior part of the vitreous body. Traction on the vitreous which usually happens with age or with rapid eye movement during sleep can rupture the fragile structure of the new vessels and lead to vitreous hemorrhaging or even retinal detachment. New vessels and fibrous tissue can also close the anterior chamber angle which leads to neovascular glaucoma with severe elevations in intraocular pressure (IOP).

Epidemiology and Socioeconomic Burden of Diabetic Retinopathy

For decades, diabetic retinopathy has remained the primary cause of blindness in adults of working age. It is the most frequent microvascular complication in a person with Diabetes. The relative

risk of developing retinopathy is higher in a person with type 1 Diabetes than with type 2 Diabetes

The overall prevalence of retinopathy was determined as being 35%, the prevalence of proliferative end-stage and of diabetic macular edema was 7%, and that of vision-threatening forms of retinopathy was 10%. Like many other studies before, this metaanalysis confirmed that persons with type 1 Diabetes were more prone to retinopathy development and that disease duration, metabolic control, and blood pressure were the major risk factors. Smoking and male sex have been identified as additional risk factors for any retinopathy in a large European study of type 1 diabetic patients (Hammes et al. 2011). An estimated 28.5% of Americans with Diabetes aged over 40 years have DR and one in 12 patients with Diabetes have advanced vision-threatening DR.

Evidence is emerging from selected cohorts with long-term follow up, such as the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) that the risk of developing any retinopathy and the incidence is declining in groups with more recent disease onset (Klein and Klein, 2010). Even more so, the annual incidence of sight-threatening proliferative diabetic retinopathy was substantially reduced in groups with more recent onset but comparative disease durations (Klein et al., 2010). The risk reduction is brought about by the implementation of timely diagnosis (in the case of type 2 Diabetes), intensified medical therapy of hyperglycemia, hypertension, and dyslipidemia; and by increasing the number of patients treated for advanced disease using photocoagulation (Klein and Klein 2010). Public awareness and available sophisticated technologies for blood glucose monitoring cannot believe the fact that a substantial number of persons with Diabetes still do not meet recommended treatment targets of metabolic and vascular risk surrogate markers.

Racial/Ethnic Differences and Familial Concordance in Diabetic Retinopathy

Racial/ethnic differences in the prevalence of diabetic retinopathy may provide insights into relative importance of genetic or environmental risk factors. A nationally representative sample of adults in the USA with Diabetes aged 40 years and over participating in the National Health and Nutrition Examination Survey found that the prevalence of DR and vision-threatening DR is especially high among racial/ethnic minorities, particularly non-Hispanic black individuals.

The Multi-Ethnic Study of Atherosclerosis (MESA) study reported moderate differences in diabetic retinopathy prevalence among different races: 36.7% in African-Americans, 37.4% in Hispanics, 24.8% in whites, and 25.7% in Chinese-Americans (Wong et al., 2006). Differences in risk factors such as Diabetes duration, glycemic control, and hypertension appears to explain the higher prevalence of diabetic retinopathy in African-Americans, but did not explain the higher prevalence observed in Hispanics compared to whites, suggesting that genetic or cultural factors may play a role in the pathogenesis of diabetic retinopathy.

Another sign of genetic influence is the increased risk of severe diabetic retinopathy among family members with Diabetes (Alcolado et al., 1998); in siblings of affected individuals (approximately 3-fold increased risk) (Leslie and Pyke, 1982); and the moderate heritability of diabetic retinopathy risk. These observations of differential response to risk factors and treatments, racial differences, and familial clustering strongly suggest a role for genetic factors in determining susceptibility to diabetic retinopathy.

Risk Factors for Diabetic Retinopathy

There is already strong evidence that longer duration of Diabetes, poorer control of blood glucose, and elevated blood pressure are the major risk factors responsible for the onset and progression of diabetic retinopathy.

However, it is clinically apparent that some patients with poor control of glycemia or blood pressure do not develop diabetic retinopathy even over prolonged periods of time; while others may develop diabetic retinopathy in relatively short periods of time despite good risk factor control. This was prominently illustrated in the Joslin Medalist study which found that almost 50% of older diabetic participants in their study had no evidence of retinopathy despite surviving over 50 years with type 1 Diabetes.

The newly completed ADVANCE trial in patients with type 2 Diabetes found that even intensive glucose control (to reduce glycosylated hemoglobin to 6.5% or lower) had no effect on the 5-year incidence of retinopathy rates. ADVANCE also reported that lowering of blood pressure to near normal levels (approximately 140/80) did not achieve further reduction in progression of diabetic retinopathy.

Finally, a recent observational study from three diverse populations reported that retinopathy signs, mainly retinal microaneurysms, characteristic of Diabetes, were detectable in 7.4-13.4% of nondiabetic participants and were present even in individuals with glycosylated hemoglobin levels <5.0%. These results suggest that processes other than hyperglycemia and elevated blood pressure contribute to the development and progression of diabetic retinopathy.

Pathophysiology of Diabetic Retinopathy

The pathophysiology of DR is a complex process and a full description is beyond the scope of this review article. Hyperglycemia-induced pericyte death and thickening of the basement membrane lead to incompetence of the vascular walls. As a consequence of this process, the blood–retinal barrier is altered, resulting in an increased permeability of retinal vessels (Ciulla et al., 2003). Hyperglycemia in patients with poorly controlled Diabetes may cause an alteration of hemodynamics of the retinal vasculature, resulting in chronic hypoxia. As a result, compensatory mechanisms will cause an upregulation of the vascular endothelial growth factor (VEGF) as well as other DR-related growth factors and inflammatory factors (e.g., erythropoietin (EPO), hepatocyte growth factor (HGF), basic fibroblast growth factor (bFGF), insulin-like growth factor, and interleukin-6). These effects result in pathologic processes such as retinal capillary microaneurysms, vascular permeability, macular edema, vascular occlusion or closure; and in the proliferative form of DR, neovascularization, vitreous hemorrhage, and tractional detachment of the retina caused by fibrovascular proliferation (Davis et al., 1999). Neuronal function alterations may be one of the first detectable defects in DR; and evidence shows that inflammatory processes may contribute to these changes as well. Processes leading to DR-associated vasculopathy include the entrapment of leukocytes, new capillary formation, and capillary dropout resulting in local hypoxia.

Moreover, in the pathogenesis of diabetic retinopathy, retinal cells, including capillary cells, Müller cells, and ganglion cells undergo accelerated apoptosis and the apoptosis of capillary cells precedes the appearance of microvascular histopathology characteristic of diabetic retinopathy suggesting that accelerated apoptosis can account for the pericyte `drop-out' and formation of `ghosts'

Biomarkers for Diabetic Retinopathy

Prediction of an accelerated course of retinopathy would identify patients in which multifactorial intervention reduces morbidity and mortality. To date, diabetic retinopathy is clinically identified by changes produced through either progressive vasoregression or abnormalities in the blood–retinal barrier, limiting the diagnostic and therapeutic focus to the vascular system. However, it has been established that diabetic retinopathy involves the neuroglial as well as the vascular compartments. Attempts have been made to identify functional changes of the retina which precede microaneurysms, such as blood flow and defects in vascular contractility upon stimulation, but these novel insights have not yet been translated into clinical practice. In fact, high-resolution imaging technique such as spectral domain optical coherence tomography (SD-OCT) is able to predict the incidence of clinical retinopathy (Parravano et al. 2008; Tam et al. 2011); and MRI provides a high-resolution image of the retina and visual pathways to the brain (Bissig and Berkowitz, 2011). Optical coherence tomography (OCT) is also able to identify the loss of ganglion cells in the retina which precedes vascular changes. Novel psychophysical testing is currently being evaluated as future means to predict development of retinopathy. For example, multifocal electroretinogram (mfERG) and frequency doubling technology (FDT) perimetry are being tested for diagnosis and treatment monitoring of DR (Bronson-Castain et al. 2012). As retinal areas that develop neuronal dysfunction found by these tests are more prone to subsequent vascular abnormalities, multiplex testing assessing both the vascular and the neuronal compartments may be more precise in

predicting the course and the visual consequences in DR.

Summary and Conclusions

1. DR is a slow progessing vision-threatening disease and has long been regarded as a vascular disorder.
2. Of the three classification of DR as mentioned above, The International Clinical Disease Severity Scale is simple to use, easy to remember, and based on scientific evidence.
3. The vascular disruptions in DR are characterized by abnormal autoregulation of retinal blood flow and capillary occlusion.
4. DR is more frequent in a person with type 1 Diabetes than with type 2 Diabetes.
5. Longer Disease duration, poorer control of blood glucose, poorer metabolic control, elevated blood pressure, and smoking are the major risk factors for the onset and progression of DR.
6. However, it is clinically apparent that some patients with poor control of glycemia or blood pressure do not develop DR even over prolonged periods of time; while others may develop DR in relatively short periods of time despite good risk factor control.
7. The differential response to risk factors and treatments, racial differences, and familial clustering strongly suggest a role for genetic factors in determining susceptibility to DR.
8. Attempts have been made to identify functional changes of the retina which precede microaneurysms, such as blood flow and defects in vascular contractility upon stimulation, but these novel insights have not yet been translated into clinical practice.

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