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MAJOR REVIEW

Diabetic Macular Edema: Pathogenesis and Treatment

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Abstract. Diabetic macular edema is a major cause of visual impairment. The pathogenesis of macular edema appears to be multifactorial. Laser photocoagulation is the standard of care for macular edema. However, there are cases that are not responsive to laser therapy. Several therapeutic options have been proposed for the treatment of this condition. In this review we discuss several factors and mechanisms implicated in the etiology of macular edema (vasoactive factors, biochemical pathways, anatomical abnormalities). It seems that combined pharmacologic and surgical therapy may be the best approach for the management of macular edema in diabetic patients. (**Surv Ophthalmol** 54:1–32, 2009. © 2009 Elsevier Inc. All rights reserved.)

Key words. AGEs • angiotensin II • blood retinal barrier • clinically significant macular edema • diabetic macular edema • intravitreal steroid injection • laser photocoagulation • leukostasis • micropulse sub-threshold laser • OCT • PEDF • PKC • RAGE • retinal thickness analyzer • steroids • vasoactive factors • VEGF • vitrectomy • vitreoretinal interface

I. Introduction

Diabetic macular edema (DME) is the most common cause of visual impairment in patients with diabetes mellitus and affects approximately 75,000 new patients in the United States every year.[42] The pathogenesis of DME is complex and multifactorial. It occurs mainly as a result of disruption of the blood–retinal barrier (BRB), which leads to increased accumulation of fluid within the intraretinal layers of the macula.[15,43,265]

Hyperglycemia is a major risk factor for development of diabetic retinopathy. It leads to high intracellular levels of glucose, formation of free radicals (oxidative stress), and protein kinase C activation.[360] Chronic hyperglycemia also leads to formation of advanced glycation end products (AGEs), which may be the inciting event for diabetic retinopathy and maculopathy. Accumulation of AGEs in the vitreous and vitreoretinal interface is associated with neurovascular injury seen in diabetic retinopathy. Although disrupted BRB plays a pivotal role in the pathogenesis of DME, altered vitreomacular interface may contribute significantly to the progression of macular edema (explained in detail in section IIC). Other factors such as hypoxia, altered blood flow, retinal ischemia, and inflammation are also associated with the progression of DME. Inflammatory processes, such as increased vascular endothelial growth factor (VEGF) levels, endothelial dysfunction, leuckocyte adhesion, decreased pigment epithelium derived factor (PEDF) levels, and increased protein kinase C production, that cause breakdown of the BRB and increased vascular permeability are upregulated within the diabetic retinal vasculature. Animal studies have shown AGEs to be involved in activation of all these processes.[183,233,276]

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The specific details of pathogenesis of DME are still unclear. Traditionally, diabetic retinopathy has been described to occur due to microvascular injury of the retinal capillaries; however, there is accumulating evidence that retinal neuronal dysfunction may be present much before vascular changes are seen.[7] Alterations in neuronal function, such as prolongation of the implicit time of the b-wave on ERG[28] and apoptosis of retinal neurons, may be seen in early diabetes. Early diabetic retinopathy may be a neurovascular disease of the retina.[28]

A. CLINICAL DESCRIPTION AND CLASSIFICATION

Diabetic macular edema is diagnosed stereoscopically as retinal thickening in the macula using fundus contact lens biomicroscopy. The Early Treatment Diabetic Retinopathy Study (ETDRS) defined DME as retinal thickening or presence of hard exudates within 1 disk diameter of the center of the macula. This definition has been used consistently in most of the diabetes related research studies.[80,190,191] To characterize the severity of macular edema and for treatment guidelines, the term *clinically significant macular edema* (CSME) is used. Macular edema is clinically significant if one of the following conditions is present: retinal thickening at or within 500 μm of the center of the macula; and/or hard exudates at or within 500 μm of the center of the macula if associated with thickening of the adjacent retina; and/or a zone or zones of retinal thickening 1 disk area in size, at least part of which is within 1 disk diameter of the macular center.[80,190]

Diabetic macular edema tends to be a chronic disease. Although spontaneous recovery is not uncommon, 24% of eyes with CSME and 33% of eyes with center-involving CSME will have a moderate visual loss (15 or more letters on the ETDRS chart) within 3 years if untreated.[80,94,95] The incidence of macular edema increases significantly with increasing severity of diabetes in both younger onset and older onset diabetic patients.[188,191]

B. FOCAL VERSUS DIFFUSE DIABETIC MACULAR EDEMA

Clinically significant macular edema is further classified into focal or diffuse, depending on the leakage pattern seen on the fluorescein angiogram (FA). Leakage noted on FA is not synonymous with edema or thickening. The FA is used to identify areas of increased vasopermeability, for example, leaking microaneurysms or capillary beds, and to evaluate retinal ischemia. Leakage on the angiogram does not necessarily indicate retinal edema since extracellular edema requires that the rate of fluid ingress into the retina (i.e., as indicated by leakage on the FA) exceed the rate of fluid clearance from the retina (e.g., via the RPE pump).

In focal CSME,[42] discrete points of retinal hyperfluorescence are present on the FA due to focal leakage of microaneurysms (Fig. 1).[22,83] The discrete leaking microaneurysms are thought to cause retinal thickening. Commonly, these leaking microaneurysms are surrounded by circinate rings of hard exudates. The exudates are lipoprotein deposits in the outer retinal layers.[40] In diffuse DME, areas of diffuse leakage are noted on the FA due to intraretinal leakage from a dilated retinal capillary bed and/or intraretinal microvascular abnormalities (IRMA), and/or (in severe cases) from arterioles and venules without discrete foci of leaking microaneurysms (Fig. 2).[22,83] There may be associated cystoid macular edema (CME). Cystoid macular edema results from a generalized breakdown of the inner BRB with fluid accumulation, primarily in the outer plexiform layer (Fig. 3).[41,179]

Focal DME is characterized by well-defined, discrete areas of leakage from the microaneurysms on the FA, in comparison to diffuse DME, which is characterized by generalized areas of leakage in the area centralis. Furthermore, focal DME is responsive to focal laser photocoagulation, whereas diffuse DME represents a more challenging clinical situation and is refractory to laser photocoagulation in many cases.[86,107,205] Grid pattern of laser treatment may be helpful in certain cases. Compared to those with less severe non-proliferative diabetic retinopathy, the relative risk for diffuse macular edema is 6.2 times greater in patients with very severe non-proliferative diabetic retinopathy and 7.7 times greater in patients with proliferative diabetic retinopathy.[85]

C. EPIDEMIOLOGY

In one study, the incidence of DME over a 10-year period was 20.1% among patients diagnosed before age 30 years (younger onset) and 39.3% among patients diagnosed after age 30 (older onset).[191] Diabetic macular edema, in this study, was defined as thickening of retina within 1 disk diameter of center of the macula. The Diabetes Control and Complications Trial (DCCT) reported that 27% of patients develop macular edema within 9 years of diabetes onset.[12,130,190,191,347] The frequency of DME increases with the duration and the severity of diabetes (Tables 1A, 1B).[189,228]

Older onset diabetic patients have a tendency to develop macular edema earlier in the course of their disease (prevalence: 3–8% with up to 3 years of disease duration) compared to younger onset diabetic patients (prevalence: 0.5% with up to 10