

Diabetic macular edema - a review

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Abstract

Diabetes affects around 220 million people globally. India is aptly regarded as the diabetic capital of the world as it is estimated that by the year 2025, every fifth diabetic would be an Indian. Diabetic retinopathy is the most common microvascular complication in diabetes mellitus causing severe visual impairment. Macular edema is characterized by the accumulation of extracellular fluid in Henle's layer and the inner nuclear layer of the retina as a non specific response to a breakdown in the blood retinal barriers. The origin of the extracellular fluid is from the intravascular compartment. Clinical diagnosis of DME is best made using fluorescein angiography (FA) and optical coherence tomography (OCT) imaging. In DME, OCT scans show hyporeflectivity, due to intraretinal and/or subretinal fluid accumulation, related to inner and/or outer blood-retinal barrier breakdown. OCT tomograms may also reveal the presence of hard exudates, as hyper reflective spots with a shadow, in the outer retinal layers, among others. An elevated blood pressure damages the endothelial cells of the retinal capillary and increase the vessel rigidity thereby increasing the chances of DME. High blood pressure is strongly associated with micro and macrovascular complications in Type II diabetes. High glycosylated hemoglobin (HbA1c) level is a well-known risk factor for DME. Elevated triglyceride and lipid levels increase the risk of DME while normalization of lipid levels reduces retinal leakage and deposition of exudates. Lipid exudation in macular edema is due to the increased vascular permeability and a dysfunctional outer blood retinal barrier. The available management options for the eyes with DME can be categorized into medical interventions and surgical interventions.

Keywords: Intravitreal triamcinolone acetonide, vascular endothelial growth factor.

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INTRODUCTION

Diabetes affects around 220 million people globally (90% type 2 diabetes) (Wei-Chun Chan 2012) and the number might increase to more than 360 million by the next 15 years (Patil M and Dhas S, 2013). India is aptly regarded as the diabetic capital of the world as it is estimated that by the year 2025, every fifth diabetic would be an Indian. Diabetic retinopathy is the most common microvascular complication in diabetes mellitus causing severe visual impairment (Lobo C *et al.*, 2012). Independent of diabetic retinopathy, severe visual impairment among diabetic

patients may also be caused by diabetic maculopathy. Diabetic maculopathy consist of macular edema and ischemia. The edema occurs as a result of breakdown in blood retinal barrier at the level of the perifoveal vessels (Oluleye 2011). Systemic Metabolic conditions like high blood pressure, high blood sugars, high serum cholesterol levels are some of the known factors responsible for Diabetic Retinopathy and Macular Edema (Thomas Ciulla, Armando Amadorand Bernard Zinman, 2003).

Pathophysiology of DME

Factors that determine the occurrence of macular edema are mostly unknown; microangiopathy is the most prevalent pathophysiological sign of DME (Romero *et al.*, 2007). Changes in retinal microvasculature, thickening of the basement membrane of retinal capillary and reduced pericytes are other associated manifestations. The oxygen diffusion mechanism is impaired due to the changes in the microvasculature leading to the production of a biochemical messenger known as vascular endothelial growth factor (VEGF) (Aiello 1994). VEGF may induce retinal vascular permeability through phosphorylation of the tight junctional protein occludin, resulting in the dissolution of the junctional complex

(Antonetti 1998) As a consequence there is increased permeability of retinal vasculature and edema. Macular edema is characterized by the accumulation of extracellular fluid in Henle's layer and the inner nuclear layer of the retina as a non specific response to a breakdown in the blood retinal barriers. The origin of the extracellular fluid is from the intravascular compartment. Since DME is characterized by increased capillary leakage in the main retinal vessels and by alterations in the microcirculation of the macula (Eckhard Zander 2000), prevailing literature suggest that poor metabolic control might be involved in haemodynamic changes of retinal circulation which consequently leads to maculopathy (Grunwald JE,1996)

DIAGNOSIS OF DME

Ocular Diagnosis

DME is an increase in retinal thickness at or within 1 disk diameter of the foveal center, whether focal or diffuse, with or without hard exudates, sometimes associated with cysts. Traditional methods for evaluating macular edema such as stereoscopic fundus photography and contact and non-contact fundus biomicroscopy are not sensitive enough to determine the details of the involved area. Clinical diagnosis of DME is best made using fluorescein angiography (FA) and optical coherence tomography (OCT) imaging.

Fluorescein Angiography

The conventional standard tool for the diagnosis of DME is fluorescein angiography (FA), which is an invasive contrast-assisted modality. Blood retinal barriers in the retina of the normal eye prevent fluorescein from passing through the retina. In DME, however, fluorescein molecules leave the intravascular space to enter the retina. The affected sites show hyperfluorescence in early to mid frames that increases in area and intensity in later frames. FA not only highlights edema for easy visualization and treatment localization, but also creates a permanent record for future comparison. While FA is a sensitive means of identifying the presence of DME, it provides relatively little information regarding the anatomical distribution of the fluid; i.e., diffuse vs. cystic vs. subretinal, and the severity of the leak over time (Ober *et al.*, 2005). FA has been an important method to evaluate DME, and although not considered a screening exam, it provides important information about retinal perfusion, blood-retinal barrier integrity, and new vessel growth. However it provides no quantitative information regarding retinal thickening. Recently, one methodology capable of measuring objective changes in retinal thickness and giving morphological and topographic surface images that has become available is the OCT

which is dramatically changing the landscape of DME diagnostic and follow up.

OPTICAL COHERENCE TOMOGRAPHY (OCT)

OCT is a non-invasive, non-contact imaging technique, well tolerated by patients, that quantitatively determines the retinal thickness and retinal volume. It directs a beam of near infra red light (830-nm) perpendicular to the surface of the retina and captures reflected light from retinal structures and provides cross-sectional images of the retina. It is also useful in visualizing the properties of the vitreoretinal interface and effectively demonstrates when vitreous traction plays a role in the formation of ME. In DME, OCT scans show hyporeflectivity, due to intraretinal and/or subretinal fluid accumulation, related to inner and/or outer blood-retinal barrier breakdown. OCT tomograms may also reveal the presence of hard exudates, as hyper reflective spots with a shadow, in the outer retinal layers, among others (Lobo *et al.*, 2012). One prospective trial examined 314 eyes of diabetic patients to compare the morphological patterns of macular edema clinically on both fluorescein angiography and OCT scanning and reported that the frequency of DME depended on the diagnostic tool being used. The highest frequency (94.5 %) of DME was revealed on OCT (Maalej, 2012). OCT brought new insights about morphological changes of the retina in DME. It showed that macular edema may assume different morphologic patterns (Otani *et al.*, 1999, Kim *et al.*, 2006). Since OCT imaging does not require intravenous administration of fluorescein and directly assesses macular thickness and the presence of intraretinal cysts—the key aspects of DME, hence it has begun to supplant FA as the method most commonly used for evaluation of DME in clinical trials regarding retinal diseases.

Visual Acuity

Visual acuity should also be measured. Although it does not aid in the diagnosis of DME initially, at least, patients may have a visual acuity of 20/20—it is an important parameter in following the progression of macular edema.

CLINICAL AND BIOCHEMICAL DIAGNOSIS

Systemic metabolic conditions like high blood pressure, blood sugars, serum cholesterol, glycosylated haemoglobin and urine albumin creatinine ratio levels are some of the known factors responsible for diabetic retinopathy and macular edema (Ciulla *et al.*, 2003).

Ambulatory Blood Pressure

An elevated blood pressure damages the endothelial cells of the retinal capillary (Olson *et al.*, 2006) and increase the vessel rigidity thereby increasing the chances of DME

(Guan *et al.*, 2006). High blood pressure is strongly associated with micro and macrovascular complications in Type II diabetes. Several studies have proven 24 hours ambulatory BP measurement (AMBP) superior to conventional office BP measurement regarding the association (55-59) and prediction of (60-61) end organ damage in diabetes. Moreover as opposed to office measurement AMBP provides the opportunity to study diurnal fluctuations. Systolic and diastolic blood pressure have been reported were independent and significant risk factors for DME (Gupta *et al.*, 2014).

Glycosylated hemoglobin (HbA1c) level

High glycosylated hemoglobin (HbA1c) level is a well-known risk factor for DME. Glycaemic control is critical in the management of DME and can be assessed by the periodic measurement of glycosylated haemoglobin (HbA1c) levels. Studies reveal significant association of higher levels of HbA1c with the incidence of DME (Klein *et al.* 1995). The Diabetes Control and Complication trial (DCCT) and the UK Prospective Diabetic Study (UKPDS), both of which were prospective randomized studies, showed that intensive glycaemic control and reduction of HbA1c levels are associated with a decrease in the rates of development and progression of diabetic retinopathy (DR) and DMO (UKPDS Group 1998; DCCT/Epidemiology of Diabetes Interventions and Complications Research Group 2000; Higgins *et al.* 2007).

Urine Albumin-Creatinine Ratio (ACR)

The "gold standard" to assess albuminuria is 24-h UAE. Because 24-h urine collection is cumbersome, American Society of nephrology guidelines suggest measuring albuminuria in a first morning void, either as urinary albumin concentration or adjusted for creatinine concentration, the albumin: creatinine ratio (ACR) (Lambers 2008.) The Albumin Creatinine Ratio is done to compare the amount of albumin that is passing into the urine from the kidneys compared with the amount of creatinine present. Although albumin levels can be directly checked in the urine by doing a simple test, the advantage of calculating the ACR is that this ratio remains unaffected by any kind of variation in the concentration in urine. The repeated presence of albuminuria in diabetics' urine samples reveal damage to the glomerular basement membrane and should be considered an early diabetic nephropathy (Miccoli R, 1989).

Total Cholesterol Levels (TCL)

Elevated triglyceride and lipid levels increase the risk of DME while normalization of lipid levels reduces retinal leakage and deposition of exudates. Lipid exudation in macular edema is due to the increased vascular permeability and a dysfunctional outer blood retinal

barrier. Few studies found positive associations between total cholesterol and LDL with diabetic macular edema (Zander *et al.*, 2000; Asensio-Sánchez *et al.*, 2008). However, in a study to compare 3 groups of patients with chronic diabetic macular edema and plaque-like hard exudates, diabetic macular edema and DM patients but without retinopathy, there was no correlation between serum lipid levels and macular edema severity (Ozer *et al.*, 2009).

Blood Sugar level

In a cross-sectional cohort study of 1563 patients of type 2 Diabetes by Zander, Herfurth, Bohletal in 2000, more than half (53%) had maculopathy. (Zander *et al* 2000)

MANAGEMENT OPTIONS FOR DME:

The available management options for the eyes with DME can be categorized into medical interventions and surgical interventions.

Medical Interventions: Non-steroidal anti-inflammatory drugs (NSAID),

Acetazolamide: Oral acetazolamide is given in ME secondary to diabetes.

Intravitreal Corticosteroids

Intravitreal triamcinolone acetonide (IVTA) has been established to considerably lessen severe DME and improves visual acuity (Patelli *et al.*, 2005). The action of the steroid is maximal in the 1st week and lasts till six months. One group of researchers are of the opinion that IVTA can be administered as a primary therapy while others are of view that IVTA can be used as a supplementary therapy to laser photocoagulation (Avitabile *et al.*, 2005). Intravitreal injections of drugs as Triamcinolone acetonide and Flucinolone acetonide are being used in DME but due to their side effects are not widely used (Ober et al, 2005; Oluleye 2011). There are several side effects of IVTA like retinal detachment, cataract and endophthalmitis.

Intravitreal Anti-VEGF drugs

Anti-VEGF agents specifically target vascular endothelial growth factor (VEGF) which causes causing abnormal blood vessels to grow under the retina. Several drugs have been developed that can block the trouble-causing VEGF. An anti-VEGF drug can help treat macular edema by reducing the growth of abnormal blood vessels and slowing their leakage, which helps to slow vision loss. Ranibizumab an intravitreal agent used in the treatment of DME is a 'recombinant humanized antibody fragment' that is active against VEGF, therefore prevents the breakdown of retinal barrier (Nguyen *et al.*, 2006). A small treatment study in DME patients revealed that a 0.5 mg dose of ranibizumab at baseline and again at 1st, 2nd, 4th and 6th month had decreased the macular volume by 60% and a reduction in retinal thickness in a period of 6

months (Blumenkranz, 2007). The various factors that need to be considered with regard to ranibizumab include the optimal dosage and its interval, length of administration, long term adverse effects.

SURGICAL INTERVENTIONS

Laser photocoagulation

Laser treatment has become the gold standard for treating macular edema after the recommendations by the Early Treatment Diabetic Retinopathy Study (ETDRS). The ETDRS set the guidelines for the treatment of DME. The study found that laser reduced the risk of visual impairment from DME by 50%. Laser treatment stopped the progression of further visual impairment in patients with DME for a period of 5 years as compared to those who had no such treatment making it an important modality of treatment. Laser spot of 100microns, Power of 100Mw, and at duration of 100ms is recommended. The slit lamp delivery method with a macular contact lens is preferred. Complications of laser treatment include transient retina edema, accidental foveolar burns, paracentral scotomas, laser scar expansion, subretinal fibrosis and choroidal new vessels (Oluleye 2011). The complications associated with laser treatment can be devastating hence the need for alternative therapy. For microaneurysms and macular edema affecting the center of fovea, laser treatment is not suitable.

Vitrectomy

In vitrectomy, low viscous saline is injected into the vitreous cavity thereby replacing the vitreous fluid. This saline transports oxygen from oxygen rich areas to oxygen depleted regions in the vitreous cavity and simultaneously clears VEGF from the retina into the vitreous. As a consequence there is a decrease in production of VEGF and increase in its clearance hence decreases the pathogenesis of DME (Stefansson 2009). Conclusion: Early recognition and prompt management of macular edema will prevent irreversible visual impairment.

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