Diabetic Macular Edema: The Indian Perspective

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Diabetic retinopathy (DR) is a major cause of preventable blindness in all parts of the world, including developed and developing countries. Diabetic macular edema (DME) is the most common cause of moderate vision loss in patients with DR. A large number of studies including those from India have been published looking at various aspects of DME.

EPIDEMIOLOGY

In the Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR),[1] the prevalence of DR in a diabetic population was reported as being 50.1%. The Diabetes Control and Complications Trial (DCCT) reported a 54.2% incidence of DR in patients with insulin-dependent diabetes mellitus (IDDM) or type 1 diabetes mellitus,[2] while in the United Kingdom Prospective Diabetes Study (UKPDS), the prevalence was 35% to 39% in patients with noninsulin-dependent diabetes mellitus (NIDDM) or type 2 diabetes mellitus.[3] The epidemiological data from India have shown a prevalence of 22.4% among self-reported diabetics in the Andhra Pradesh Eye Disease Study (APDES).[4] In the Chennai Urban Rural Epidemiological Study (CURES),[5] which evaluated 26 000 patients, the prevalence of DR was 17.6% in an urban population. The Sankara Nethralaya Epidemiologic and Molecular Genetic Study (SN-DREAMS)[6] evaluated a sample of 5999 patients in southern India. The prevalence rate of DR in an urban diabetic population was 18%, which correlated with the CURES report. A study of 4067 diabetic patients in Northern India noted the prevalence of DR to be 28.9%.[7] These data suggest that the prevalence of DR appears to differ among populations in India. The incidence of DR also appears to be significantly lower than that noted in western literature. The size of Indian population, however, translates to a significant risk of blindness to a large number of people due to DR.

PATHOGENESIS OF DME

A varied number of metabolic pathways, such as the sorbitol pathway, nonenzymatic glycation, protein kinase C pathway, and growth factors, such as VEGF, have been implicated in the development of DME. These pathophysiological changes lead to microvascular changes such as loss of capillary pericytes, formation of microaneurysms, thickening of capillary basement membrane, and damage to vascular endothelium. Microvascular changes ultimately cause breakdown of the inner blood-retinal barrier leading to leakage of fluid, proteins, and lipids.

Various risk factors have been documented for development and progression of DR and DME. According to the SN-DREAMS study, the duration of DM, gender (male), and insulin treatment were significantly associated with DR prevalence.[6] Although prevalence of DR and DME increased in the fifth and sixth decade of life, it was found to have tapered off in the seventh decade. Factors that did not influence the prevalence of DR were socioeconomic status, smoking status, systemic diseases such as ischemic heart disease or hypertension, family history of diabetes, and the presence of other microvascular complications such as diabetic nephropathy of neuropathy.

Genetic predisposition to development and progression of DR is suggested by some studies but remains poorly understood. Meta-analyses of various genetic studies have shown that certain types of polymorphism of aldose reductase gene are associated with high risk of development and progression of DR while other types have protective effect against DR.[8] Various polymorphisms of VEGF and ACE gene are not seen to be statistically significant with DR.

CLASSIFICATION OF DME

The Early Treatment of Diabetic Retinopathy (ETDRS)[9] study established the term *clinically significant macular*

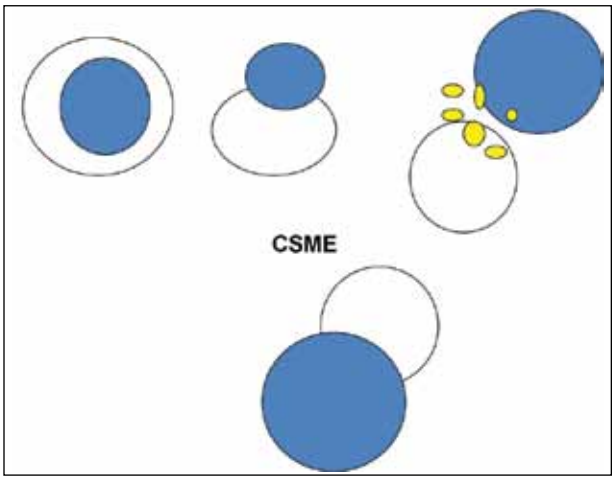

Figure 1. Clinically significant macular edema defined by ETDRS.

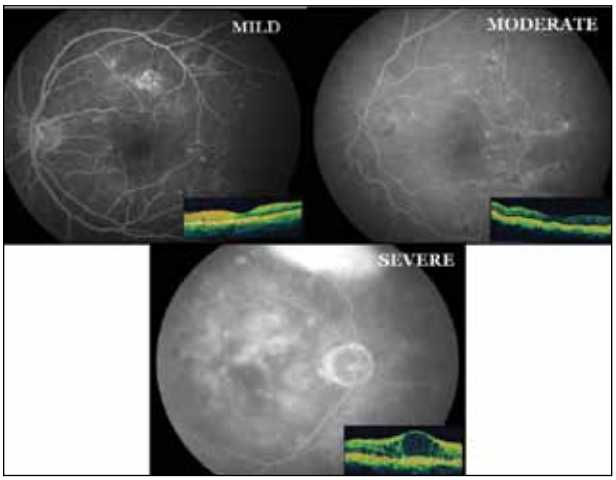

Figure 2. International classification of DME.

edema when edema involves or threatens the center of the macula. Clinically significant macular edema (Figure 1) is defined as:

1. Thickening of the retina at or within 500 µm of the center of the macula.
2. Hard exudates at or within the center 500 µm from the center of macula, if associated with thickening of retina
3. A zone or zones of retinal thickening 1 disc area or larger, any part of which is within 1 disc diameter of the center of the macula.

Newer international classification of DME classifies it into mild, moderate, and severe depending on the proximity of retinal thickening and hard exudates from the center of the macula (Figure 2).

DIAGNOSIS OF DME

Although fluorescein angiography (FA) has been a gold standard in the diagnosis of DME, optical coherence tomography (OCT) is becoming a widely used diagnostic modality, as it allows examiners to assess the type and severity of DME and is useful in posttreatment follow-up in a noninvasive manner.

FA is the only imaging modality that accurately assesses the presence and extent of enlargement of foveal avascular zone depicting macular ischemia. It is also essential for marking leaking microaneurysms, which is important for focal laser photocoagulation. The type of leakage pattern helps to differentiate between different types of macular edema such as diffuse, ischemic, cystoid, or mixed.

OCT generates cross-sectional images of retina by measuring echo-time delay and intensity of reflected light. It gives quantitative measurements of the macula in a noninvasive manner with excellent repeatability. Certain morphological changes are seen in eyes with DME with time-domain OCT (OCT). These are retinal swelling, cystoid macular edema, serous macular detachment, and presence of epimacular traction. Presence of epimacular traction points to the need for surgical management (Figure 3). Studies have shown a significant correlation between the foveal and mean macular thickness and visual acuity. Eyes with higher thickness often have poor visual acuity. Although in eyes with poor visual acuity, foveal thickness might be decreased due to macular ischemia or foveal hard exudates.

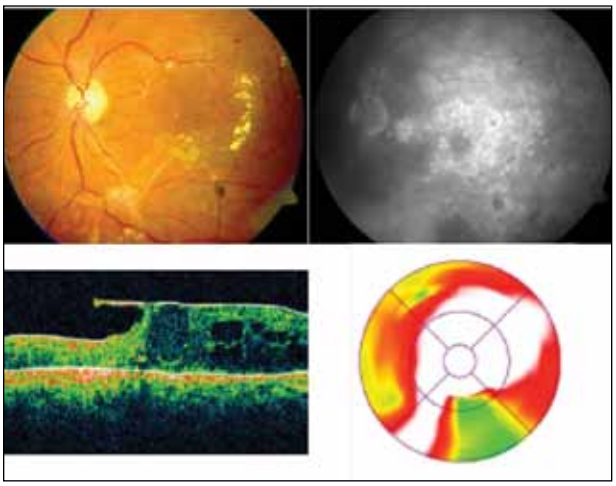

Figure 3. Diffuse DME with taut posterior hyaloids causing vitreomacular traction.

In recent years, spectral-domain OCT (SD-OCT) has been developed, which gives higher-resolution images of macular structures. SD-OCT can accurately evaluate the integrity of inner-outer segment (IS/OS) junction, which is seen as the hyperreflective line just above photoreceptors. Disruption of the IS/OS junction indicates damage to macular photoreceptors. Maheshwary et al[10] have shown a direct relationship between percent disruptions of the IS/OS junction and visual acuity in DME. It is possible to

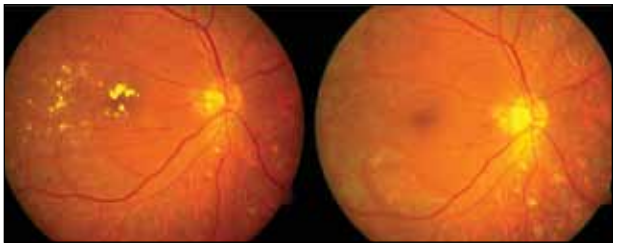

Figure 4. Resolution of macular hard exudates after treatment with systemic atorvastatin.

prognosticate visual outcome in these DME patients prior to treatment with SD-OCT.

SYSTEMIC CONTROL

Systemic control of hyperglycemia, blood pressure levels, hyperlipidemia, and anemia is found to have a beneficial effect on the extent of DME. The highest HbA1c levels of 7.0% are recommended by American Diabetes Association guidelines. Tighter control, although desirable, may be associated with episodes of hypoglycemia. Levels above this value are commonly associated with poor response to laser photocoagulation and bilateral disease. Both WESDR and DCCT have documented the effect of HbA1c levels on occurrence and progression of DME. The CURES study has documented that with every 2% increase in HbA1c levels, there is an increased risk of DR by 1.7-fold. This study doesn't mention its effect on DME.

In the UKPDS, patients with tight control of blood pressure had a 47% reduced risk of losing 3 lines of vision on the ETDRS chart. The WESDR study has also documented higher risk of developing macular edema in patients with poorly controlled diastolic blood pressure. Another study, however, the Appropriate Blood pressure Control in Diabetes (ABCD)[11] study, failed to demonstrate any favorable effect on DME with tighter control of blood pressure levels. The SN-DREAMS study did not find significant correlation between hypertension and DR.

The ETDRS and DCCT studies have found a positive correlation between elevated lipid levels and development of macular edema. A study by Gupta et al[12] from northern India has demonstrated effectiveness of oral atorvastatin therapy in reducing hard exudates and the chance of subfoveal migration of lipids in patients with clinically significant macular edema. They concluded that oral atorvastatin therapy is an effective adjunct therapy in management of DME (Figure 4).

SYSTEMIC PHARMACOTHERAPY

Potential systemic pharmacotherapeutic agents that have generated interest are oral protein kinase C-β inhibitors, aldose reductase, advanced glycation end inhibitors, and antioxidants. Although these agents were found to be effective in in vivo and animal studies, their beneficial effects in a clinical scenario have yet to be seen to a significant extent.

LASER PHOTOCOAGULATION

Guidelines for photocoagulation for macular edema were established by the ETDRS study more than 2 decades ago. In the ETDRS, patients with macular edema along with mild to moderate DR in 1 or both eyes were randomized either to an immediate treatment group or a deferred treatment group. FA was used to identify treatable lesions, which included microaneurysms, intraretinalmicrovascular anomaly, retinal avascular areas outside the foveal center, and diffusely leaking capillaries. Focal laser was applied to leaking microaneurysms. The endpoint of either whitening or darkening of microaneurysms without damage to underlying Bruch's membrane was achieved. Other areas of microvascular abnormality were treated with grid pattern of laser photocoagulation. All lesions up to 2 disc diameters but at least 500 µm away from the center of the fovea were treated.

The following visual benefits were noted:

1. In eyes with clinically significant macular edema, treated eyes had 50% reduction in moderate visual loss at 3 years as compared to the deffered group (15% vs 30%). Moderate visual loss was defined as a loss of 15 or more letters on the ETDRS chart.
2. Eyes with macular edema, but not clinically significant macular edema, had 8% moderate visual loss in the treated group as compared with 14% in the deferred group.
3. In eyes with visual acuity less than 20/40 in the presence of clinically significant macualar edema, laser photocoagulation improved chances of moderate visual gain from 5% to 17%.

ETDRS laser protocol was modified to use a lower power setting. According to modified ETDRS laser photocoagulation protocol, direct treatment of leaking microaneurysms is done while grid laser photocoagulation is applied to other areas of retinal thickening. While performing grid laser photocoagulation, mild-intensity laser spots of 100 to 200 µm are applied with at least 1 burn width between the spots (Figure 5).

INTRAVITREAL AGENTS FOR DME

Intravitreal injection of triamcinolone. Although the efficacy of laser photocoagulation in reducing the risk of moderate visual loss was established by the ETDRS, almost 12% of patients suffered moderate visual loss despite laser. Almost 24% of treated eyes continued to have edema involving the center of the macula at the end of 3-year follow-up, indicating a need for additional treatment options.

Figure 5. Resolution with DME with modified grid laser photocoagulation.

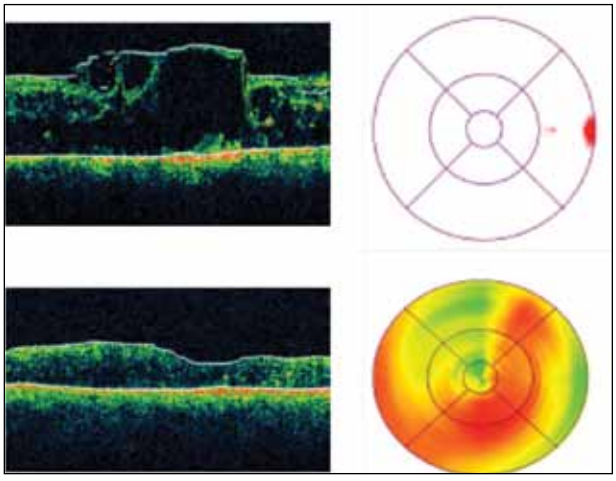

Figure 6. Resolution of chronic DME with single dose of intravitreal triamcinolone acetonide: 4 weeks post injection.

Triamcinolone (9-fluoro, 16-hydroxy prednisolone) has been used as an intravitreal injection. It is shown to provide excellent outcomes in terms of reduction of macular edema and improvement in visual acuity. Intravitreal triamcinolone acts by reducing the expression of VEGF, thereby stabilizing the blood-retinal barrier. The antiinflammatory action of intravitreal triamcinolone helps in regression of macular edema (Figure 6). The most commonly used dose is 4 mg in 0.1 mL.

The limitation of intravitreal triamcinolone is its transient action, with macular edema reappearing once intravitreal triamcinolone crystals disappear from the vitreous cavity. The side effects of intravitreal triamcinolone include rapid progression of cataract and development of glaucoma. In rare cases, endophthalmitis has also been reported after intravitreal triamcinolone injection. With the the advent of newer therapeutic agents, triamcinolone is used as adjuvant therapy.

Dexamethasone intravitreal implant (Ozurdex, Allergan). The dexamethasone intravitreal implant is a biodegradable, sustained-release drug delivery system that releases dexamethasone into the vitreous cavity gradually over a period of several months. It is US Food and Drug Administration-approved for patients with macular edema following retinal vein occlusion (RVO). Currently, a prospective randomized clinical trial is under way to evaluate the efficacy of the dexamethasone intravitreal implant in refractory DME. A report by Rishi et al[13] showed encouraging results with the dexamethasone intravitreal implant for refractory DME in a group of Indian patients. The visual acuity improvement and reduction in central macular thickness was best noted at 1 month. The effect gradually reduced up to 4 months. The authors have suggested repeat injections of the dexamethasone intravitreal implant at 4 monthly intervals instead of 6 monthly as advised in RVO patients.

Anti-VEGF agents. VEGF causes phosphorylation of tight junction proteins between the endothelial cells, thereby increasing vascular permeability and resultant breakdown of the blood retinal barrier, which, in turn, lead to macular edema in diabetic patients. Various studies have shown significantly higher levels of VEGF in the vitreous cavities of patients with diffuse DME than in those with minimal leakage.

The use of anti-VEGF agents in the treatment of diffuse DME has been found to be effective in various studies. A large number of randomized controlled trials have been carried out. A trial conducted by the Diabetic Retinopathy Clinical Research Network (DRCR.net)[14] compared the use of sham injection with prompt laser vs intravitreal ranibizumab with prompt and deferred laser and intravitreal triamcinolone with prompt laser. The rationale of treatment was to continue anti-VEGF injections and laser until stabilization of vision or lack of improvement was noted. Treatment with ranibizumab with either prompt or deferred laser was found to be most effective, with one-third of patients gaining 15 or more letters on the ETDRS chart.

The BOLT study[15] compared an intravitreal bevacizumab injection regimen with focal laser. The group treated with bevacizumab showed median improvement of 8 letters, while the laser group showed a median loss of 0.5 letters at 12 months.

Meta-analyses of randomized controlled trials have been carried out. A study by Virgili et al[16] included 11 studies comparing anti-VEGF therapy against sham treatment, laser photocoagulation, and a combination of anti-VEGF with laser photocoagulation. They concluded that anti-VEGF treatment had a small but definitive benefit over laser photocoagulation. The study could not establish the superiority of any specific anti-VEGF agent over the other. Another meta-analysis was carried out by the Institute of Clinical and Economic Review (ICER) for

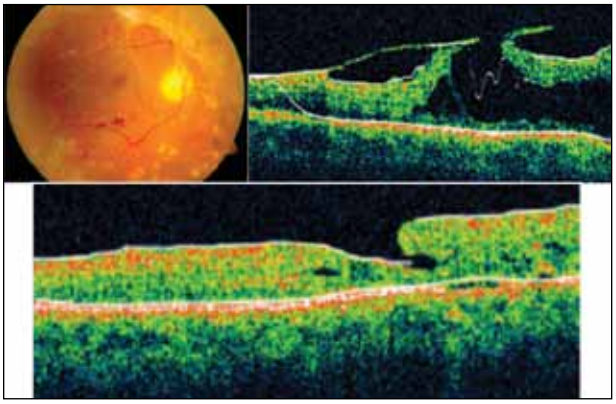

Figure 7. Resolution of tractional DME after vitrectomy.

Medicare Evidence Development and Coverage Advisory Committee (MEDCAC).[17] This study included 15 RCTs and 8 observational case series. It concluded that anti-VEGF therapy was effective in improvement of visual acuity as compared with sham injection or macular laser photocoagulation. The study did not find any difference between efficacy of various agents. Systemic side effects of bevacizumab as compared with other anti-VEGF agents, however, were found to be of uncertain nature.

SURGICAL MANAGEMENT

Vitrectomy has been used extensively in the treatment of DME. It has been used in eyes with or without taut posterior hyaloids. It is thought to act by removal of biomechanical traction as well as by removal of inflammatory mediators such as VEGF and IL-6. Vitrectomy is often associated with additional procedures such as epiretinal membrane and/or internal limiting membrane (ILM) peeeling (Figure 7). Although ILM peeling is associated with better visual outcomes, mechanical removal of hard exudates is found to have mixed outcomes. Although some studies have shown positive outcomes, others have shown that anatomic reduction in macular thickness was not associated with improvement in visual acuity.

The DRCR.net[18] conducted a prospective study to assess the effect of vitrectomy on eyes with moderate visual loss due to DME or vitreomacular traction. It included 87 patients. The median central macular thickness was reduced by 160 µm from a baseline thickness of 491 µm. Sixty-eight percent of the patients had at least a 50% reduction in macular thickness. Visual acuity showed improvement of 10 or more letters on the ETDRS chart between 28% to 49% of eyes, while between 13% and 31% lost 10 or more letters. Although vitrectomy achieved consistent reduction in macular thickness, visual outcomes were inconsistent.

CONCLUSION

DME is a significant cause of moderate visual loss in India's diabetic population. Although relative to Western countries, the prevalence is lower, a large number of patients are affected, thereby immensely increasing disease burden. Successful anatomic and visual outcomes of DME remain an enigma even in the presence of a variety of treatment modalities available.

In the management of DME, strict systemic control is as important as local treatment. The advent of OCT has offered insights into various patterns of DME as well as confirming the presence or absence of vitreous traction on the macula. It helps in planning treatment for individual cases and in follow-up. A wide variety of therapeutic options are available for the treatment of DME. This includes laser photocoagulation, steroids, anti-VEGF agents, and vitrectomy. A combination of treatment modalities may bring the most favorable outcomes. ■

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