Management Corner

Diabetic Macular Edema

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Diabetes mellitus and its systemic and ophthalmic complications represent an enormous public health threat in the 21st century. The ophthalmic complications of diabetes are the leading cause of blindness in adults. Numerous major clinical trials have demonstrated that complications of diabetes, including diabetic eye disease, can be reduced with adequate control of blood glucose, blood pressure, and hemoglobin A1C (Hb_{A1C}) levels, but unfortunately, as many as 30% to 40% of patients with diabetes are currently undiagnosed and are not being monitored and treated to control their disease and prevent systemic complications.

One of the most common causes of vision loss in patients with diabetes is diabetic macular edema (DME). All patients with diabetes are at risk of developing DME. The onset is usually insidious and painless, and manifests with blurring of central visual acuity. The severity may range from mild and asymptomatic to profound loss of vision.

DME is a general term defined as retinal thickening within two disc diameters of the foveal center; it can be either focal or diffuse in distribution. Focal edema is often associated with circinate rings of hard exudates (lipoprotein deposits) resulting from leakage from microaneurysms. Diffuse edema represents more extensive breakdown of the blood-retinal barrier, with leakage from both microaneu-rysms and retinal capillaries. Cystic changes may appear within the macula, representing focal coalescence of exudative fluid.

Clinically significant macular edema (CSME) is a form of DME that was precisely defined by the Early Treatment Diabetic Retinopathy Study (ETDRS). CSME exists if any of the following criteria are met:

- Any retinal thickening within 500 µm of the foveal center;
- Hard exudates within 500 µm of the foveal center that are associated with adjacent retinal thickening (which may lie more than 500 µm from the foveal center);
- An area of retinal thickening at least 1 disc area in size, any part of which is located within 1 disc area of the foveal center.

Making the diagnosis of DME requires a careful ocular retinal examination. The optimal examination technique is biomicroscopy under stereopsis with high magnification. This examination should be performed on all diabetic patients to avoid missing subtle and asymptomatic cases of DME. As adjuncts to clinical examination, both fluorescein angiography and optical coherence tomography (OCT) can be useful in evaluating DME.

The prevalence of DME among diabetics approaches 30% in adults who have had diabetes for 20 years or more, and varies with the stage of diabetic retinopathy. It can occur at any stage of diabetes and can predate the appearance of other findings of diabetic retinopathy. In eyes with mild nonproliferative retinopathy, the prevalence of DME is 3%. This rises to 38% in eyes with moderate to severe nonproliferative retinopathy, and reaches 71% in eyes with proliferative retinopathy. Untreated, 20% to 30% of patients with DME will experience a doubling of the visual angle within 3 years; with current treatment, this risk drops by 50%.

Diabetic retinopathy becomes nearly ubiquitous with long-standing diabetes. After 20 years with the disease, 60% of type 2 diabetics and virtually 100% of

type 1 diabetics will manifest some form of retinopathy. Poor control of blood sugar increases the risk of diabetic retinopathy, and diabetic nephropathy may be a marker for retinopathy. Systemic hypertension is a risk factor for the development of both diabetic retinopathy and DME, and hyperlipidemia increases the risk of leakage and exudative deposits in the macula.

The hallmark of diabetes mellitus is hyperglycemia, and chronic hyperglycemia lies at the root of all complications of diabetes through its detrimental effects on blood vessels, leading to vascular dysfunction and eventually vascular occlusion. Diabetes is likely also a chronic low-grade inflammatory disease, a recent finding that may have important therapeutic implications. Chronic inflammation may also promote vascular dysfunction and occlusion.

Hypoxia is the natural consequence of vascular dysfunction, and local hypoxia occurs in diabetic eye disease as a consequence of retinal vascular dysfunction. In response to local hypoxia, affected tissues in the retina and elsewhere upregulate the production of growth factors, such as vascular endothelial growth factor (VEGF). VEGF is a potent angiogenic stimulus, but it also induces vascular permeability. In fact, VEGF was initially called vascular permeability factor, and its pro-permeability activity has been shown to be 50,000 times more potent than that of histamine. This action of VEGF may be mediated by reductions in the levels of occlusion at tight junctions within the retinal vessels, leading to impaired cellular interactions and adhesion, with resulting breakdown of the blood-retina barrier and accumulation of extracellular fluid.

On a cellular level, hypoxia results in thickening of the basement membrane of the vascular endothelium, and also in a reduction of the supportive pericytes lining retinal blood vessels. These changes also promote incompetence of the retinal vasculature, with leakage of extracellular fluid and the manifestation of macular edema.

The ideal treatment for DME is primary prevention. Prevention does not always work, and retinopathy and DME are often the initial presenting signs of diabetes. Once CSME exists, treatment is recommended. The ETDRS clearly demonstrated that timely treatment with photocoagulation significantly reduces vision loss associated with diabetic retinopathy. In the Diabetic Retinopathy Study (DRS), panretinal photocoagulation reduced the incidence of severe vision loss from proliferative retinopathy by 50%, and macular grid and/or focal photocoagulation reduced the incidence of moderate vision loss from CSME by 50%. Despite laser photocoagulation, however, 12% of eyes with CSME still experienced vision loss of 3 or more lines within 3 years.

Laser photocoagulation became the standard of care in the treatment of DME primarily as a result of the findings of the ETDRS. In general, green wavelength is employed. Other wavelengths have also been utilized; while they may be advantageous in specific cases, there is no evidence that the choice of wavelength impacts visual outcomes. The green wavelength is readily absorbed by hemoglobin, which has the advantage of improved uptake when photocoagulating microaneurysms but may limit its uptake at the level of the retina in eyes with mild or moderate vitreous hemorrhage. In such cases, red or infrared wavelengths, provided by krypton or diode lasers, may be more efficacious and have the benefit of passing more easily through media opacities such as cataracts. In addition, longer wavelengths, such as the 810-nm diode, may be better suited for treatment of diffuse macular edema close to the foveal center, because they can produce deep burns while sparing the inner neurosensory retina, minimizing the risk of perifoveal scotomas.

Laser photocoagulation may work through its absorption by melanin granules in the retinal pigment epithelium (RPE) and choroid and also by hemoglobin especially in microaneurysms. The use of laser photocoagulation results in significant improvement of oxygen supply to the inner retina directly from the choroid, which eventually reduces neovascularization. Microaneurysms, the sources of leakage in DME, are targeted by the laser, and hemoglobin in the microaneurysms absorbs the laser energy. This promotes thrombosis within the microaneurysm, halting further leakage.

In general, laser photocoagulation prevents further vision loss but does not routinely restore vision already lost to DME. Therefore, laser photocoagulation should be performed when a patient is first diagnosed with CSME. Also, panretinal photocoagulation for proliferative diabetic retinopathy can acutely worsen DME. In eyes with both DME and proliferative retinopathy, it is often useful to perform macular treatment at the same time as, or even before, panretinal photocoagulation.

The technique for macular photocoagulation in eyes with DME begins with identifying the areas of retinal thickening and leakage. Fluorescein angiography can be utilized as an adjunct to determine these areas (and areas of nonperfusion). Focal treatment involves discretely treating every identifiable microaneurysm to stop further leakage.

For diffuse macular edema treatment, grid treatment is applied over areas of retinal thickening to promote resorption of existing edema. The foveal avascular zone is fastidiously avoided to prevent central scotomas. Usually, no treatment is placed within 500 microns of the center of the fovea.

The advantages of photocoagulation have been made clear by the ETDRS, in which laser photocoagulation was shown to halve the risk of doubling the visual angle, from 24% to 12% over 3 years. However, macular photocoagulation is not without risks. Complications of macular laser treatment include paracentral scotomas, lateral creep of juxtafoveal laser scars into the fovea, accidental foveal photocoagulation, subfoveal fibrosis, and choroidal neovascularization at the sites of laser scars. In addition, there can be residual massive hard exudates after the resolution of edema, and patients often experience color vision impairment.

In eyes with media opacities precluding photocoaguation, or eyes refractory to photocoagulation, vitrectomy is an alternative approach to treatment of DME. Initially advocated for clearing of media opacities and relief of retinal traction, vitrectomy techniques have advanced, leading to more complex indications for treatment of DME. Vitrectomy facilitates greater blood flow through retinal vessels. Vitrectomy can be useful in eyes with DME if there is evidence of vitreomacular traction. There is a higher rate of posterior vitreous detachment in eyes without DME than in diabetic eyes with DME. Supplementing vitrectomy with the removal of the internal limiting membrane may improve outcomes. Vitrectomy is not without complications. Cataract formation is common, retinal detachments and recurrent vitreous hemorrhage may occur; and intraocular pressure (IOP) may rise, leading to glaucoma.

Inhibition of VEGF has become a topic of interest in recent years in the area of age-related macular degeneration. The properties of VEGF, and the consequences of its inhibition, also suggest a role for this approach in the management of DME.

In the pathophysiologic cascade leading to DME, chronic hyperglycemia leads to oxidative damage to endothelial cells as well as to an inflammatory response. The ensuing ischemia results in overexpression of a number of growth factors, including not only VEGF but also insulin-like growth factor-1, angiopoeitin-1 and -2, stromal-derived factor-1, fibroblast growth factor-2, and tumor necrosis factor. Synergistically, these growth factors mediate angiogenesis, protease production, endothelial cell proliferation, migration, and tube formation. Tumor necrosis factor-alpha (TNF-alpha) and VEGF play a role in the early stages of angiogenesis, with TNF-alpha promoting leukocyte adhesion and VEGF promoting leukostasis, resulting in ischemia. Blockade of all involved growth factors will likely be necessary to completely suppress the detrimental effects of ischemia, but even isolated blockade of VEGF may have beneficial effects on DME. VEGF increases vascular permeability by relaxing endothelial cell junctions, which increases permeability and leakage. Inhibition of VEGF blocks this effect to some extent.

Pegaptanib sodium (Macugen) is an anti-VEGF aptamer, a small piece of RNA that self-folds into a shape that binds to and blocks the effects of VEGF, one isoform of the VEGF family of molecules. The drug is approved by the FDA for the treatment of age-related macular degeneration, and it has recently been studied in a trial for DME.

Ranibizumab (Lucentis) is an antibody fragment that also binds and blocks the effects of VEGF. Unlike pegaptanib, ranibizumab binds and inhibits all isoforms of VEGF. Ranibizumab is also approved by the FDA for the treatment of age-related macular degeneration.

Bevacizumab (Avastin) is the full antibody from which ranibizumab is derived. This anti-VEGF molecule is FDA approved for systemic treatment of metastatic colon cancer, but not for any ophthalmic indications. Its use in conditions such as age-related macular degeneration, diabetic retinopathy, and DME is currently off-label.

Anti-VEGF therapy for DME shows promise in preliminary studies. Larger studies are ongoing. VEGF inhibition may represent an important component of DME therapy in the future. Improvements in drug delivery will be necessary in order to avoid repeated intravitreal injections and the cumulative risk of endophthalmitis associated with this route of administration.

Increasingly, corticosteroids have been employed to treat macular edema. Recently, intravitreal injection of triamcinolone acetonide has become a popular treatment, subsequently, a number of corticosteroid-based intravitreal implants have been developed to provide a sustained release of drug and make repeated intravitreal injections unnecessary. Currently following corticosteroid-based intravitreal implants are under development:

Dexamethasone implant is a small biodegradable pellet designed to be injected in the operating room or the examination lane using a 20-gauge needle through the pars plana, delivering the drug in sustained release over approximately 1 month. A statistically significant reduction in both central macular thickness and leakage by fluorescein angiography was also seen in implanted eyes versus controls, with a notable dose-response effect favoring the higher dose.

Triamcinolone acetonide has been reported to be effective in the management of macular edema, because it suppresses inflammation, reduces extravasation of fluid from leaking blood vessels, inhibits fibrovascular proliferation, and down-regulates production of VEGF. Triamcinolone can be administered by several routes, including intravitreal depot injection, periocular injection, posterior subtenon injection, and intravitreal implant. After depot injection, corticosteroid action peaks at 1 week, with residual activity persisting for 3 to 6 months. Intravitreal injection of triamcinolone is associated with significant adverse events, including elevated intraocular pressure in up to half of injected eyes and cataract formation, as well as injection-related complications such as endophthalmitis and retinal detachment. Periocular injections reduce the risk of serious complications such as endophthalmitis, but the duration of effect is shorter, and the therapeutic efficacy of triamcinolone administered by this route against DME is unclear.

Fluocinolone acetonide has also been incorporated into an implant and has several properties that make it a logical choice for incorporation into a sustained-release drug delivery device. The drug has low solubility, ensuring slow delivery of drug over a long period of time and increasing the useful lifespan of the device once implanted. The low solubility also decreases the amount of corticosteroid in the anterior chamber as the drug will preferentially clear by passing out through the retina – more soluble compounds will achieve higher aqueous levels. Fluocinolone acetonide is a potent corticosteroid, which reduces the amount of drug required to be incorporated into the device, consequently minimizing device size. Furthermore, fluocinolone acetonide has a short half-life in the systemic circulation, reducing the likelihood of systemic side effects. The fluocinolone acetonide intravitreal implant is FDA approved for the treatment of chronic noninfectious posterior segment uveitis.

Corticosteroid-based intravitreal implants provide effective treatment for DME while avoiding the risks associated with repeated transscleral injections into the eye. Implants under investigation utilize corticosteroids with different properties, which will ensure that the best compounds are utilized in the final implants approved for public use. Larger studies are needed to clarify the long-term safety and efficacy profiles of some of these implants.

CONCLUSION

Diabetic macular edema represents a significant public health challenge. Many patients are undiagnosed and untreated, and even those treated with standard therapy may respond poorly and progressively lose vision. Insight into the pathophysiology of DME has led to novel treatments, including anti-VEGF and corticosteroid-based treatment strategies. Drug delivery into the vitreous cavity remains an important limitation of many of these new treatments, as the risks of endophthalmitis, retinal detachment, and other adverse events become cumulative with repeated intravitreal injections. Injectable and/or implantable drug delivery devices may offer the benefits of chronic therapy while reducing the adverse events associated with repeated drug delivery.