RECENT DEVELOPMENTS IN THE TREATMENT OF DIABETIC MACULAR EDEMA

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Diabetic macular edema is the most common cause of moderate visual loss in patients with diabetes. It is believed that macular edema accounts for approximately 50% of patients with diabetes with symptoms of blurred vision seeking care in an eye clinic. Macular edema may be the first symptom of diabetic retinopathy and may be associated with proliferative or non-proliferative (background) retinopathy. Based on data from the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), it is estimated that, of approximately 7.8 million patients affected with diabetes in 1993, 95,000 are expected to develop macular edema annually. This problem presents a significant form of impairment for working patients with diabetes since it may affect their ability to read and to drive and to maintain a productive career.

Macular edema results from the breakdown of the blood-retinal barrier in the retinal capillaries. The tight endothelial cell junctions break down resulting in increased vascular permeability and increased fluid accumulation in the outer layers of the retina. Microaneurysms are believed to play a significant role by acting as sources for fluid and lipid transudation. Factors that are believed to cause the formation of microaneurysms are loss of pericytes and supporting astrocytes in the retina, increased capillary transmural pressure, and local production of vasoproliferative factors such as vascular endothelia growth factor (VEGF). Hyperglycemia is believed to be the main factor that causes increased oxidative stress, the accumulation of advanced glycation endproducts, and generation of diacylglycerol. The substances activates protein kinase C which in turn increases VEGF expression.

Clinically the findings in patients with diabetic macular edema are micraneurysms, dot and blot hemorrhages, and lipid (hard) exudates. These result in areas of retinal thickening around the macula and cystic changes in the macula. In advanced stages, there may be atrophy of the pigment epithelium or fibrous changes within the central foveal area. Sometimes lipid deposits surround a group of actively leaking microaneurysms in a circinate pattern (circinate rings). When exudates occupy the foveal area it is believed that permanent visual loss will occur even if the exudates reabsorb after treatment. In other cases, diffuse macular edema may also occur. In this condition there is diffuse leakage from capillaries surrounding the macular, without identifying specific focal areas of leakage. This type of edema is more recalcitrant to treatment by laser photocoagulation. The Early Treatment Diabetic Retinopathy Study (ETDRS) defined the term “clinically significant macular edema” to include the following characteristics:

1. Thickening of the retina at or within 500 microns of the center of the macula
2. Hard exudates at or within 500 microns of the center of the macula if associated with thickening of the adjacent retina
3. A zone or zones of retinal thickening 1 disk diameter (DD) or larger, any part of which is within 1DD of the center of the macula

Fluorescein angiography is used in the diagnosis and treatment of diabetic macular edema. The dye is injected intravenously and demonstrates the retinal capillary circulation and areas of increased vascular permeability that is associated with macular edema. This is used to guide laser therapy when indicated. A new diagnostic modality most useful in the diagnosis and treatment of macular edema is optical coherence tomography (OCT). This modality uses a low intensity infrared laser to scan the

retina, and using reflectance interferometry, images of the retina are obtained that appear similar to a histologic section of the macula. In diabetic macular edema, the macular thickness can be several times normal and the cystic spaces of fluid accumulation are easily demonstrated. This tool is gradually replacing most methods of assessing the treatment response to any treatment modality for diabetic macular edema.

Systemic factors that may contribute to the progression of diabetic retinopathy and macular edema are blood glucose control, hypertension, and nephropathy and proteinuria. The Diabetes Control and Complications Trial (DCCT), a randomized, controlled clinical trial involving 1441 patients demonstrated that improved glucose control resulted in a lower rate of progression of diabetic retinopathy, a lower incidence of clinically significant macular edema, and less frequent need for laser photocoagulation. The United Kingdom Prospective Diabetes Study (UKPDS) showed in type 2 diabetes that better glucose control over a twelve year period reduced the progression of retinopathy from 48.7% to 38.6%. Tight control of blood pressure with atenolol or an angiotensin converting enzyme inhibitor reduced the progression of diabetic retinopathy by 34% and a reduction of visual loss by 47% over a 7.5 year period. While little can be done to control the rate of progression of proteinuria, it seems prudent to consider the use of an ACE-inhibitor and frequently monitor the blood pressure in patients with diabetic retinopathy and nephropathy.

The classic form of treatment of for diabetic macular edema is laser photocoagulation. The ETDRS showed that focal/grid photocoagulation reduced the rate of moderate visual acuity loss by 50% in patients with CSME. Moderate visual loss is defined as a doubling of the visual angle, e.g. from 20/40 to 20/80. However while laser photocoagulation reduced the rate of progression of visual loss, once visual acuity was already reduced, eyes treated with laser were unlikely to improve to 20/40 or better. Also, the degree of visual gain following laser is moderate, and may take months to occur. These observations have led to the search for other new approaches for the treatment of diabetic macular edema, both primary cases and those not responding to laser photocoagulation.

In some cases it is believed that vitreous traction plays a role in the development of DME. A thin epiretinal membrane forms on the retinal surface resulting in tangential traction. Surgical removal of the membrane has resulted in reduction of edema and a modest improvement of visual acuity.

More promising is the pharmacologic treatment of diabetic retinopathy. Currently clinical trials are in progress to study the efficacy and safety of PKC inhibitors administered systemically. Early reports appear promising. In addition, recent trials are starting for local treatment of diabetic macular edema using intravitreal injection of triamcinolone. These new treatment modalities offer potential for medical treatment and possibly better visual outcomes.

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