Recent trends in management of Diabetic Macular Edema

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Of Master degree in Ophthalmology

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Introduction

Diabetic macular edema (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. Cystic changes may appear within the macula, representing focal coalescence of exudative fluid giving rise to what is called cystoid macular edema ***(Khan & Lam, 2006).***

DME is a leading cause of legal blindness in patients with type 2 Diabetes. The prevalence of DME among US 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 ***(Klein R et al., The Wisconsin epidemiologic study of diabetic retinopathy, 1991).***

Retinal hypoxia is the natural consequence of retinal vascular dysfunction associated with diabetic eye disease. In response to local hypoxia, affected tissues in the retina and elsewhere

upregulate the production of vascular endothelial growth factor (VEGF). VEGF is a potent angiogenic stimulus, and it also induces vascular permeability up to 50,000 times more potent than that of histamine. This will result in breakdown of the blood-retina barrier and accumulation of extracellular fluid with the subsequent development of macular edema ***(Ferrara & Gerber, 2003).***

The onset of DME is usually insidious and painless, and manifests with blurring of central visual acuity, which may range from mild and asymptomatic to profound loss of vision. 25-30% of patients with CSME exhibit a doubling of the visual angle within 3 years if left untreated. Also, metamorphopsia is a significant symptom of diabetic macular edema ***(Khan & Lam, 2006).***

It should be noticed that DME is a clinical diagnosis and according to the definition stated by the Early Treatment Diabetic Retinopathy Study (ETDRS) clinically significant macular edema CSME is said to exist 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 ***(Khan & Lam, 2006).***

Fundus Fluorescein angiography (FFA) is generally used for confirmation of the diagnosis and treatment planning. The method is useful in detecting early alterations of the blood-retinal barrier, capillary closure, and microaneurysm formation. The major advantage of FFA is its ability to detect macular ischemia denoted by non-perfusion of the retinal capillaries and to detect subtle DME as evidenced by fluorescein leakage from the capillaries ***(Cunha-Vaz, 2000).***

Optical coherence tomography (OCT) is an imaging technique that produces high resolution cross sectional images of optical reflectivity. OCT in the setting of diabetic macular edema may be useful in the evaluation of the following:

1. Presence and size of retinal thickening.
2. Proximity of retinal thickening to the center.
3. Presence or absence of cyst formation.
4. Presence or absence of clinically significant macular edema (ETDRS definition).
5. Assessment of the efficacy of newly introduced treatments of diabetic macular edema.

6. Provides insight about the vitreoretinal interface, such as whether or not the posterior hyaloid is detached or thickened or creating traction on the retina ***(Hee et al, 1995)***.

The ideal treatment for DME is *primary prevention*. However, prevention alone does not always work. Once CSME exists, treatment is recommended. ***Laser photocoagulation*** became the standard of care in the treatment of DME primarily as a result of the findings of the ETDRS, which prevents further vision loss as it prevents doubling of the visual angle by 50% but does not routinely restore vision already lost to DME. Therefore, laser photocoagulation should be performed when a patient is first diagnosed with CSME ***(Early Treatment Diabetic Retinopathy Study, 1995).***

Increasingly, ***intravitreal corticosteroids*** have been employed to treat macular edema. Recently, Intravitreal triamcinolone (IVTA) has been shown to significantly reduce macular edema and to improve visual acuity, particularly when the macular edema is pronounced, subsequently, a number of corticosteroid-based intravitreal implants have been developed to provide a sustained release of drug and make repeated intravitreal injections unnecessary. However, intraocular tension had increased in 30-40% of cases, which was considered as a major side effect although it can be medically controlled. Other side

effects include 1% chance of retinal detachment, cataract, and endophthalmitis ***(Jonas et al., 2003).***

Anti-VEGF therapy for DME shows promise in preliminary studies. 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. Anti-VEGF agents include ***Pegaptanib sodium (Macugen®)***, ***Ranibizumab (Lucentis™)***, ***Bevacizumab (Avastin®)***. Pegaptanib sodium is an anti-VEGF aptamer that binds to and blocks the effects of $VEGF_{165}$, one isoform of the VEGF family of molecules. It was found that mean visual acuity has been improved to 20/50 after 36 weeks from intravitreal injection of 0.3mg Pegaptanib sodium; also mean central retinal thickness decreased by 68 μm ***(Macugen Diabetic Retinopathy Study Group, 2005).*** Bevacizumab is the full antibody from which ranibizumab is derived. It was initially used for systemic treatment of metastatic colon cancer. Later on, it was proved to treat macular edema secondary to central retinal vein occlusion as evidenced by decrease in mean central macular thickness by about 500 microns and improvement of mean visual acuity from 20/600 to 20/138 at 3 months after the initial intravitreal injection. However, its role in treatment of DME is still negotiable and under clinical trials ***(Iturralde et al., 2006).*** Ranibizumab is an antibody fragment derived from the full antibody molecule of

Bevacizumab that also binds and blocks the effects of all isoforms of VEGF unlike pegaptanib. It was found that mean central retinal thickness was reduced by 198 μm after 3 months of intravitreal injection of Ranibizumab ***(Chun et al., 2006).***

Vitrectomy can be useful in eyes with DME if there is evidence of vitreomacular traction ***(Lewis, 2001).***

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Aim of Work

This review of literature aims to elicit the role of the recent lines of management of ***diabetic macular edema*** regarding the modality, the efficacy, and the stability of the condition following administration of each.

Anatomy of the macula

Gross anatomy:

The retina (nervous coat) is the innermost delicate layer of the eye that is responsible for photochemical transduction of light into nerve impulses and measures approximately 42 mm in diameter and varies in thickness from about 0.56 mm near the optic disc and 0.1 mm at the ora serrata ***(Snell & Lemp, 1997).***

The macula (macula lutea) is defined anatomically as the area of the central retina that measures approximately 5.5 mm in diameter and is located approximately 4mm temporal and 0.8 mm inferior to the center of the optic disc. Clinically, the macula is identified as the yellow, capillary-free zone temporal and slightly below the center of the optic nerve head. The yellow color of the macula is due to its content of two xanthophyll pigments, lutein and zeaxanthin. Histologically the macula is subdivided into the fovea, foveola (foveal pit), parafovea, and perifovea and the umbo ***(Snell & Lemp, 1997).***

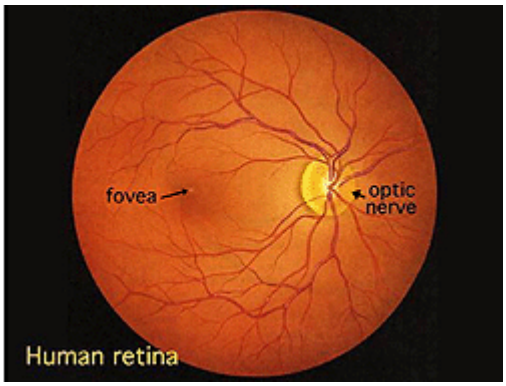

Fig.1 Retina as seen by the ophthalmosope ***(quoted from Rootatlas.com)***

The central fovea (fovea centralis) is a small pit in the vitreal surface of the retina (fig.1). The fovea is approximately 1.5mm in diameter and the depth of the fovea is about 0.25 mm. The foveal avascular zone (FAZ) is a landmark in flourescin angiography and represents the area of the central fovea and measures about 0.25 mm to 0.6 mm in diameter ***(Gass, 1997).***

The foveola (foveal pit) lies in the center of the fovea where thickness is reduced to approximately 0.13 mm as the inner nuclear layer, the inner plexiform, ganglion cell, and nerve fiber layers are absent from the pit and the photoreceptor layer contains only cones. This rod-free zone measures about 350-600 micron in diameter. The sloping sides of the foveal pit are called **the clivus** ***(Gass, 1997).***

The parafovea (foveal rim) is next to the foveola and is approximately 0.5 mm wide and about 2.5 mm in diameter. This is the thickest part of the retina due to lateral displacement into this region of ganglion cells and inner nuclear layer neurons during development of the fovea ***(Gass, 1997).***

The perifovea is the outermost region of the macula and measures 1.5 mm in width. This region ends where ganglion cells are reduced to a single row, as found elsewhere in the retina (fig.2) ***(Gass, 1997).***

The umbo is a tiny depression located at the very center of the foveal pit and corresponds for the foveal reflex ***(Kanski, 1997).***

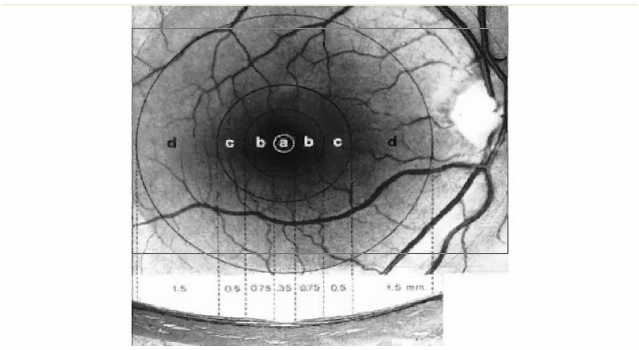

Fig.2: Fundus photograph shows a.foveola b.fovea c.parafovea d.perifovea ***(quoted from Gass, 1997)***

Microscopic anatomy of the retina:

Based on the light microscopic findings, the whole retina is said to be composed of 10 layers which are from outside inward: the retinal pigment epithelium, the photoreceptors, the external limiting membrane, the outer nuclear layer, the outer plexiform layer, the inner nuclear layer, the inner plexiform layer, the ganglion cell layer, the nerve fiber layer, and the internal limiting membrane (Fig.3) ***(Kolb, Fernandez& Nelson, 2003).***

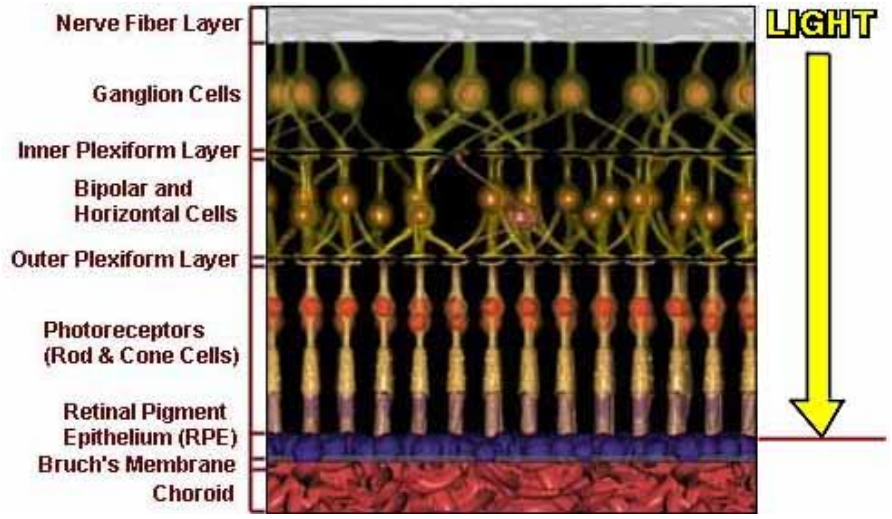

Fig.3 Diagram shows the 10-layered structure of the retina

(quoted from Kolb, Fernandez& Nelson, 2003)

It should be noted that the macular area is made up of only four layers of these ten, the retinal pigment epithelium, the photoreceptors, the external limiting membrane and the internal limiting membrane while the nerve cells and fibers of the inner

layers of the retina are displaced peripherally and this explains the relative thinness of the macular area in comparison with the rest of the retina.

Blood supply of the retina:

There are two sources of blood supply to the retina: the central retinal artery and the choroidal blood vessels. The choroid receives the greatest blood flow (65-85%) and is vital for the maintenance and nourishment of the outer five retinal layers (particularly the photoreceptors) and the remaining 20-30% flows to the retina through the central retinal artery to nourish the inner five retinal layers. The central retinal artery has 4 main intraretinal branches each one supplies a quadrant of the retina with no overlap or anastomosis between branches within a quadrant ***(Zhang, 1994).***

The 4 main intraretinal branches supply three layers of capillary networks whose walls are lined by non-fenestrated endothelial cells with numerous pericytes beneath the endothelial basement membrane. These capillary networks are the radial peripapillary capillaries (RPCs), an inner and an outer layer of capillaries. The radial peripapillary capillaries are the most superfical layer of capillaries lying in the inner part of the nerve

fiber layer, and run along the paths of the major superotemporal and inferotemporal vessels 4-5 mm from the optic disc. The RPCs anatomose with each other and with the deeper capillaries. The inner capillaries lie in the ganglion cell layers under and parallel to the RPCs. The outer capillary network runs from the inner plexiform layer to the outer plexiform layer thought the inner nuclear layer ***(Zhang, 1994).***

As noticed from the fundus flourescein angiography, there is a ring of blood vessels in the macular area around a blood vessel- and capillary-free zone 450-600µm in diameter, denoting the foveal avascular zone (FAZ) (Fig.4). The macular vessels arise from branches of the superior temporal and inferotemporal arteries. At the border of the avascular zone, the capillaries become two layered and finally join as a single layered ring. The arteries tend to lie superficial i.e toward the vitreal surface to the veins. The venules arise from the capillary networks and join each other to form the large superficial retinal veins, which finally drain into the central vein of the retina ***(Snell, 1997).***