Correlation of visual acuity with optical coherence tomography findings in diabetic macular edema

Thesis
Submitted for Partial Fulfillment of Master Degree of Ophthalmology

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2011

Acknowledgment

*First and foremost, I thank **Allah** the most gracious, the most merciful, for blessing this work until it reached its end as a part of his generous gifts throughout my life.*

*I wish to express my sincere thanks and deepest gratitude to **Prof Dr Alaa Fathy Mahmoud** "Professor of Ophthalmology, Faculty of medicine, Ain Shams University" and **Dr Tamer Fahmy Eliwa"Lecturer of Ophthalmology, Ain shams University"** for their kind supervision, constructive guidance, continuous encouragement and the valuable advice they offered me to achieve this work.*

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List of abbreviations

ATP	Adenosine-5'-Triphosphate
BBB	Blood Brain Barrier
BRB	Blood Retinal Barrier
CME	Cystoid Macular Edema
CMT	Central Macular Thickness
CRT	Central Retinal Thickness
CSME	Clinically Significant Macular Edema
DAG	Diacylglycerol
DCCT	Diabetes Control And Complications Trial
DME	Diabetic Macular Edema
DR	Diabetic Retinopathy
DRCR NET	Diabetic Retinopathy Clinical Research Network
ETDRS	Early Treatment Of Diabetic Retinopathy Study
FA	Fluorescein Angiography
FAZ	Foveal Avascular Zone
FDA	Food And Drug Administration
FFA	Fundus Fluorescein Angiography
ILM	Internal Limiting Membrane
INL	Inner Nuclear Layer
IOP	Intraocular Pressure
IS	Inner Segment
LM	Light Microscope
MT	Macular Thickness
No	Number

NPDR	Non Proliferative Diabetic Retinopathy
NFκB	Nuclear factor kappa-light-chain-enhancer of activated B cells
OCT	Optical Coherence Tomography
ONL	Outer Nuclear Layer
OPL	Outer Plexiform Layer
OS	Outer Segment
PDR	Proliferative Diabetic Retinopathy
PKC	Protein Kinase C
PKC-DMES	Protein Kinase C Inhibitor Diabetic Macular Edema Study
PPV	Pars Plana Vitrectomy
PROS	Photoreceptor Outer Segment
PVD	Posterior Vitreous Detachment
RCT	Random Clinical Trial
RPE	Retinal Pigment Epithelium
RT	Retinal Thickness
SD	Standard Deviation
SD-OCT	Spectral Domain Optical Coherence Tomography
SR	Subretinal
TD-OCT	Time Domain Optical Coherence Tomography
TGF	Transforming Growth Factor
TJ	Tight Junction
TNF	Tumor Necrosis Factor
VEGF	Vascular Endothelial Growth Factor
VMTS	Vitreomacular Traction Syndrome

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Introduction

Diabetic retinopathy (DR) is one of the major complications of diabetes mellitus, which can eventually lead to blindness. DR affects up to 80% of all patients who have had diabetes for 10 years or more. Despite these intimidating statistics, research indicates that at least 90% of these new cases could be reduced if there was proper and vigilant treatment and monitoring of the eyes **(*Tapp et al, 2003*)**.

DME is increasing in prevalence throughout the world. In cross-sectional studies, the prevalence of DME in patients with diabetes has been reported to be 1.0–5.7%. The prevalence of DME in patients with diabetic retinopathy has been reported to be 2.7–11.0% ***(Xie et al, 2008)***.

Retinal hypoxia is the natural consequence of retinal vascular dysfunction associated with diabetic retinopathy. In response to local hypoxia, affected tissues in the retina and elsewhere upregulate the production of vascular endothelial growth factor (VEGF). VEGF is not only a potent angiogenic stimulus, but 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, 2003*)**.

The onset of Diabetic Macular Edema (DME) is usually insidious and painless however, patients with macular edema may complain from impairment of central vision which is the main symptom (positive scotoma),

metamorphopsia, micropsia and macropsia. Clinical examination includes visual acuity, which is the most important test of macular function and amsler grid which evaluates 10 degrees of the visual field surrounding fixation and is useful for both screening and monitoring of macular diseases **(*Hainsworth, 2005*).**

Common methods of evaluating clinically significant macular edema (CSME) include slit-lamp biomicroscopy, with contact or non contact lens, indirect ophthalmoscopy, and fundus stereophotography. CSME was defined according to the Early Treatment of Diabetic Retinopathy Study (ETDRS) classification protocol as existence of any of the following criteria:

(A) Presence of any retinal thickening within 500 μm of the foveal center.

(B) Hard exudates within 500 μm of the foveal center with adjacent thickening.

(C) An area of thickening > 1 Macular Photocoagulation Study disc area (1 disc area ≅ 1.767 mm2) within 1 disk diameter (1.5 mm) of the foveal center. However, none of these methods provides an objective quantitative measurement of CSME **(*ETDRS, 1985*)**.

Fundus Fluorescein angiography (FFA) has been used to detect leakage of fluorescein from microaneurysms and other leakage sources in diabetic retinopathy. The major advantage of FFA is the ability to detect early alterations of the blood retinal barrier (BRB), capillary closure and microaneurysm formation ***(Cunha-Vaz, 2000)***. However, FFA does not assess the function of the retinal pigment epithelial pump, thus the correlation of fluorescein leakage with macular thickening is modest ***(Sander et al, 2008)***.

Optical coherence tomography (OCT) provides high-resolution (5 microns) imaging of the vitreoretinal interface, retina, and subretinal space. Optical coherence tomography can be useful for quantifying retinal thickness, monitoring macular edema, and identifying vitreomacular traction in selected patients with diabetic macular edema. However, optical coherence tomography measures of retinal thickness correlate poorly with visual acuity **(*Strom et al, 2002*)**.

Although fluorescein angiography has been used to assess vascular leakage qualitatively in macular edema, optical coherence tomography (OCT) can offer high-resolution cross-sectional images of the retina and quantitative measurement of the retinal thickness. Therefore, the physiologic aspect of clinically significant diabetic macular edema can be assessed with fluorescein angiography, and the anatomical features of clinically significant diabetic macular edema such as the extent of thickening and the retinal layer involved can be assessed with OCT **(*Brancato, 1999*)**.

In addition to laser photocoagulation, the appearance of new therapeutic modalities such as intravitreal corticosteroid injection or vitrectomy for treatment of clinically significant diabetic macular edema has made it worthwhile to classify clinically significant diabetic macular edema with fluorescein angiography and OCT and to make correlations between them to choose the best line of treatment **(*Yang, 2001*)**.

Anatomy of the Macula

The macula lutea is an oval, yellowish area at the center of the posterior part of the retina. It measures about 5 mm in diameter and lies about 3 mm to the lateral side of the optic disc. The yellow coloration of the macula is caused by the yellow carotenoid pigment Xanthophyll which is present in the retina from the outer nuclear layer inwards ***(Mafee et al, 2005)***.

The fovea centralis is a depressed area in the center of the macula lutea measuring about 1.5 mm in diameter. The sides of the depression are called the clivus. The floor of the depression is known as the foveola. The depression is formed of the nerve cells and fibres of the inner layers of the retina being displaced peripherially, leaving only the photoreceptors in the center (Fig.1-2). The fovea shows the highest concentration of cones (147,000/mm^2) and no rod cells in the floor of the fovea. There are no ganglion cells directly overlying the cones, they are displaced laterally. One cone synapses with one bipolar cell which links to one ganglion cell. These anatomic features enhance resolution, provide color vision and make the fovea the center of vision ***(Snell, 1998)***.

The outer retina throughout the macula is avascular and receives oxygenation by diffusion from the deeper choriocapillaris ***(Stefansson et al, 2006)***.

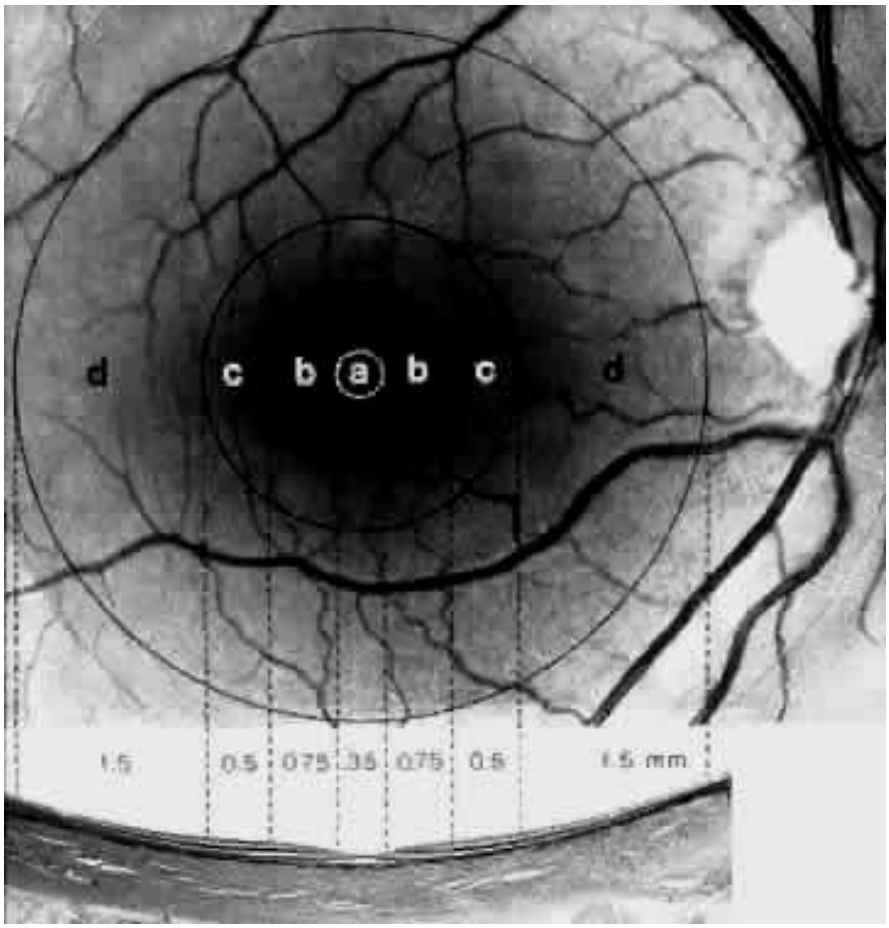

Fig.1: A fundus photograph is matched with a meridional light micrograph of the macular region. The fundus photograph shows the foveola (a), fovea (b), parafovea (c), and perifovea (d) ***(Hogan MJ et al., 1971)***.

The inner nuclear layer cells are displaced laterally so that photoreceptor axons in the outer plexiform layer course radially to synapse onto horizontal and bipolar cells. The thick layer of radial axons is termed the *fiber layer of Henle*. Rods with long, thin outer segments are present in the slope of the wall of the fovea. The central rod-free area is 350 to 600 μm in diameter ***(Curcio CA et al, 1990)***.