INTRODUCTION

Diabetic macular edema (DME) is a major cause of vision loss worldwide. [1] Over the past decade, several clinical trials have assessed the effect of various treatments for DME. [2] It is highly specific retinal vascular disorder that occurs as a complication of diabetes mellitus.

Diabetes mellitus is considered the most common ocular complication of DM, and its prevalence is higher in type I diabetics than in those with type II disease.[3]

The correlation between OCT-measured macular thickness and visual acuity obtained in various clinical studies, however, has been modest and variable. Furthermore, in some cases paradoxical changes in visual acuity occur in response to changes in OCT-measured thickening.[4]

These findings suggests that although OCT can serve as a valuable tool in the clinical evaluation of patients with DME, OCT derived macular thickness measurements may not be appropriate as surrogate markers of visual acuity.[5] The clinical utility of other OCT-derived measurements, such as measures of photoreceptor length, remains to be determined.[6]

Time domain OCT using the Stratus™ OCT instrument (Carl Zeiss Meditec, Inc., Dublin, CA) has been extensively used for the determination of macular measurements in the Clinical setting[5]. Qualitative assessment of the inner segment/outer segment (IS/OS) junction Using Stratus™ OCT has demonstrated that the integrity of the IS/OS junction is valuable in Predicting visual acuity in patients with retinitis pigmentosa (RP), birdshot chorioretinopathy (BCR)[7] as well as in patients following macular hole repair.[8]

Prototype software algorithms used with Stratus™ OCT and other OCT systems have allowed for quantitative assessment of photoreceptor structure.[9] In patients with RP, such quantitative measures of photoreceptor structure have been shown to correlate with visual acuity.

Qualitative or quantitative examination of the photoreceptor layer in patients With DME remains to be performed. [10]

Function and Structure of photoreceptors:-

Photoreceptor cells are highly specialized, photosensitive neurons that function in the transduction of light into an electrical signal and the transmission of this signal to other neurons in the retina as the initial steps in vision. Rod and cone photoreceptor cells consist of five principle regions: the outer segment where the process of phototransduction takes place, a thin connecting cilium that joins the outer segment to the inner segment and allows for the passage of proteins and other molecules between the inner and outer segments, the inner segment that contains the biosynthetic and metabolic machinery of the cell, the cell body harboring the nucleus, and the synaptic region containing the synaptic vesicles and the ribbon synapse for transmission of electrical signals to secondary neurons of the retina.[11]

The rod outer segment (ROS) consists of an ordered stack of over 1000 closed disks surrounded by a separate plasma membrane. Cone outer segments (COSs) have a similar stacked membrane organization, although the disk membranes are continuous with the plasma membrane. Outer segments undergo a continual renewal process in which new disk membrane is added at the base of the outer segment while packets of aged disks are shed from the distal end and removed by a phagocytic process mediated by adjacent retinal pigment epithelial (RPE) cells. This enables the outer segment to be completely renewed over a period of 10 days.[12]

Studies over the past several decades have led to a comprehensive understanding of phototransduction. In rod cells photoexcitation of rhodopsin in disk membranes activates the G-protein (transducin)-mediated visual cascade resulting in the stimulation of phosphodiesterase, hydrolysis of cGMP, closure of cGMP-gated channels in the plasma membrane, and hyperpolarization of the cell. Following photoexcitation, the rod cell returns to its dark state through a series of reactions involving inactivation of rhodopsin and other protein components of the visual cascade, resynthesis of cGMP, and regeneration of rhodopsin from 11-*cis*-retinal and opsin. Similar photoexcitation and recovery mechanisms take place in COSs although in many cases the proteins involved are encoded by different although related genes.[13]

Photoreceptor outer segments also contain proteins that function in other essential cellular processes. Retinol dehydrogenase (RDH8) and the photoreceptor-specific ABC transporter ABCA4 (also known as the rim protein or ABCR) play important roles in the removal of all-trans-retinal from disk membranes following the photobleaching of rhodopsin as part of the visual cycle . The GLUT-1 glucose transporter and enzymes of the glycolytic and creatine phosphate shuttle pathways function in the production of energy in the form of ATP for phototransduction and other energy-dependent processes, whereas hexose monophosphate shunt and nucleotide-processing enzymes play essential roles in the generation of NADPH and interconversion of adenosine and guanine nucleotides . Finally a number of membrane and soluble proteins including peripherin-2 (peripherin/rds), rom-1, prominin-1, glutamic acid rich proteins, and RP1 have been implicated in outer segment structure and morphogenesis, but their exact roles remain to be determined .[14]

Epidemiology and risk factors

Many risk factors are incriminated for the development and progression of DR. Some of them are proved to affect both the development and progression of DR as duration of DM, type of control of DM, associated hypertension (HTN), associated renal disease and pregnancy. Others are not well proved yet as use of insulin and hyperlipidemea.[15]

The best predictor of DR is the duration of the disease. Longer duration of DM was associated with more severe retinopathy. Patients who had type 1 DM for 5 years or less rarely show any evidence of DR. However, 27% of type 1 patients who have DM for 5-10 years and 71-90% of those who had DM for longer than 10 years have DR. After 20-30 years, the incidence rises to 95%, and about 30-50% of these patients have proliferative diabetic retinopathy (PDR).[16]

The younger-onset, long duration DM patients are suggested to be at higher risk for worsening of retinopathy.[17]

The Diabetes Control and Complications trial (DCCT) showed emphatically that patients who closely monitored their blood glucose (four measurements/day= tight control) do far better than patients treated with conventional therapy (one measurement/day). In the United Kingdom

Prospective Diabetes Study (UKPDS), after 12 years of follow-up of people newly diagnosed with type 2 DM, intensive glycemic control reduced the rate of progression of DR by 21%.[18]

It is now established that hypertension (HTN) is a risk factor both for the development and the progression of retinopathy. High blood pressure is detrimental to each aspect of DR. In the UKPDS, tight blood pressure control in hypertensive patients independently resulted in a 34% reduction in the rate of progression of DR.[19]

Renal disease as evidenced by proteinuria, elevated blood urea nitrogen levels, and elevated creatinine is an excellent predictor of the presence of retinopathy.[13]

In women who begin a pregnancy without retinopathy, the risk of developing non-proliferative diabetic retinopathy (NPDR) is about 10%. Those with NPDR at the onset of pregnancy and those who develop systemic hypertension tend to show progression of DR. Fortunately, there is usually some regression after delivery. Women who begin pregnancy with poorly controlled DM who are suddenly brought under strict control frequently have severe deterioration of their retinopathy and do not always recover after delivery. [20-21]

Pathogenesis of Diabetic Retinopathy

A- Biochemical Mechanisms

The final metabolic pathway which causes DR is unknown. Several theories exist involving aldose reductase, protein kinase C pathway, retinal leukostasis, oxidativestress and vaso-proliferative factors, growth hormone, platelets and blood viscosity. [22-23]

I. Sorbitol metabolic pathway: (aldose reductase pathway (AR)

Aldose reductase (AR) is present in high concentrations in the retinal pericytes of patients with DR suggesting that DR may be caused by AR mediated damage by causing alterations in the cellular metabolism and osmolarity. However, a clinical trial of sorbinil, an AR inhibitor, failed to reduce the incidence of DR. [24]

II. Protein Kinase C Pathway: (PKC)

PKC pathway leads to elevated levels of PKC isozymes, which in turn phosphorylates proteins involved in endothelial function (permeability and vasodilator functions), smooth muscle cell growth and contractility, and neovascularisation. Excessive PKC activation therefore underlies the triad of micro-vascular ischemia, leakage and angiogenesis in DR. [25]

III. Retinal Leukostasis:

Retinal leukocytes contain large cell volume, high cytoplasmic rigidity, a natural tendency to adhere to the vascular endothelium, and a capacity to generate toxic superoxide radicals and proteolytic enzymes. In DM, there is increased retinal leukostasis, which affects retinal endothelial function, retinal perfusion, angiogenesis, and vascular permeability. [24]

IV. Oxidative stress:

Oxidative stress is an integral and possibly causative part in diabetic retinopathy pathogenesis. There is evidence for increased level of oxidants, products of oxidation and rates of oxidants generation in diabetics.[26]

V. Vaso-proliferative factors: (Figures 1, 2)

Hyperglycemia induces retinal hypoxia, which regulates a range of vaso-active factors that may lead to macular edema and/or angiogenesis, and hence potentially to sight-threatening retinopathy.[27]

The ischemic retina is assumed to secrete growth factors that stimulate residual vessels to proliferate. Interest has focused on vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), erythropoietin, insulin-like growth factor-1 (IGF-1) and transforming growth factor beta (TGFβ).[28]

VEGF is a major mediator of angiogenesis. It mediates retinal ischemia-associated intra-ocular neovascularization. Many cell types within the eye produce VEGF. In patients with PDR, VEGF levels are markedly elevated in the vitreous and aqueous fluids. Retinal VEGF expression is high in DR[29].VEGF isoforms increase permeability at blood–tissue barriers; hence the original name, vascular permeability factor.[30]

PEDF is synthesized in the retinal pigment epithelium (RPE) and elsewhere in the eye. It has been identified as one of the most potent of endogenous negative regulators of blood vessel growth in the body. PEDF has been shown to act by inhibiting the angiogenic response to factors such as VEGF and FGF. PEDF selectively inhibits the formation of new vessels from endothelial cells but does not appear to harm the existing vascular structure. [31] The level of intraocular PEDF has been shown to decrease with advancing stages of DR. [32]

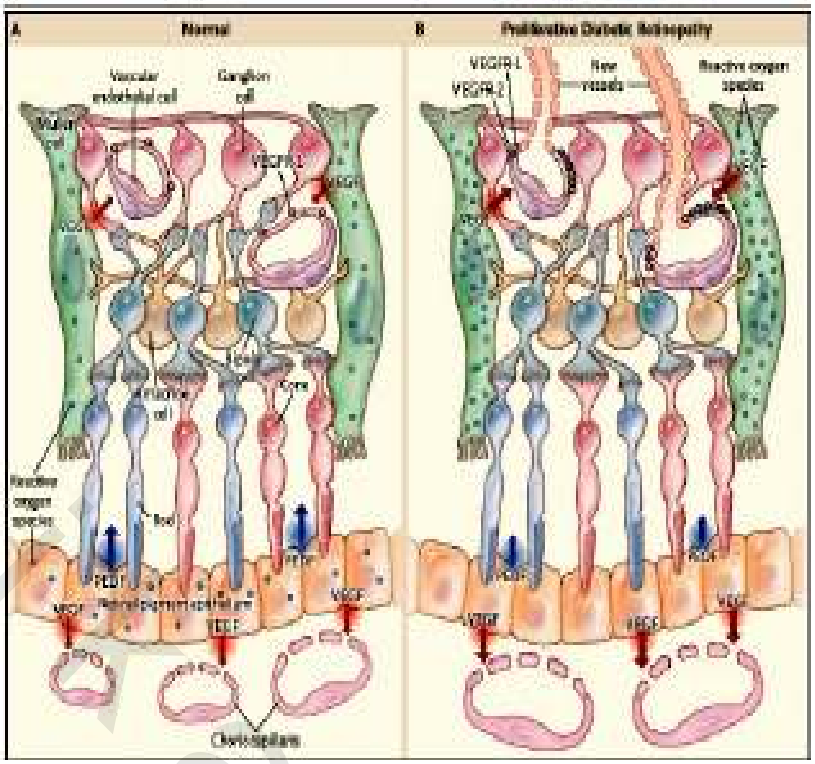


Figure (1): Retinal Anatomy and Mechanisms of Diabetic Retinopathy.[33]

- Pericytes is the term for vascular mural cells embedded within the vascular basement membrane of blood micro-vessels, where they make specific focal contacts with the endothelium.[34] Pericytes play an important role in the angiogenic process by providing survival signals for endothelial cells and promoting capillary maturation mainly platelet derived growth factor (PDGF)[35]

- Pericyte loss and micro-aneurysm formation are the hallmarks of early changes of DR. Pericyte loss is considered a prerequisite of micro-aneurysm formation, possibly by local weakening and subsequent out pouching of the capillary wall, micro-aneurysm formation and ultimately angiogenesis.[36]Erythropoietin is an ischemia-induced paracrine factor that promotes angiogenesis. It promotes the proliferation and differentiation of erythroid precursors through the induction of anti-apoptotic proteins and inhibition of apoptosis.[37]

- Growth hormone (GH) appears to play a causative role or at least an important supportive role in the development and progression of diabetic vascular complications.[38]

- Muller cells, the principal glia of the retina, generate traction forces in response to IGF-I and platelet derived growth factor and are present in diabetic fibro-vascular scar tissues causing tractional retinal detachment (TRD) and these traction forces may cause a tear in the retina causing what is called combined tractional rhegmatogenous retinal detachment (TRD/RRD).[39]

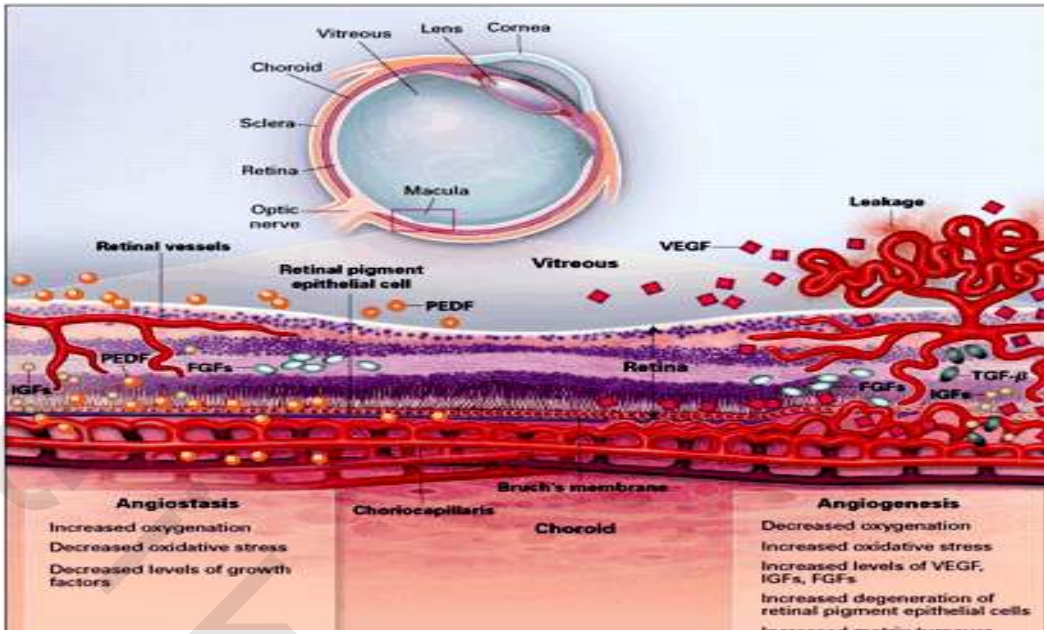


Figure (2): Balance between angiostatic and angiogenic factors[37]

B- Role of vitreous

The structure of the vitreous body is known to play an important role in the pathogenesis of PDR.[40-41] There are structural changes as vitreous liquefaction and posterior vitreous detachment (PVD) that are associated with the earlier onset of DR.[42]

Furthermore, there are angiogenic and angiostatic factors in the vitreous which influence neovascularization by means of endothelial cell proliferation.[43]

The effect of DR on the visual acuity

DR could affect the visual acuity by many mechanisms:-

- Central vision may be impaired by macular edema or capillary non-perfusion
- The new blood vessels of PDR and contraction of the accompanying fibrous tissue can distort the retina and lead to TRD producing severe and often irreversible vision loss.
- The new blood vessels may bleed, adding the further complication of pre-retinal or vitreous hemorrhage.[44]

Classification of Diabetic Retinopathy

The Diabetic Retinopathy Study (DRS) and the Early Treatment Diabetic Retinopathy Study (ETDRS).[45-46] classified DR into Non proliferative diabetic retinopathy (NPDR) {mild, moderate (Figure 3) and severe NPDR (Figure 4)} and proliferative diabetic retinopathy (PDR) {early (Figure 5), high risk and advanced PDR .

Non propliferative diabetic retinopathy (NPDR)

Is characterized by structural damage to small retinal blood vessels, causing them to dilate, leak, or rupture.[47]Retinal micro-vascular changes are limited to the retina and don't extend beyond the ILM.[48]

Visible retinal lesions include micro-aneurysms (first detectable lesion ophthalmoscopically. [49-50] intra- retinal hemorrhages (dot and blot and flame shaped), hard exudates, soft exudates or cotton-wool spots, intra-retinal micro-vascular abnormalities (IRMA), venous abnormalities (beading, narrowing, venous loops and/or reduplication or sheathing) and arteriolar abnormalities (narrowing or sheathing). [45]

Proliferative diabetic retinopathy (PDR)

1. Neovascularization:

It is the Hallmark of PDR. New vessels that are clearly on the surface of the retina or further forward in the vitreous cavity are considered to be new vessels elsewhere (NVE), except for those on the disc or within one disc diameter (DD) of its margin that are designated new vessels of the disc (NVD) (Figure 5) they stain and leak in fluorescein angiography (FA).[45]

2. Fibrous proliferations: figure 6

They also occur either on the disc (FPD) or elsewhere (FPE), along the same criteria of NVDs and NVEs, with or without new vessels. They include fibrous strands or sheets that comprise a thickened PH surface, as well as, completely atrophic new vessels. The distance of these proliferations from the normal position of the attached retina is estimated and the highest point of elevation determines the grade of PDR. [45]

3. Hemorrhages: figure 7

Pre-retinal hemorrhage (PRH), vitreous hemorrhage (VH) and rarely sub-retinal hemorrhage can occur. [51]

Diabetic Macular Edema (DME)

Macular edema is the major cause of visual loss in patients with DR. The incidence of diabetic macular edema (DME) after 10 years of follow-up has been reported to be 20.1% in type I diabetes, 25.4% in type II insulin-dependent diabetes, and 13.9% in type II non-insulin-dependent diabetes. [52]

DME appears biomicroscopically as an intra-retinal swelling accompanied by varying amounts of hemorrhage and lipid exudates.

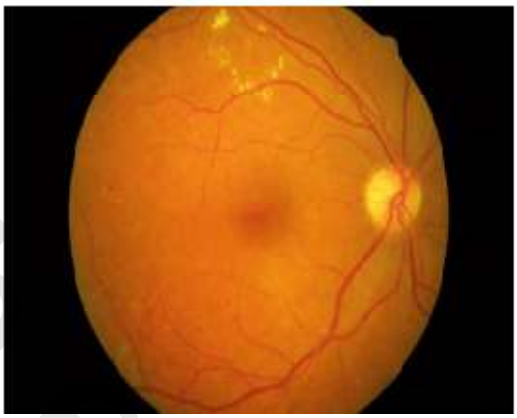


Figure (3): Moderate NPDR showing circinate ring of hard exudates.[47,48]

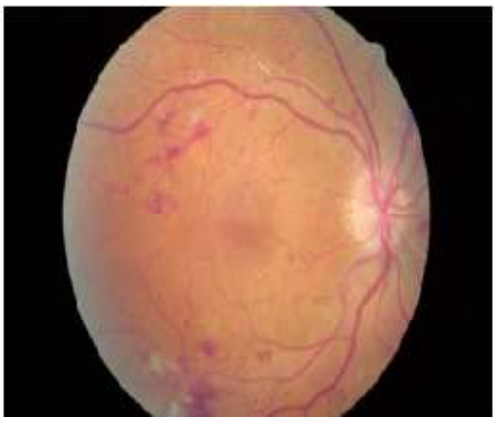


Figure (4): Severe NPDR showing venous beading.[49,50]

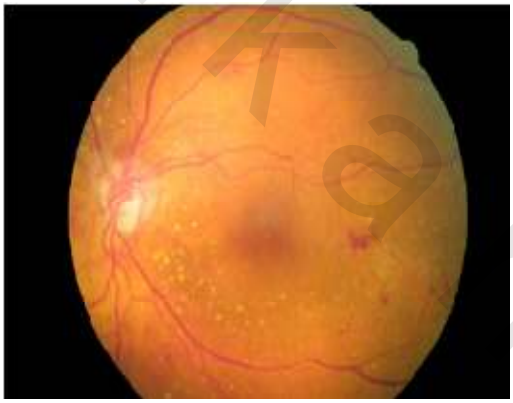


Figure (5): Early PDR with NVD.[45]

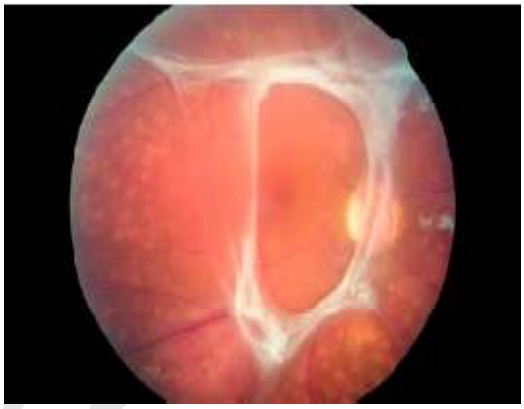


Figure (6): Advanced PDR showing fibrous proliferation.[45]

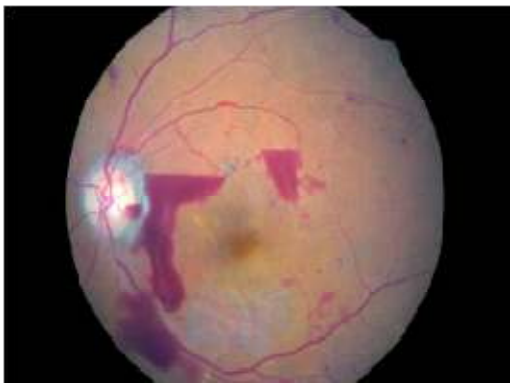


Figure (7): PDR with PRH & VH.[51]

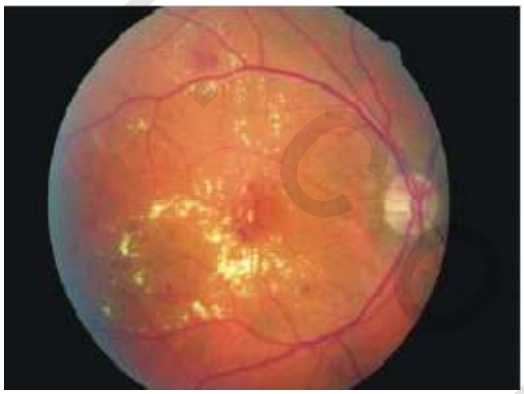


Figure (8): CSME.[55]

Diagnosis of diabetic macular Edema

1. Clinical diagnosis

Macular edema is best detected by stereoscopic examination techniques. Slit-lamp examination with contact or non-contact lens makes it possible to detect retinal thickening and the use of a narrow slit beam is useful in detecting cystoid spaces.(53)

The Early Treatment Diabetic Retinopathy Study (ETDRS) defined macular edema as thickening of the retina and/or hard exudates within 1 disc diameter of the center of the macula. Clinically significant macular edema (CSME) (figure 8) was defined as 1 or more of the following: retinal thickening at or within 500 μm of the center of the macula; hard exudates at or within 500 μm of the center of the macula if associated with adjacent retinal thickening; or a zone or zones of retinal thickening 1 disc area in size, at least part of which is within 1 disc diameter of the center of the macula. (54)

2. Investigations

Clinical suspicion of macular edema can be confirmed with the aid of a wide variety of investigations. Tests may be grouped into three categories according to whether one is analyzing the underlying pathogenesis, the effect of the macular edema on the retina, or its impact on visual function. (55-56)

A. Tests detecting disturbance in the blood retinal barrier

1- Fluorescein angiography.
2- Vitreous fluorophotometry.

B. Tests assessing retinal function

1- Contrast sensitivity charts.
2- Electroretinography.

C. Tests detecting disturbance in retinal thickness

1- Optical coherence tomography.
2- Retinal thickness analyzer.
3- Scanning laser ophthalmoscope.

A. Tests detecting disturbance in the blood retinal barrier

1. Fluorescein Angiography (FA)

FA: permits studying the circulation of the retina and choroid in normal and diseased states and is clinically the most widely available and useful test. (57) In DME, the amount of fluorescein leakage is dependent on the dysfunction of the retinal vascular endothelium.(58)

FA: findings in DME can be categorized into three types: focal leakage with well-defined areas of leakage from microaneurysms or localized dilated capillaries; diffuse leakage, showing predominantly widespread and ill-defined leakage involving the whole circumference of the fovea; and diffuse cystoid leakage, which

is predominantly diffuse leakage but with pooling of dye in the cystic spaces of the macula in the late phases. [59]

Once the diagnosis and the decision to treat macular edema have been made, FA is extremely useful in helping to guide the treatment pattern. Angiography will identify treatable lesions and delineate the foveal avascular zone and the status of the macular perfusion. FA will also confirm the presence of thickening by leakage in the late stage of the angiogram. [60]

2. Vitreous fluorophotometry (VF)

Vitreous fluorophotometry is a technique used to quantitate fluorescein leakage with the aid of a slitlamp fluorophotometer. [61]

B. Tests assessing retinal function

1. Contrast sensitivity charts

Macular edema may potentially affect macular function as far as visual acuity and contrast sensitivity are concerned. Tests assessing macular function may be used indirectly to detect the effects of macular edema and to follow up its treatment. Contrast sensitivity has been documented to suffer specific changes in macular edema. [62]

Reduction in contrast sensitivity may account for persistent difficulties experienced by patients despite good Snellen acuity. [63]

2. Electroretinography

Electroretinography may be utilized to follow up the treatment of macular edema. The focal electroretinogram (ERG) is the response evoked by the foveal cones of the retina to a brief flash of light focused on the fovea. Pattern and multifocal electroretinogram is the most commonly used now. [64]

The mean implicit time is significantly longer in eyes with clinically significant macular edema as compared to normal. The amplitudes are directly correlated with the best corrected Snellen visual acuity. This tends to support the role of outer retinal dysfunction in eyes with macular edema. Generally the focal ERG will vary depending on the severity and stage of macular edema. [65]

C. Tests detecting disturbance in retinal thickness

1. Optical Coherence Tomography (OCT)

Optical coherence tomography performs micron resolution cross sectional imaging in biological tissues. It is analogous to B-mode imaging except that light is used instead of acoustic waves. OCT permits non-contact measurement of structures on a 10 micron scale, versus the 100-micron scale of ultrasound. The principal disadvantage of OCT is that light is highly scattered in biological tissues constraining optical imaging to tissues which are optically accessible. [66]

Low coherence interferometry

The operation of OCT is based on the optical measuring technique of low coherence interferometry. Measurement of the axial distances is performed by reflecting light waves with wavelength in the near infrared (830 nm) from different microstructures within the eye. The thickness of the tissue is calculated by measuring the optical echo delay and multiplying it by the speed of light in the tissue.

$$\text{Distance} = \text{Time delay} \times \text{Speed of light}$$

Light from a superluminescent diode source is directed into a partially reflecting mirror and is split by a beam splitter into a reference beam and a measurement beam. The measurement beam is focused into the patient's retina by a 78 D lens and is reflected with different time delays according to the tissue internal microstructure. The reference beam is reflected from a reference mirror. The two beams coincide and recombine by the same beam splitter to produce interference which is measured by a light sensitive detector (Figure 9). [67-68]

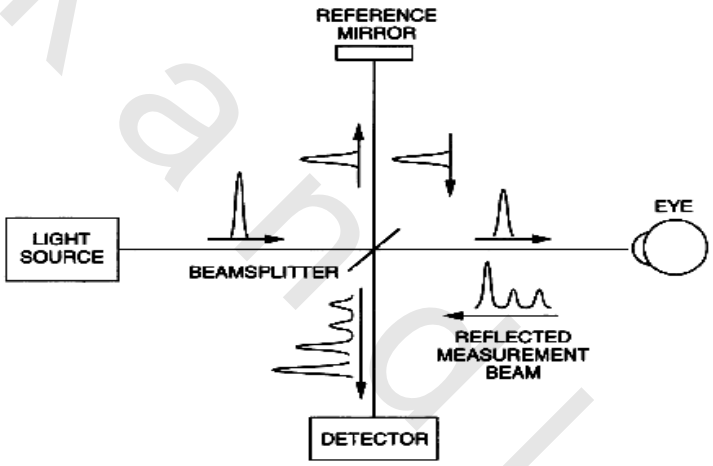


Figure (9): Optical interferometry; high resolution time and distance measuring by correlating one light beam with another. [68]

Normal retina by OCT: (Figure 10)

Although the OCT image closely approximates the histological appearance of the retina, correlation with histological retinal features is quite accurate only with ultra-high-resolution OCT.[69] The currently available OCT is not able to discriminate the more subtle microstructural differences, but is able to discriminate accurately the cellular and noncellular elements of the retina.[68]

On OCT, the fovea appears as a thinning of the retina with lateral displacement of the retina anterior to the photoreceptors demonstrating a central foveal depression while the optic disc shows evidence of cupping.

The vitreoretinal interface is demarcated by the contrast between the non-reflective (black) vitreous and the highly reflective (red) anterior surface of the retina. The inner

margin of the retina shows a red line of bright backscattering corresponding to the nerve fiber layer. The retinal pigment epithelium, Bruch's membrane and choriocapillaris complex collectively comprise the highly reflective external red band which is 70 µm thick, while weak scattering returns from the deep choroid and the sclera due to attenuation of the signal.[70-71]

Just anterior to the red band is another highly reflective line representing the junction between the photoreceptor inner and outer segments? Moderate backscattering (green) arises from the inner and outer plexiform layers, which, like the nerve fiber layer, consists of a fibrous structure perpendicular to the incident beam. In contrast, minimal backscattering (blue) occurs from the nuclear layers (outer nuclear, inner nuclear, and ganglion cell layer) in which the cell bodies are oriented parallel to incident light.[72-73]

Retinal blood vessels are identified by their increased backscattering and by shadowing of the reflections from the RPE and choriocapillaris. The larger choroidal vessels appear and have minimally reflective dark lumen.[74-75]

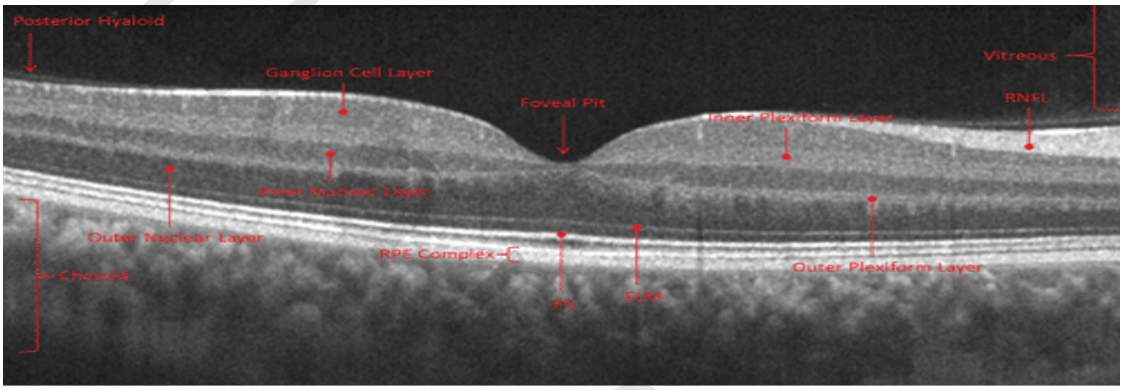


Figure (10): High resolution OCT image of a healthy fovea showing the layered structure of the retina. [72]

Role of OCT in DME

- Following ETDRS guidelines, diagnosis and follow up of macular thickening is made by biomicroscopy, and fluorescein angiography is used to guide laser treatment. However, given the relative lack of ability of these methods to quantify macular edema, alternate objective methods such as the OCT have been applied.[72]

- Biomicroscopy is not reliable for detecting macular thickness unless it was approximately 100 microns more than the normal mean. OCT allows accurate tracking of changes in retinal thickness with more sensitivity than slit-lamp biomicroscopy. OCT is more sensitive than biomicroscopy in identifying vitreomacular adhesions and allows earlier diagnosis of shallow partial PVD.[73]

- It has been shown to produce highly reproducible measurements and it is as effective at detecting macular edema as fluorescein angiography, but is superior at demonstrating axial distribution of the fluid. [74]

- In addition estimation of retinal thickness has a more reliable correlation with visual acuity than fluorescein leakage since angiographic leakage is not always accompanied by retinal thickening.(75)

- OCT has been shown to be effective in the qualitative and quantitative description of DME.OCT has demonstrated that macular edema is a complex clinical entity with various morphologies that have to be described in order to choose the correct therapeutic approach. This makes OCT the preferred indicator of therapeutic benefit of different treatment strategies.(76)

- The morphological changes in diabetic macular edema include a decreased intraretinal reflectivity mostly in the outer layers corresponding to cystic changes and fluid accumulation. Hard exudates and hemorrhages appear as areas of high backscattering with shadowing of the reflections from the deeper layers due to high attenuation of the propagating light. Preretinal membranes and retinal traction are visible in cross-section. Cotton wool spots appear as regions of increased reflectivity of the nerve fiber layer and inner retina.(77)

Generations of OCT

1- Time domain OCT

Using the Stratus™ OCT instrument (Carl Zeiss Meditec, Inc., Dublin, CA) has been extensively used for the determination of macular measurements in the clinical setting. Qualitative assessment of the inner segment/outer segment (IS/OS) junction using Stratus™ OCT has demonstrated that the integrity of the IS/OS junction is valuable in predicting visual acuity in patients with retinitis pigmentosa (RP) and birdshot chorioretinopathy (BCR), as well as in patients following macular hole repair(5,9).

2 - Spectral domain OCT:

Spectral domain OCT (SD OCT) is a new method of OCT measurement that replaces mechanical moving parts with a spectrometer and Fourier transform. Echo time delay is detected by measuring the interference spectrum of the reflected light without the use of an interferometer. This results in a more rapid data acquisition. The system can acquire data 50 times faster than other systems and is therefore able to capture 3D-OCT data before the subject shifts fixation. It has an axial resolution of 2 μm. (78)

Many studies as in Farzin Forooghian et al study, had developed prototype software algorithm For the Cirrus™ HD-OCT that allows for Qualitative and quantitative assessment of photoreceptor outer segment (PROS) length which is also valuable in DME by measuring the distance between the IS/OS junction and the RPE (79, 81). The stronger correlation of PROS length with visual acuity suggests that PROS more directly related to visual function than retinal thickness. PROS length may be a useful physiologic outcome measure, both clinically and as a direct assessment of treatment effects. (82)

1) OCT-based morphological patterns of DME

OCT studies of CSME, as defined by the ETDRS, have revealed 4 basic structural changes in the neurosensory retina but this classification is not widely used now which is: sponge-like retinal swelling (Type 1), cystoid macular edema (Type 2), serous retinal detachment (Type 3) and tractional retinal detachment (Type 4).[83-84] The presence of CME on OCT is associated with more severe reduction in visual acuity and poorer response to treatment than OCTs displaying sponge-like retinal thickening alone.[85] Improved characterization of DME on OCT may allow clinicians to determine when irreversible structural damage has occurred and, therefore, the point at which further treatment is unlikely to be of benefit.

- **Type 1: Sponge-Like Retinal Swelling (Figure 11-a)**

This is the most common configuration of DME, approximately 90% of patients with DME who are examined using OCT show evidence of sponge-like retinal thickening .[83] It is identified as increased retinal thickness with reduced intraretinal reflectivity.

- **Type 2: Cystoid Macular Edema (Figure 11-b)**

Round or oval hyporeflective areas on OCT are consistent with intraretinal cystoid space formation . This form of edema, isolated or in combination with other patterns, presents in approximately 50% of patients with DME Panozzo, et al further classified this type of DME according to the number of cystoid spaces into Type **2A** (presence of 1 or 2 small cysts in the IPL; the normal macular profile is still visible but the central foveal thickness is

>325 microns), Type **2B** (petaloid pattern of intraretinal cysts; central foveal thickness >485 microns), and Type **2C** (chronic cystoid edema, major intraretinal damage with cysts fused in large cavities resembling retinoschisis; central foveal thickness >405 microns). [86-88]

- **Type 3: Serous Retinal Detachment**

Although rare (15%), subfoveal shallow retinal detachment can be seen in some cases of DME. [86, 88] serous retinal detachment is seen on OCT as an optically clear/hyporeflective space between the outer layer of photoreceptors and the highly hyper-reflective RPE band.

- **Type 4: Tractional Retinal Detachment (Figure 11-c)**

In some cases, DME can be associated with changes of the internal retinal surface; characterized by diffuse or focal traction by the thickened, taut posterior hyaloid, thickened ILM; or by epiretinal membranes [89,90] The presence of tangential or anterior-posterior forces can be demonstrated by OCT and may help in directing the patient to surgery as the most appropriate therapeutic intervention.

Evaluation of the vitreomacular interface is an essential component in the work up of patients with DME, particularly when retinal thickening is present on clinical examination without fluorescein angiographic evidence of significant leakage or ischemia. (91)

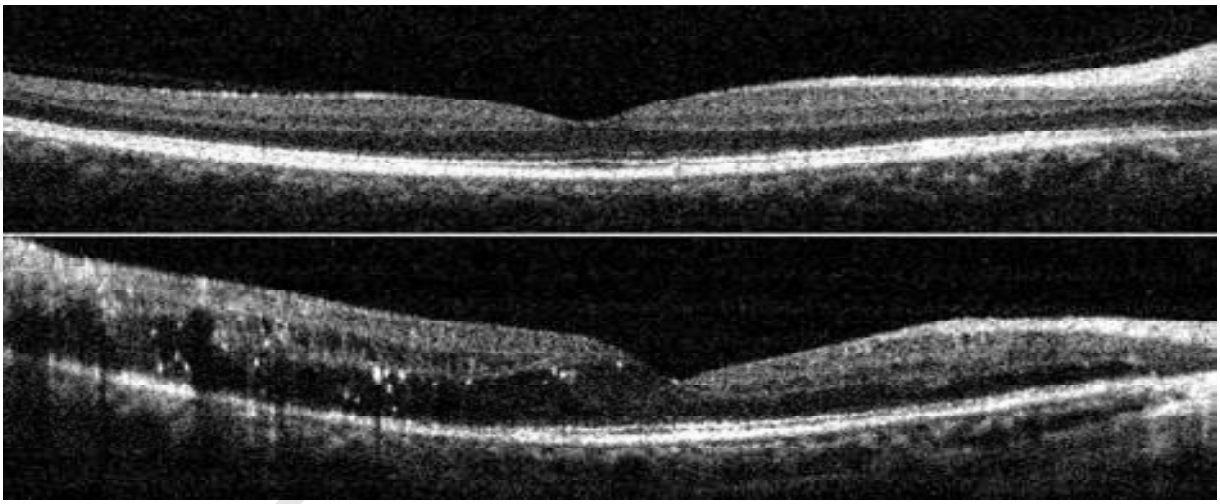


Figure (11-a): OCT image, horizontal line centered at fovea, scan length = 8 mm. **Top**: normal eye. **Bottom**: CSME patient, left side of the scan shows outer retinal spongy thickening, loss of the definition of the IS/OS line, and multiple highly reflective deposits with relative preservation of the foveal contour [TYPE 1].(86)

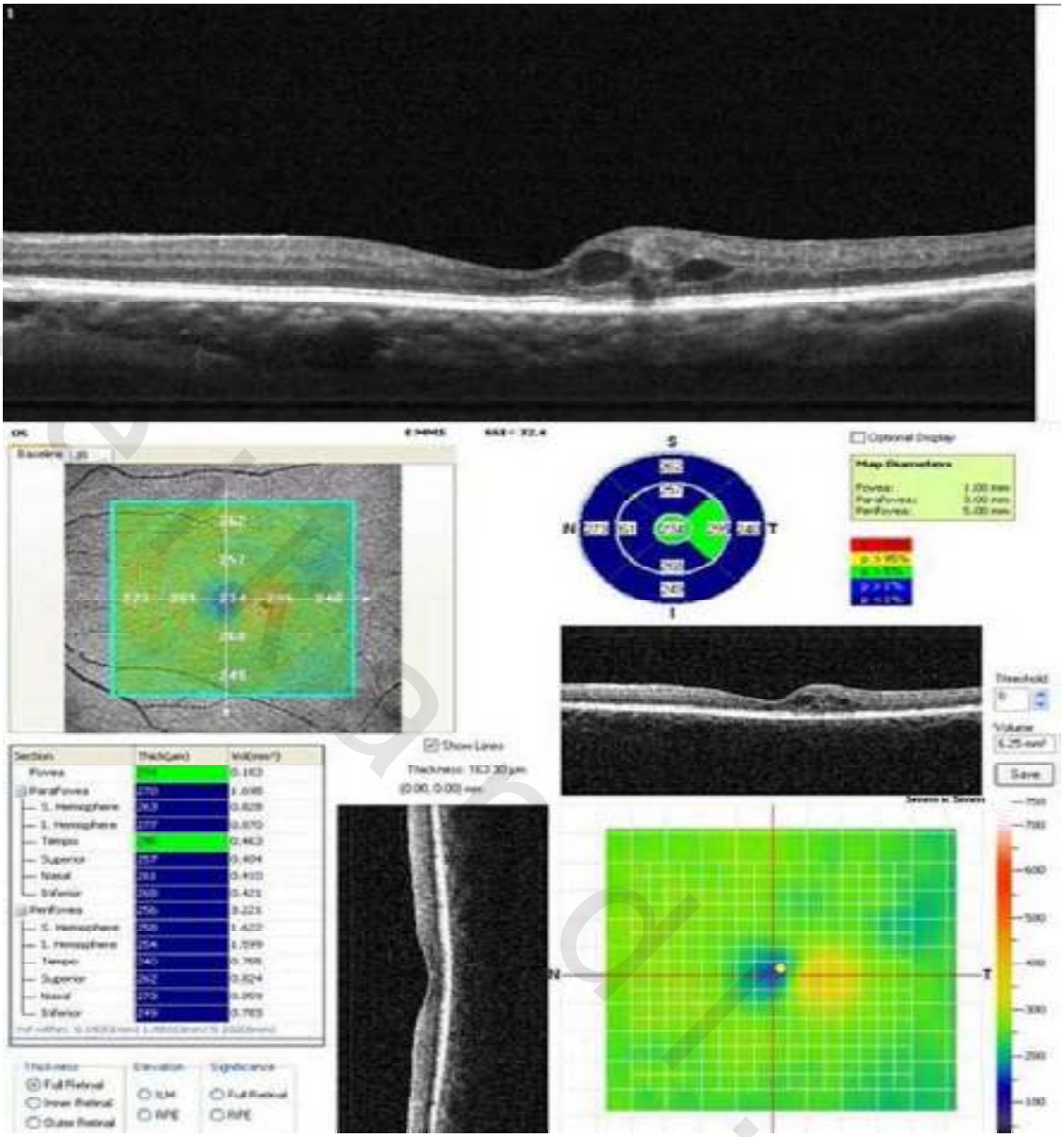


Figure (11-b): High-definition line scan (16x averaged lines) through the fovea illustrating an example of Type 2A cystoid maculopathy, with only 2 cysts seen in the OPL. Bottom map illustrates the focal location of those cysts, and the relative pres-ervation of the foveal contour with their effect on the temporal parafovea. In this particular patient the maximum thickening does not exceed 300 microns, which makes this probable subclinical thickening.[TYPE 2]. (86)

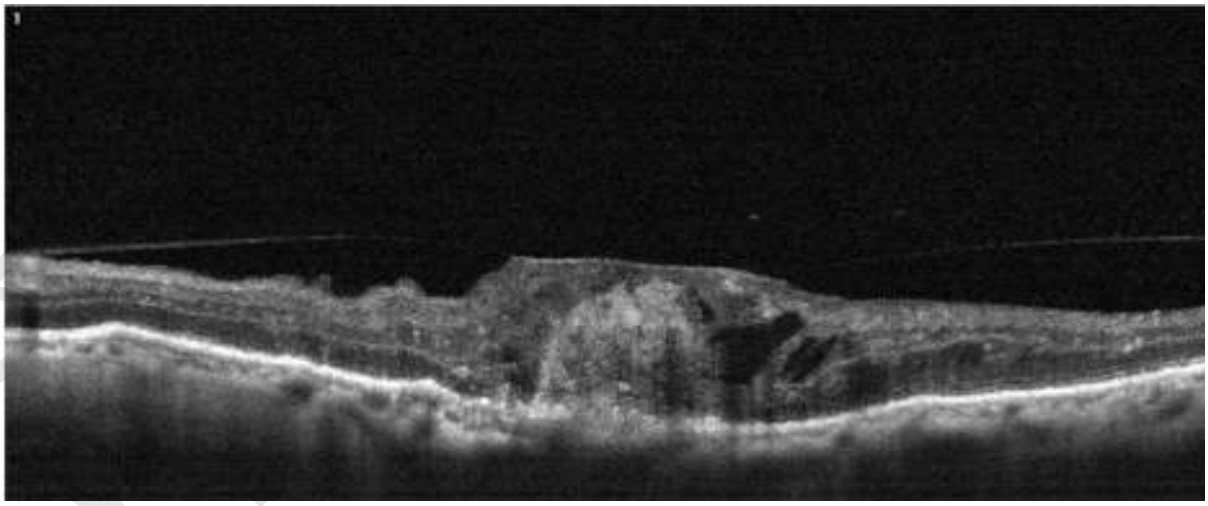


Figure (11-c): High-definition OCT of the fovea demonstrating vitreous traction, taut posterior hyaloid and subfoveal cholesterol. This patient had a chronic tractional component contributing to her DME (focal vitreous traction, taut posterior hyaloids, and epiretinal membrane formation). The presence of organized subfoveal cholesterol (highly reflective deposits above the RPE) disrupting the outer retinal integrity including the IS/OS junction and ONL, portends a very poor prognosis.[TYPE 4].[86]

2) OCT-based classification of DME

In Panozzo et al study.[76] which is the most commonly used now , using OCT 2 (Humphrey Zeiss Inc.), they analyzed more than 1200 eyes with DME and organized the data in a simple classification that took into account five parameters: retinal thickness (RT), extension of retinal thickening, macular volume, retinal morphology and vitreoretinal relationship.

All the parameters were acquired by "*Radial Lines"* using 6 mm scans, and analyzed by *"Retinal Map"* which was divided into one central area of 1.0 mm diameter, and two concentric peripheral rings of 3mm and 6mm. Two oblique lines divide each of the two rings in four quadrants for a total of 9 areas.

1- Retinal thickness (Figure 12)

Retinal thickness in Panozzo et al study was taken for the fixation point, for the central macular zone, and cumulatively for the perifoveal and peripheral areas and its values were classified as normal, borderline or edema. [76]

a. Fixation Point

- Normal: 150 ±20 μm Borderline: 170–210 μm Edema: ≥ 210 μm

b. Central Zone

- Normal: 170 ±20 μm Borderline: 190–230 μm Edema: ≥230 μm

c. Perifoveal and peripheral areas

- Normal: 230 ±20 µm Borderline: 250–290 µm Edema: ≥290 µm

2- Extension

The zones with retinal thickness over borderline values were recorded to give information on the extension of the edema. CSME corresponded to a RT ≥ 300µ involving the central zone and/or a RT > 320µ in the 1st ring. Edema confined to the 2nd ring was not considered clinically significant.

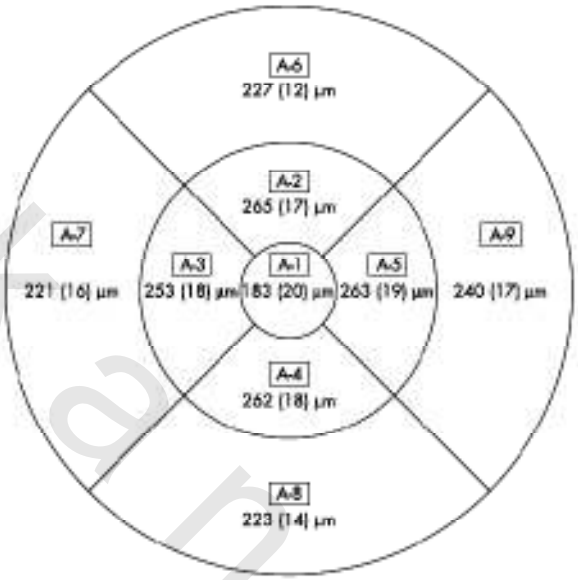


Figure (12): Macular thickness means (SD) in ETDRS areas A1 - A9 measured using OCT in 20 eyes of 20 healthy individuals in Laursen et al study.[92]

3- Volume

This parameter was not essential for the diagnosis of edema; however, it offered important data on the thickness of the macular area considered as a whole. The data were meaningful only for diffuse edema involving at least the center and the 1st ring, and not for Focal edema.

- Normal: 6.5mm ±1
- Borderline: up to 8.0 mm
- Abnormal: ≥8.0 mm

4- Morphology

Three main morphologies were recognized and each was present isolated or in association (Figure 13).[76]

E1: **Simple thickening:** Compact retinal thickening not associated with visible cystoid spaces.

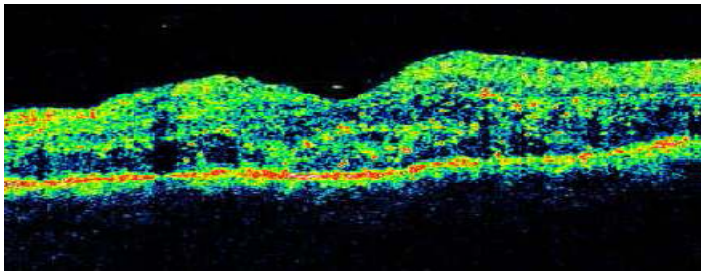
E2: **Cystoid thickening:** Retinal thickening associated with cysts, defined as circular or ovoid spaces with no reflectivity with minimum horizontal diameter of 150 μm and minimum vertical diameter of 300 μm as measured by manual caliper.

E2a: **Mild:** Retinal thickening associated with 2–4 central small cysts (horizontal diameter 150-200 μm, vertical diameter 300- 400 μm).

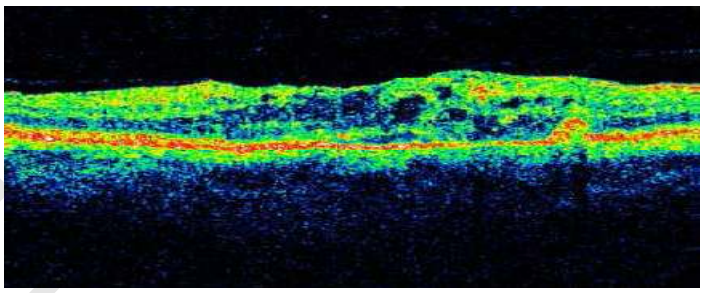
***E2b*:** ***Intermediate*:** Retinal thickening associated with cysts with petaloid configuration or with central big cysts (horizontal diameter 200- 300 μm, vertical diameter 400-600 μm).

***E2c*:** ***Severe*:** Retinal thickening associated with coalescence of cysts with retinoschisis appearance.

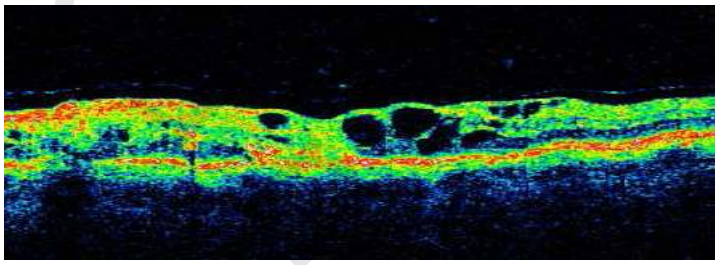
E3: ***Neuroepithelial detachment*:** The retinal detachment was diagnosed by the presence of non-reflecting subretinal liquid above the hyperreflecting line of the pigmented epithelium. This detachment was either isolated or associated with simple or cystoid retinal thickening. It was considered as a sign of longstanding fluid deposit when associated with cystoid changes [100,104]



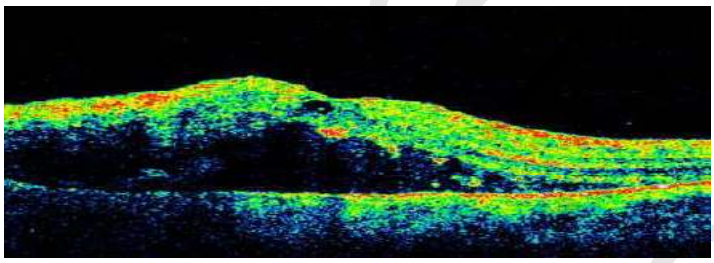
(A)



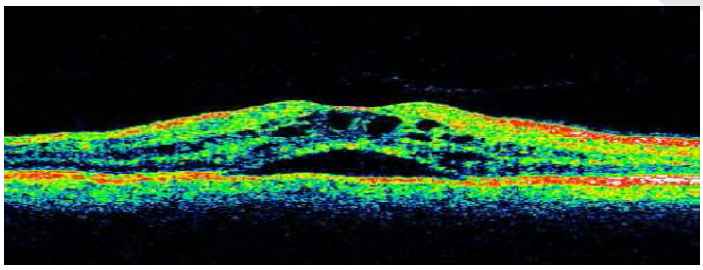
(B)



(C)



(D)



(E)

Figure (13): OCT scans showing the morphological patterns of DME; simple thickening(A), mild CME (B), moderate CME (C), severe CME (D) and neuroepithelial detachment(E).[93,96]

5- Epiretinal traction

Presence of well-defined and continuous hyper-reflecting line over the inner retinal surface with at least one point of adhesion to the retina in at least one of the six scans of the retinal map.

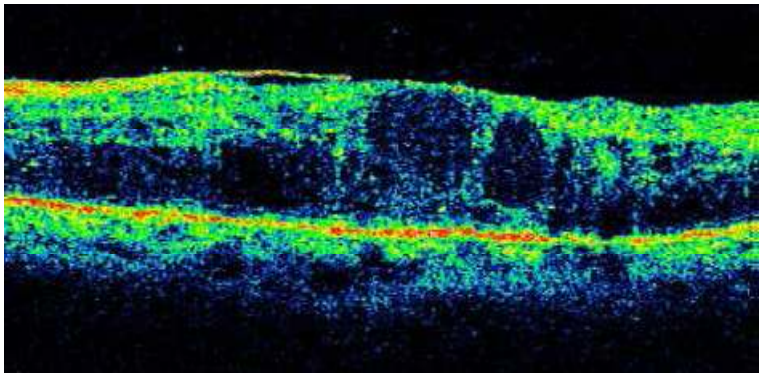
Four grades of increasing severity were given: (Figure 14)

***T0*:** Absence of epiretinal hyper-reflectivity.

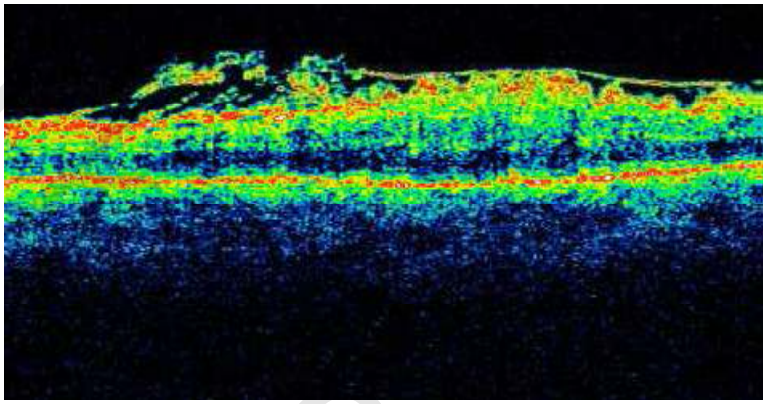
***T1*:** Presence of a continuous line of flat hyper-reflectivity and adherent to the retina without significant retinal distortion.

***T2*:** Presence of continuous line of hyper-reflectivity with multiple points of adhesion to the retina and with significant retinal distortion.

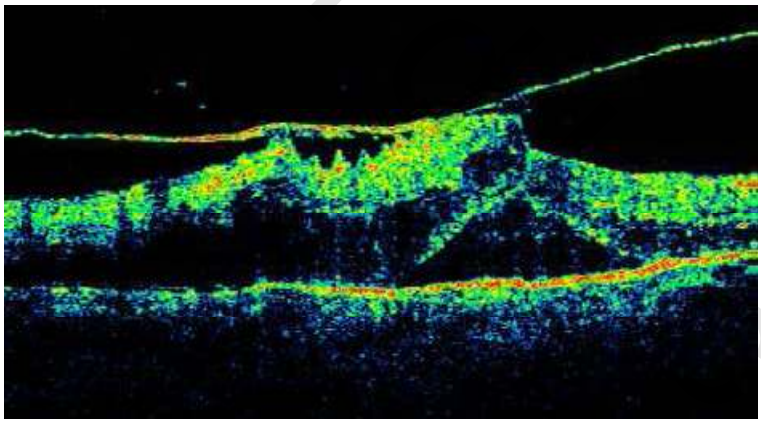
***T3*:** Antero-posterior traction with "gull wings" configuration. [96]



(A)



(B)



(C)

Figure (14): Grades of taut posterior hyaloid; T1 (A), T2 (B), and T3(C)[96]

2. Retinal thickness analyzer (RTA)

The RTA is a rapid screening instrument that generates a detailed map of retinal thickness. [97]Multiple cross sectional imaging generates a 3D reconstruction of the retina. The major advantage of the RTA is the option to scan a relatively wide area of the retina in a short acquisition time. RTA has been shown to be a useful and sensitive tool, which provides objective measurement of the retinal thickness and facilitates the diagnosis and follow-up of DME. [98]

3. Scanning laser ophthalmoscope (SLO)

The SLO is a rapid and non-invasive imaging method that provides quantitative analysis in addition to qualitative information not seen clinically. The chief advantage of the SLO is *scanning a small focused spot* to generate an image, (rather than illuminating a large area), which *provides a high contrast image.* [99]

The infrared imaging of the SLO offers advantages over current imaging techniques by minimizing light scatter through cloudy media. Additional advantages include the ability to image through small pupils, retinal hyperpigmentation, blood, heavy exudation, or subretinal fluid. Scanning laser ophthalmoscope has been used to assess photoreceptor function in various stages of macular edema. Recent studies have reported that the results of SLO measurements were related to Snellen visual acuity and to findings using fluorescein angiography. [99]

Management of Diabetic Retinopathy

I. Medical treatment

The control of diabetes associated metabolic abnormalities (i.e., hyperglycemia, hyperlipidemia) and HTN is important in preserving visual function because these conditions have been identified as risk factors for both the development and progression of DR and DME.[100]

a- Control of systemic factors:

- Good glycemic control.
- Tight blood pressure control.
- Lipid control.

b- Pharmacologic treatment:

Hyperglycemia result in a wide range of biochemical effects in vascular tissues, including the generation of reactive oxygen radicals, activation of protein kinase C pathway (PKC), increased flow through the AR pathway and the formation of advanced glycation end products (AGEs) .[101]

The proposed drugs are antioxidants, PKC inhibitors and aldose reductase and AGEs inhibitors. But the role of pharmacologic treatment is still under research.[102]

c- Screening and Follow up: [108]

Fundus photography is a valuable examination for diagnosing and monitoring progression of DR. [100,101]

Recommended follow up schedule for DR is illustrated in Table (I). [103]

Severity of Condition	Natural Course Rate of Progression to		Frequency of Follow-up	Components of Follow-up Evaluations	
	PDR (1 year)	HRC * (5 years)		Fundus Photography	OCT/ Fluorescein Angiography
Mild NPDR	5%	15%			
No macular edema			12 months	No	No
Macular edema			4 to 6 months	Yes	Based on clinical judgment
CSME			2 to 4 months**	Yes	Yes
Moderate NPDR	12-27%	33%			
No macular edema			6 to 8 months	Yes	No
Macular edema (not CSME)			4 to 6 months	Yes	Based on clinical judgment
CSME			2 to 4 months**	Yes	Yes
Severe NPDR	52%	60-75%			
No macular edema			3 to 4 months	Yes	No
Macular edema (not CSME)			2 to 3 months	Yes	Based on clinical judgment
CSME			2 to 3 months**	Yes	Yes
Very Severe NPDR	75%	75%			
No macular edema			2 to 3 months	Yes	No
Macular edema (not CSME)			2 to 3 months	Yes	Based on clinical judgment
CSME			2 to 3 months**	Yes	Yes

II. Anti-VEGF treatment

A. Intra-vitreal bevacizumab

Intravitreal administration of bevacizumab, a humanized monoclonal antibody to vascular endothelial growth factor, has been reported to be of benefit.[104] Short-term results suggest that intra-vitreal bevacizumab is well tolerated and associated with a rapid regression of retinal and iris neovascularization secondary to PDR. A consistent biologic effect was noted, even with the lowest dose (6.2 µg) tested, supporting proof of concept. The observation of a possible therapeutic effect in the fellow eye raises concern that systemic side effects are possible in patients undergoing treatment with intra-vitreal bevacizumab (1.25 mg), and lower doses may achieve a therapeutic result with less risk of systemic side effects. Further study is indicated. [105,106]

The speed and degree of neovascular regression after the injection of intra-vitreal bevacizumab may make this procedure an important adjunctive treatment in the management of selected cases with severe PDR. [107]

Most of the studies reported absence of any side effects of intravitreal Avastin. But sporadic cases of tractional retinal detachment [108,109] and endopthalmitis were recently reported.

B. Intra-vitreal ranibizumab

Intravitreal administration of ranibizumab , a humanized monoclonal antibody to vascular endothelial growth factor (VEGF-A), has been reported to be of benefit.In a recent clinical trial, intravitreal ranibizumab,either with prompt or deferred (24 weeks) focal/grid laser, resulted in superior visual acuity and OCT outcomes compared with focal/grid laser treatment without ranibizumab at both 1 and 2 years of follow-up. Approximately half of the eyes treated with ranibizumab had substantial visual acuity improvement (10 letter gain from baseline), whereas approximately 30% gained 15 letters, equivalent to 3 lines on the eye chart. (110)

C. Intra-vitreal Triamcinolone acetonide: (IVTA)

IVTA is used in the treatment of DME and . (111,112) TA has been applied as an intra-vitreal injection in suspension form the drug is conveniently available in concentrations of 40 Mg/ml in a sterile preparation (Kenalog®, Bristol-Myers Squibb,USA) and is commonly used in other specialties, such as orthoppedics, for treating inflammatory processes. We usually inject intravitreal drugs up to a volume of 0.1 ml without causing an unacceptable pressure elevation, and this is the maximum dose we can inject from the available preparation of TA. (113) in the treatment of diffuse DME and it has resulted in a very favorable functional outcome. Karacorlu, et al found that IVTA may be useful for treatment of NVDs in PDR. (111)

Mechanism of Action

The rationale for the use of corticosteroids in the treatment of diabetic macular edema follows from the observation that the breakdown of the blood retinal barrier leads to the edema. And is in part mediated by vascular endothelial growth factor (VEGF). Corticosteroids have been shown to inhibit VEGF and other cytokines and growth factors, thereby regulating endothelial cell tight junctions. In addition, they inhibit prostaglandin and leukotriene synthesis, which results in a local reduction of inflammatory mediators. The resultant anti-inflammatory effect contributes to the reduction of edema. Increased diffusion by modulation of calcium channels. Could also account for the efficacy of the corticosteroids in reducing macular edema.(114)

Complication of IVTA

There are however certain serious complications that could occur due to the injection, such as glaucoma, cataract, endophthalmitis, and pseudoendophthalmitis.(113) The last mentioned condition is caused if a 30-G needle is used instead of a 26 G needle, which causes a partial jamming due to the crystalline steroid in the barrel of the needle as the injection is given. This results in spraying of the drug into the vitreous at a high velocity, causing a pseudo-endophthalmitis like reaction. This can be differentiated from true endophthalmitis by virtue of the immediate nature of visual loss, lack of pain, swelling and anterior segment reaction, as well as a spontaneous resolution without antibiotic therapy, all of which are not consistent with an infectious process.(114)

III. Laser treatment

Results of the DRS (46-47) and the ETDRS [115,116] have conclusively established the efficacy of Laser treatment in DR. It is used for two sight threatening aspects of DR: PDR and CSME. [117,118]

The effectiveness of PRP in reducing VA loss and preventing subsequent neovascularization in cases of severe non-proliferative diabetic retinopathy and mild proliferative retinopathy has been shown in multicenter trials. [119,120]

IV. Combination treatment

A new model of treatment of diffuse diabetic macular oedema was established, not only injecting intravitreal triamcinolone acetonide as a primary line of treatment but also followed by a second line of treatment which is grid pattern argon laser photocoagulation.

The combination therapy (Intravitreal triamcinolone acetonide with deferred grid pattern argon laser photocoagulation six months after IVTA) revealed optimistic and marvelous results regarding improvement in BCVA & improvement in the central macular thickness. These results have the upper hand rather than using either type of treatment alone. [110]

V. Surgical treatment {Pars Plana Vitrectomy (PPV)}

PPV with posterior hyaloid removal could be beneficial in eyes with DME with massive hard exudates that have responded poorly to conventional laser photocoagulation. PPV can improve anatomic features and functional VA even for patients with advanced disease and indeed has become a mainstay of therapy for complications of PDR. VA is the most important indicator of surgical success to both the surgeon and the patient. [121]