# INTRODUCTION

International diabetes federation (IDF) estimates that 1 in 10 adults have diabetes in the Middle East and North Africa region. In Egypt, 42 % of diabetic patients have early stage of diabetic retinopathy and 5% of them are classified as legally blind[(1)].

Diabetic retinopathy (DR) is one of the leading causes of blindness in developed countries. The clinically visible onset of DR with microaneurysms, capillary nonperfusion, hemorrhages, and/or lipoprotein exudates has led to the assumption that DR is primarily a microvascular disease. Several studies have shown neural apoptosis, loss of ganglion cell bodies, glial reactivity, and reduction in thickness of the inner retinal layers in the earliest stages of DR. Some have proposed that diabetes causes retinal neuropathy through a microvascular mechanism. The structural neuropathy is corroborated by previous functional studies showing neuroretinal deficits in patients with diabetes, even before the onset of visible vascular lesions, including electroretinogram abnormalities, loss of dark adaptation and contrast sensitivity, color vision disturbances, and abnormal microperimetry[(2)].

The debate is still open as to whether diabetic retinal neuropathy is the effect of vascular diabetic retinopathy or

is primarily caused by direct neurologic damage from chronic hyperglycemia. Relationships between specific inner retinal layer thicknesses and DR status, on the one hand, as a proxy for vascular damage, and specific inner retinal layer thicknesses and duration of diabetes, on the other hand, as a proxy for chronic hyperglycemia, may shed additional light on this debate[(2)].

Optical coherence tomography (OCT), which provides B-mode retinal images, has become essential for diagnosing retinal disease and glaucoma since the technology was first reported by Huang et al. in 1991 .OCT also provides quantitative retinal thickness data, which are useful to monitor retinal changes in clinical and research settings[(3)].

Spectral domain (SD)-OCT allows imaging of the macula, with higher scan resolution and reduced motion artifacts compared with TD-OCT. TD-OCT collects 400 axial measurements per second with an axial resolution of approximately 10 μm. The scan rate of SD-OCT is at least 18,000 axial measurements per second with an axial resolution of 5μm, so that SD-OCT allows detailed three-dimensional (3-D), close-to-isotropic volumetric scans. The primary advantage of the more isotropic imaging in measuring retinal thickness is that fewer assumptions have to be made about the tissue between measured samples,

potentially leading to more accurate RT measurements. The high resolution of SD-OCT allows for enhanced definition of the retinal layers. We have recently developed a fully three-dimensional, automated algorithm to segment multiple surfaces in SD-OCT scans in the retina based on differences in refractive index, with an accuracy comparable to that of human experts[2].

# Aim of the Work

The aim of the study is the early detection of diabetic retinopathy before clinical signs appear by determining which retinal layers are most affected by diabetes.

# DIABETIC RETINOPATHY

Diabetic retinopathy, also known as diabetic eye disease, is that when damage occurs to the retina due to diabetes. It can eventually lead to blindness[4].

It is an ocular manifestation of diabetes, a systemic disease, which affects up to 80 percent of all patients who have had diabetes for 10 years or more[5]. Despite these intimidating statistics, research indicates that at least 90% of these new cases could be reduced if there were proper and vigilant treatment and monitoring the eyes[6].

## Pathophysiology

The exact mechanism by which diabetes causes retinopathy remains unclear, but several theories have been postulated to explain the typical course and history of the disease[7].

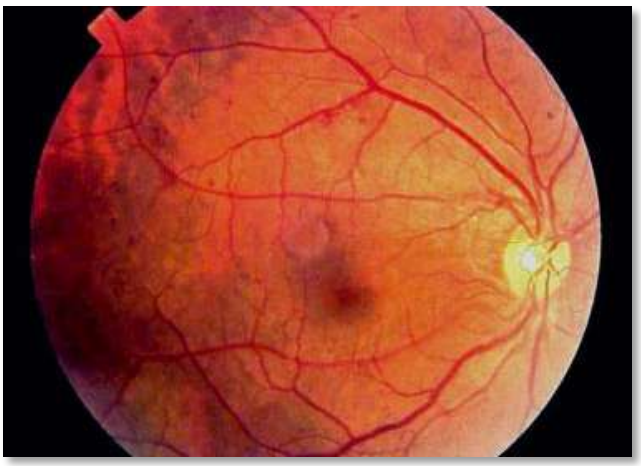

**Figure (1):** Fundus photograph of early background diabetic retinopathy showing multiple microaneurysms[11].

## Growth hormone

Growth hormone appears to play a causative role in the development and progression of diabetic retinopathy. Diabetic retinopathy has been shown to be reversible in women who had postpartum hemorrhagic necrosis of the pituitary gland (Sheehan syndrome). This led to the controversial practice of pituitary ablation to treat or prevent diabetic retinopathy in the 1950s. This technique has since been abandoned because of numerous systemic complications and the discovery of the effectiveness of laser treatment[8].

## Platelets and blood viscosity

The variety of hematologic abnormalities seen in diabetes, such as increased erythrocyte aggregation, decreased red blood cell deformability, increased platelet aggregation, and adhesion, predispose the patient to sluggish circulation, endothelial damage, and focal capillary occlusion. This leads to retinal ischemia, which, in turn, contributes to the development of diabetic retinopathy[8].

## Aldose reductase and vasoproliferative factors

Fundamentally, diabetes mellitus (DM) causes abnormal glucose metabolism as a result of decreased levels or activity of insulin. Increased levels of blood glucose are thought to have a structural and physiologic

effect on retinal capillaries causing them to be both functionally and anatomically incompetent[8].

A persistent increase in blood glucose levels shunts excess glucose into the aldose reductase pathway in certain tissues, which converts sugars into alcohol (eg, glucose into sorbitol, galactose to dulcitol). Intramural pericytes of retinal capillaries seem to be affected by this increased level of sorbitol, eventually leading to the loss of their primary function (ie, autoregulation of retinal capillaries). This results in weakness and eventual saccularoutpouching of capillary walls. These microaneurysms are the earliest detectable signs of DM retinopathy[8] (See the image below).

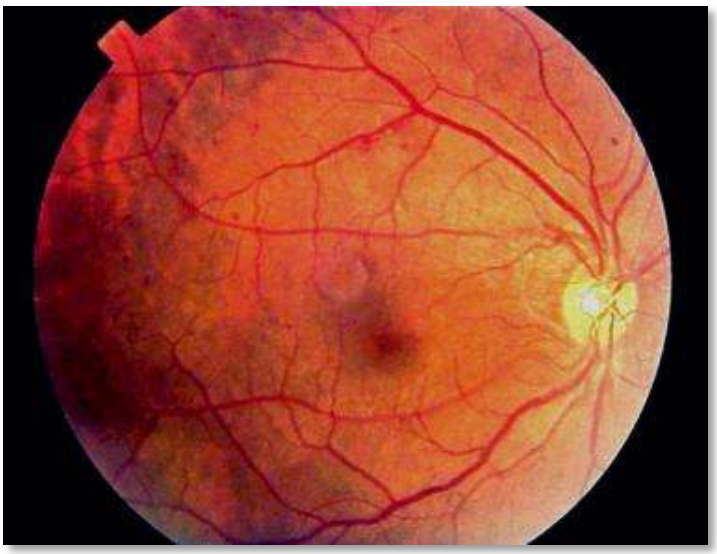

**Figure (2):**Fundus photograph of early background diabetic retinopathy showing multiple microaneurysms[11].

Using nailfold video capillaroscopy, a high prevalence of capillary changes is detected in patients with diabetes, particularly those with retinal damage.This reflects a generalized microvessel involvement in both type 1 and type 2 diabetes[8].

Ruptured microaneurysms result in retinal hemorrhages either superficially (flame-shaped hemorrhages) or in deeper layers of the retina (blot and dot hemorrhages)[8]. (See the image below)

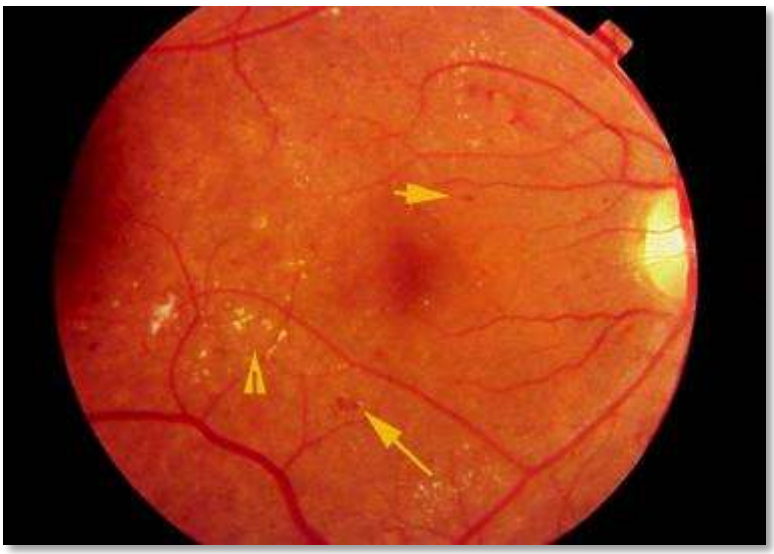

**Figure (3):** Retinal findings in background diabetic retinopathy, including blot hemorrhages (long arrow), microaneurysms (short arrow), and hard exudates (arrowhead)[11].

Increased permeability of these vessels results in leakage of fluid and proteinaceous material, which clinically appears as retinal thickening and exudates. If the swelling and exudation involve the macula, a diminution in central vision may be experienced[8].

## Macular edema

Macular edema is the most common cause of vision loss in patients with nonproliferative diabetic retinopathy (NPDR). However, it is not exclusively seen in patients with NPDR; it may also complicate cases of proliferative diabetic retinopathy.

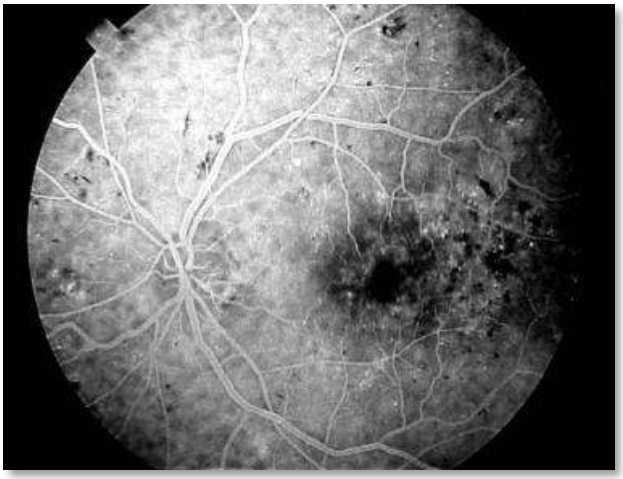

**Figure (4):** Fluorescein angiogram demonstrating foveal dye leakage caused by macular edema[11].

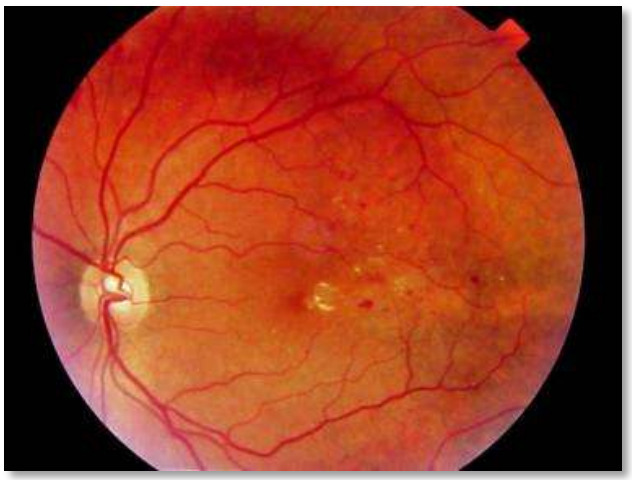

**Figure (5):** Fundus photograph of clinically significant macular edema demonstrating retinal exudates within the fovea[11].

Another theory to explain the development of macular edema focuses on the increased levels of diacylglycerol from the shunting of excess glucose. This is thought to activate protein kinase C, which, in turn, affects retinal blood dynamics, especially permeability and flow, leading to fluid leakage and retinal thickening[9].

## Hypoxia

As the disease progresses, eventual closure of the retinal capillaries occurs, leading to hypoxia. Infarction of the nerve fiber layer leads to the formation of cotton-wool spots, with associated stasis in axoplasmic flow. More extensive retinal hypoxia triggers compensatory mechanisms in the eye to provide enough oxygen to tissues. Venous caliber abnormalities, such as venous beading, loops, and dilation, signify increasing hypoxia and almost always are seen bordering the areas of capillary nonperfusion. Intraretinalmicrovascular abnormalities represent either new vessel growth or remodeling of preexisting vessels through endothelial cell proliferation within the retinal tissues to act as shunts through areas of nonperfusion[9].

## Neovascularization

Further increases in retinal ischemia trigger the production of vasoproliferative factors that stimulate new vessel formation. The extracellular matrix is broken down first by proteases, and new vessels arising mainly from the

retinal venules penetrate the internal limiting membrane and form capillary networks between the inner surface of the retina and the posterior hyaloid face[9]. (See the images below.)

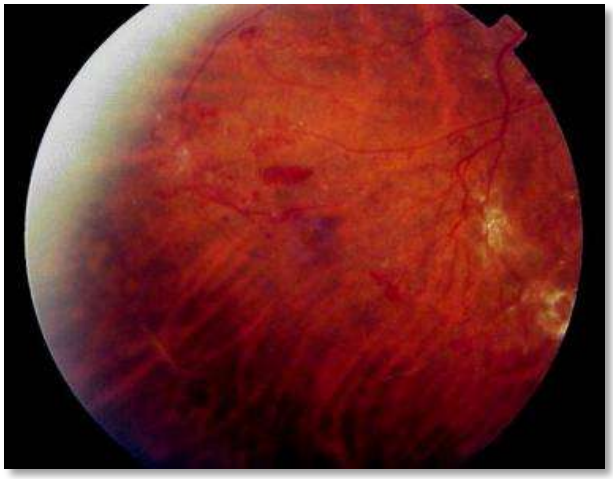

**Figure (6):** New vessel formation on the surface of the retina (neovascularization elsewhere (NVE)) associated with hemorrhage localized to the area of NVE[11].

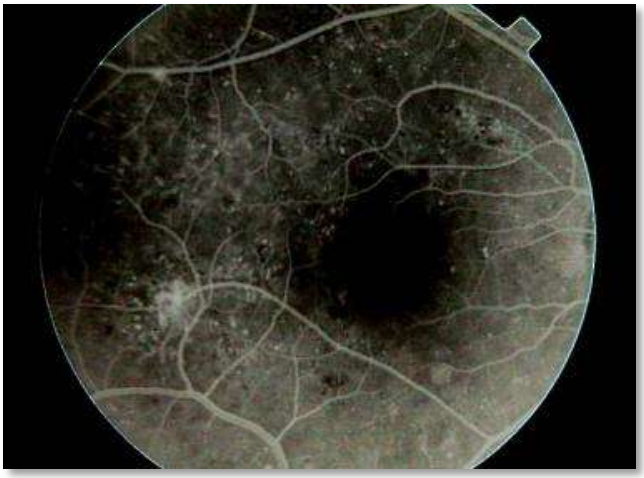

**Figure (7):** An area of neovascularization that leaks fluorescein on angiography associated with widening of foveal avascular zone and absence of perifovealnetwork[11].

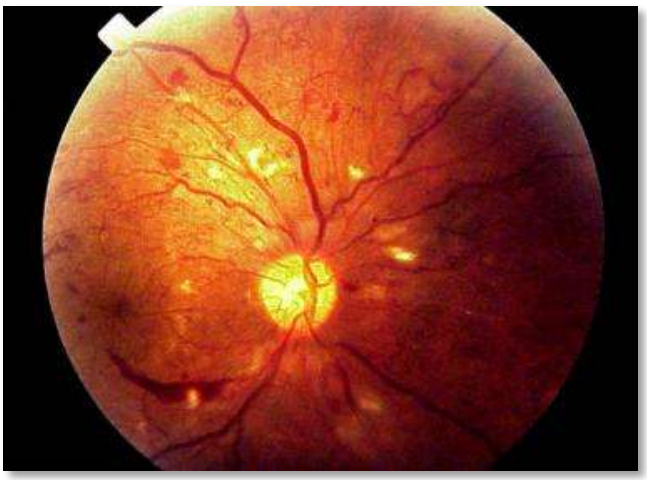

**Figure (8):** Boat-shaped preretinal hemorrhage associated with neovascularization elsewhere[11].

In patients with proliferative diabetic retinopathy (PDR), nocturnal intermittent hypoxia/reoxygenation that results from sleep-disordered breathing may be a risk factor for iris and/or angle neovascularization. Neovascularization is most commonly observed at the borders of perfused and nonperfused retina and most commonly occurs along the vascular arcades and at the optic nerve head. The new vessels break through and grow along the surface of the retina and into the scaffold of the posterior hyaloid face. By themselves, these vessels rarely cause visual compromise, but they are fragile and highly permeable. These delicate vessels are disrupted easily by vitreous traction, which leads to hemorrhage into the vitreous cavity or the preretinal space. These new blood vessels initially are associated with a small amount of fibroglial tissue formation. However, as the density of the neovascular frond increases, so does the degree of fibrous tissue formation. In later stages, the vessels may regress, leaving only networks

of avascular fibrous tissue adherent to both the retina and the posterior hyaloid face. As the vitreous contracts, it may exert tractional forces on the retina via these fibroglial connections. Traction may cause retinal edema, retinal heterotropia, and both tractional retinal detachments and retinal tear formation with subsequent detachment[9].

## Risk Factors:

### *Duration of diabetes:*

There is a direct correlation between the frequency and severity of DR and the duration of DM.

### *Glycemic control:*

There is an indirect relationship between the glycemic control and the development and progression of DR. DCCT and Early Treatment of Diabetic Retinopathy Study (ETDRS) have convincingly shown the reduction in risk of progression of DR with intensive treatment. Decrease in glycosylated hemoglobin levels was associated with a significant decrease in the progression of DR as well as the incidence of PDR. Intensive diabetic control leads to reduction in the development and progression of all diabetic complications.

### *Age and sex:*

The prevalence and severity of DR increases with increasing age in type 1 DM but not in type 2 DM.

## Hypertension:

Studies, such as WESDR and UKPDS, suggest that hypertension increases the risk and progression of DR and DME. In UKPDS, tight control of blood pressure resulted in 34% reduction in progression of retinopathy with 47% reduced risk of deterioration in visual acuity of three lines.

## Nephropathy:

The presence of gross proteinuria at baseline has been reported to be associated with 95% increased risk of developing DME among type I patients in the WESDR. The prevalence of PDR was much higher in patients with persistent microalbuminuria.

## Genetics:

In WESDR, patients with HLA DR4 and absent HLA DR3 were found to be at a greater risk of having PDR. Data from the DCCT also suggested genetic predisposition to diabetes. However, it is probable that both genetic and environmental factors play a role in the expression of DR .

## Serum lipid:

In WESDR, higher total serum cholesterol was associated with increased risk of having retinal hard exudates. ETDRS has reported a positive correlation between serum lipids and risk of retinal hard exudates in type 2 DM. Recently, Gupta et al. have reported reduction

in edema, severity of hard exudates and subfoveal lipid migration in patients with type 2 diabetes and dyslipidaemia, using a lipid-lowering drug, atorvastatin, asan adjunct to macular photocoagulation .

## Anemia:

In ETDRS, low hematocrit levels at baseline were identified as independent risk factor for the development of high-risk PDR and severe visual loss. It showed an increased risk of retinopathy in patients with the hemoglobin level of less than 12 g/dl. Anemia-induced retinal hypoxia is speculated as cause of development of microaneurysms and other retinopathy changes.

## Puberty:

In WESDR, younger onset subjects who were post-menarchal stood a 3.2 times greater risk of developing DR as compared to pre-menarchal subjects. Those who were older than 13 years at the time of diagnosis were more likely to have retinopathy than those who were younger. The exact mechanism by which puberty might exert its effect on the development of early retinopathy is not yet understood, but a possible role of hormonal factors is suspected.

## Socioeconomic status:

Although educational attainment was inversely associated with retinopathy in women in the WESDR,