INTRODUCTION

Diabetes Mellitus (DM) and its systemic and ophthalmic complications represent an enormous public health threat in the 21st century. The ophthalmic complications of diabetes are the leading cause of legal blindness in adults ***(Mahmood, 2008)***.

The World Health Organization (WHO) has estimated that by the year 2030 there will be 370 million persons affected with DM in the world, and every one of them will be at risk of developing diabetic retinopathy (DR) ***(Wild et al., 2004).***

The prevalence of DR remains high at 40% of diabetic patients. Globally, there are approximately 93 million people with DR, 17 million with proliferative diabetic retinopathy (PDR), 21 million with diabetic macular edema (DME) and 28 million with sight-threatening retinopathy as proliferative diabetic retinopathy (PDR) ***(Yau et al., 2012).***

DME is one of the most common causes of visual loss in patients with DM ***(Klien et al., 2009).***

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 ***(Yang et al., 2009),*** The pathophysiology of DME involves dilated capillaries, retinal microaneurysms, and loss of pericytes, with eventual impairment of the blood-retinal barrier

(BRB) ***(Ciulla et al., 2003)***, Breakdown of the BRB results in fluid leakage into the extracellular space, which disrupts macular structure and function on a cellular level ***(Knudsen et al., 2002; Rotsos and Moschos, 2008)***.

Risk factors that contribute to the progression of DME include increasing level of hyperglycaemia, diabetes duration, severity of diabetic retinopathy at baseline, diastolic blood pressure and the presence of gross proteinuria ***(Stitt et al., 2013)***.

The common diagnostic tools for assessing macular edema are stereo-ophthalmoscopy and fluorescein angiography. Stereoscopic examination of the fundus at the slit-lamp or on stereoscopic color fundus photographs is the standard method, as defined by the Early Treatment Diabetic Retinopathy Study (ETDRS), for evaluating macular thickening and for starting treatment when the clinical significant macular edema level has been reached ***(Kim et al., 2006)***.

Optical Coherence Tomography (OCT) is a high-resolution, cross-sectional imaging technique that allows detailed assessment of retinal thickness and morphologic evaluation of the neurosensory retinal layers. OCT imaging has rapidly been integrated into diagnosis and management of DME in routine clinical practice and clinical trials ***(Al-latayfeh et al., 2010)***.

One major advantage of OCT is that it allows measurement of retinal thickness from the tomograms by means of computer image-processing techniques ***(Hee et al., 1995).*** OCT is more sensitive to small changes in retinal thickness than slit-lamp biomicroscopy ***(Browning et al., 2004).***

Vascular Endothelial growth factor (VEGF) levels are elevated in the retina and the vitreous of eyes with diabetic retinopathy ***(Miller et al., 2013)***.

The effectiveness of intra vitreal injection of anti VEGF in regression of diffuse DME was dependent on the duration of diabetes in the SDRT and CME groups but not the SRD or Full groups, indicating that effectiveness of intravitreal injection of anti VEGF is dependent on the OCT tomography pattern indicating that VEGF plays a critical role in pathogenesis of SDRT and CME ***(Shimura et al., 2013).***

AIM OF THE WORK

To study the relationship between control and duration of diabetes mellitus and different OCT patterns of diffuse diabetic macular edema.

Chapter 1:

ANATOMY OF THE MACULA

Gross anatomy of the macula:

The retina proper is a thin, delicate layer of nervous tissue that has a surface area of about 266 millimeter² (mm²). The major landmarks of the retina are the optic disc, the retinal blood vessels, the area centralis with the fovea and foveola **(Figure 1)**, the peripheral retina (which include the equator) and the ora serrata. The retina is thickest near the optic disc, where it measures 0.56 mm. It becomes thinner towards the periphery, the thickness reducing to 0.18 mm at the equator and to 0.1 mm at the ora serrate ***(Bron et al., 1997)*.**

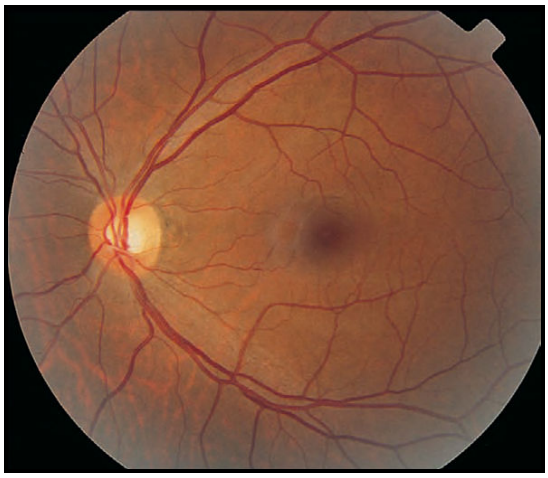


Figure (1): Normal fundus with macula encompassed by major vascular arcades ***(Quoted from Schubert, 2014)***.

The optic disc:

In the normal human eye, the optic disc is a circular to slightly oval structure that measures approximately 1.5 mm in diameter. Centrally it contains a depression which is known as the physiological cup ***(Bron et al., 1997)*.**

The area centralis:

The area centralis or central retina is divisible into the fovea and foveola, with a parafoveal and perifoveal ring around the fovea. This region of the retina, located in the posterior fundus temporal to the optic disc, is demarcated approximately by the upper and lower temporal retinal vessels and has an elliptical shape horizontally. With an average diameter of about 5.5 mm, the area centralis corresponds to approximately 15° of the visual field and it is adapted for accurate diurnal vision and color discrimination **(Figure 2)** ***(Bron et al., 1997)*.**

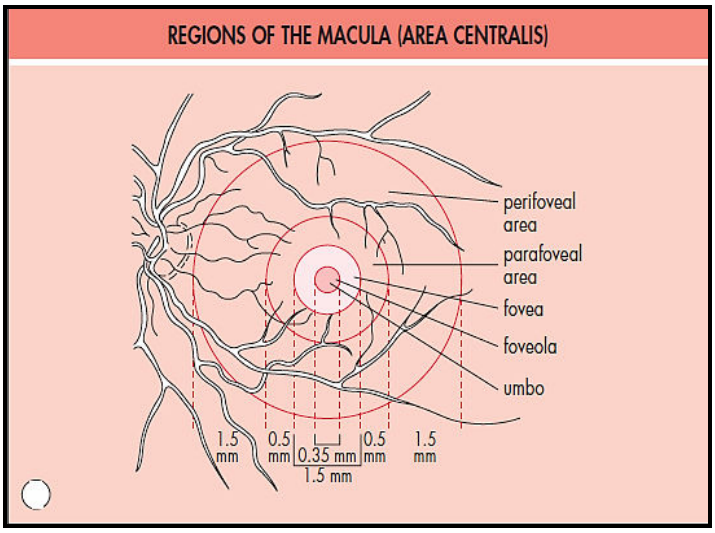


Figure (2): Diagram showing regions of the macula ***(Quoted from Schubert, 2014).***

The macula lutea:

The macula lutea is an oval zone of yellow coloration within the central retina. It is not only easily discernible on ophthalmoscopic examination of the living eye, but in red-free light and in darkly pigmented individuals it is seen as a horizontally oval zone that includes the fovea. In freshly enucleated eyes, the macula lutea appears as a greenish-yellow elliptical region some 3 mm in diameter, with the center being the foveola, which itself is colorless. With special optical devices, however, the faint yellow color can be observed as a wider zone, approximately 5 mm in diameter, in the central retina. The yellow coloration probably derives from the presence of the carotenoid pigment, xanthophylls, in the ganglion and bipolar cells ***(Bron et al., 1997).***

The fovea:

The fovea **(Figure 3)** is located at the posterior pole of the globe, 4 mm temporal to the center of the optic disc and about 0.8 mm below the horizontal meridian It has a diameter of 1.85 mm (which represents 5° of the visual field) and an average thickness of 0.25 mm, it represents an excavation in the retinal center and consists of a margin, a declivity, and a bottom. The bottom corresponds to the foveola, the center of which is called the umbo. The umbo represents the precise center of the macula, the area of retina that results in the highest visual acuity. Usually, it is referred to as the center of the fovea or macula. Although both terms are commonly used clinically, neither is a precise anatomical designation ***(Schubert, 2014).***

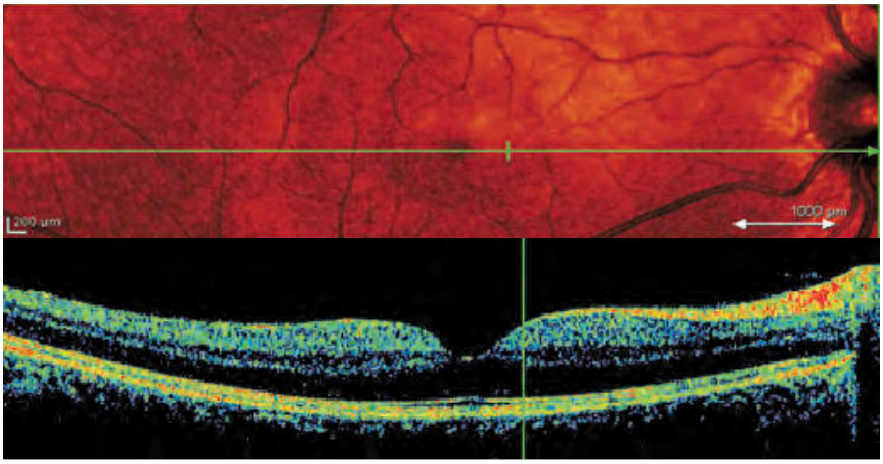


Figure (3): Normal fovea by OCT scan ***(Giani et al., 2009).***

The foveola:

The foveola which measures 0.35 mm in diameter and 0.13 mm in thickness represents the area of the highest visual acuity in the retina, even though its span corresponds to only 1° of the visual field. This is due partly to the sole presence of cone photoreceptors and partly to its avascular nature. The foveola usually appears deeper red than does the adjacent retina because of the rich choroidal circulation of the choriocapillaris, which shines through it, also because the retinal pigment epithelium in this area is darker and more pigmented with tall and narrow cells ***(Bron et al., 1997).***

The peripheral retina:

The peripheral retina **(Figure 4)** is divided arbitrarily into belts of near, middle, far, and extreme periphery.The belt of the near periphery is 1.5 mm wide, and the belt of the middle periphery, or equator, is 3 mm wide. The far periphery extends from the equator to the ora serrata. The width of this belt varies, depending on ocular size and refractive error. The average circumference of the eye is 72 mm at the equator and 60 mm at the ora serrata, and the average width of this belt is 6 mm ***(Schubert, 2014)***.

Since peripheral retinal pathology is usually charted in clock hours, 1 clock hour corresponds to 5–6 mm of far peripheral circumference. Therefore, the far periphery of the

retina may be divided into 12 squares that measure approximately 6 × 6 mm. As a result of the insertion of the posterior vitreous base, most peripheral pathology falls into these squares. The ora serrata and pars plana are referred to as the extreme periphery ***(Schubert, 2014)*.**

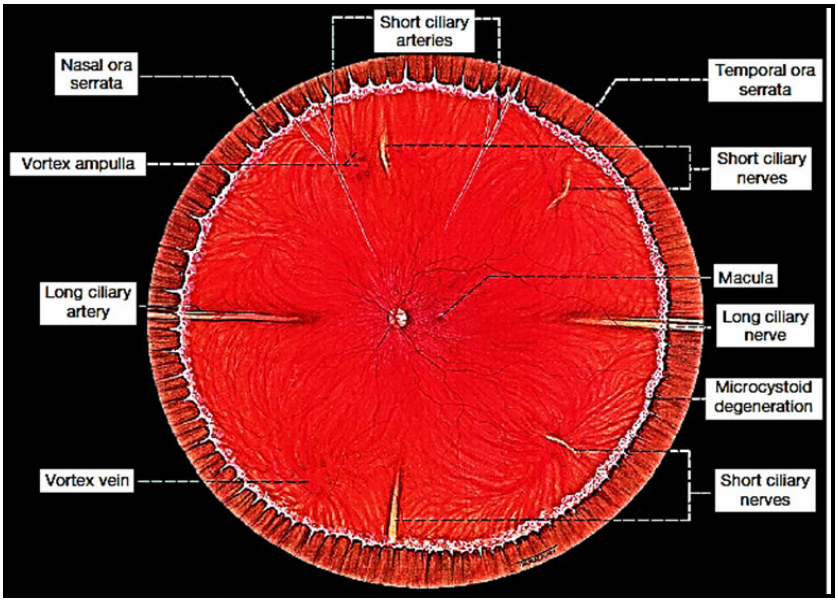


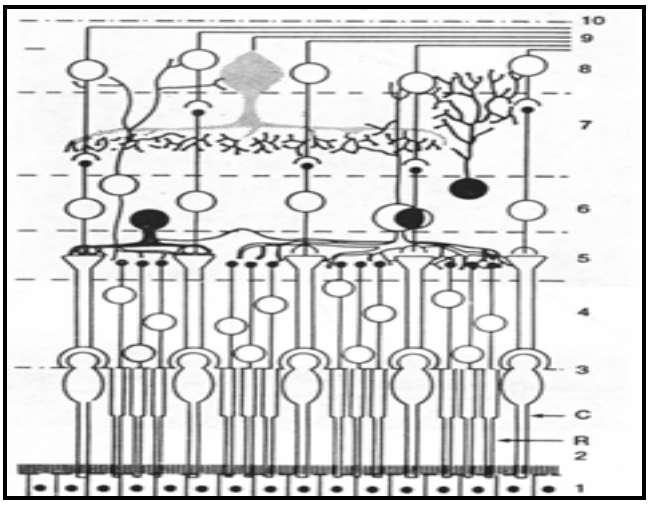
Figure (4): The ora serrata and normal anatomical landmarks ***(Quoted from Kanski and Bowling, 2011).***

Microscopic anatomy of the macula:

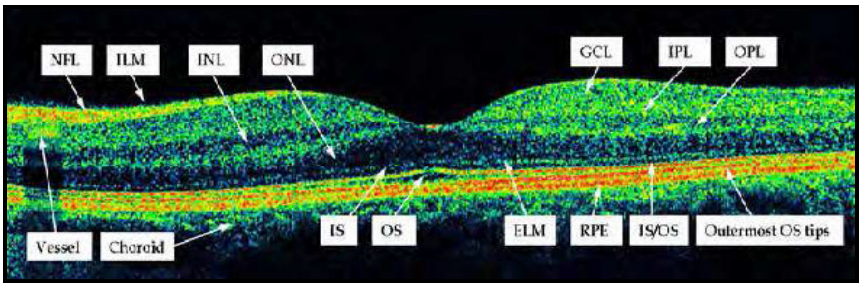
As seen in cross section by light microscopy, the retina is represented by 10 layers **(Figure 5)**, from the scleral side inward they are:

1- Retinal pigment epithelium (RPE).
2- Photoreceptor layer of rods and cones.
3- External limiting membrane (ELM).
4- Outer nuclear layer (ONL).
5- Outer plexiform layer (OPL).
6- Inner nuclear layer (INL).
7- Inner plexiform layer (IPL).
8- Ganglion cell layer (GCL).
9- Nerve fiber layer (NFL).
10- Internal limiting membrane (ILM).

(Bron et al., 1997)



(A)



(B)

Figure (5): Morphological organization of the retina. (A) Diagrammatic representation of the elements that comprise the retina. 1 = Pigment epithelium; 2 = photoreceptor layer consisting of rods (R) and cones (C); 3 = external limiting membrane; 4 = outer nuclear layer; 5 = outer plexiform layer; 6 = inner nuclear layer; 7 = inner plexiform layer; 8 = ganglion cell layer: 9 = nerve fiber layer, 10 = internal limiting membrane ***(Quoted from Bron et al., 1997).***

(B) Cross section of the retina using Spectral Domaion-OCT: RPE: retinal pigment epithelium, IS: photo receptor inner segment, OS: Photoreceptor outer segment, ELM: external limiting membrane, ONL: outer nuclear layer, OPL: outer plexiform layer, INL: inner nuclear layer, IPL: inner plexiform layer, GCL: ganglion cell layer, NFL: nerve fiber layer, ILM: internal limiting membrane ***(Quoted from Koleva-Georgieva, 2012)***.

At the fovea the only layers that are present are the retinal pigment epithelium, the photoreceptors (cones only), the external limiting membrane, the outer nuclear layer (which contains the nuclei of the cone cells), the inner fibers of the photoreceptors (the so called 'Henle´s fiber layer'), and the internal limiting membrane **(Figure 6)** ***(Bron et al., 1997).***

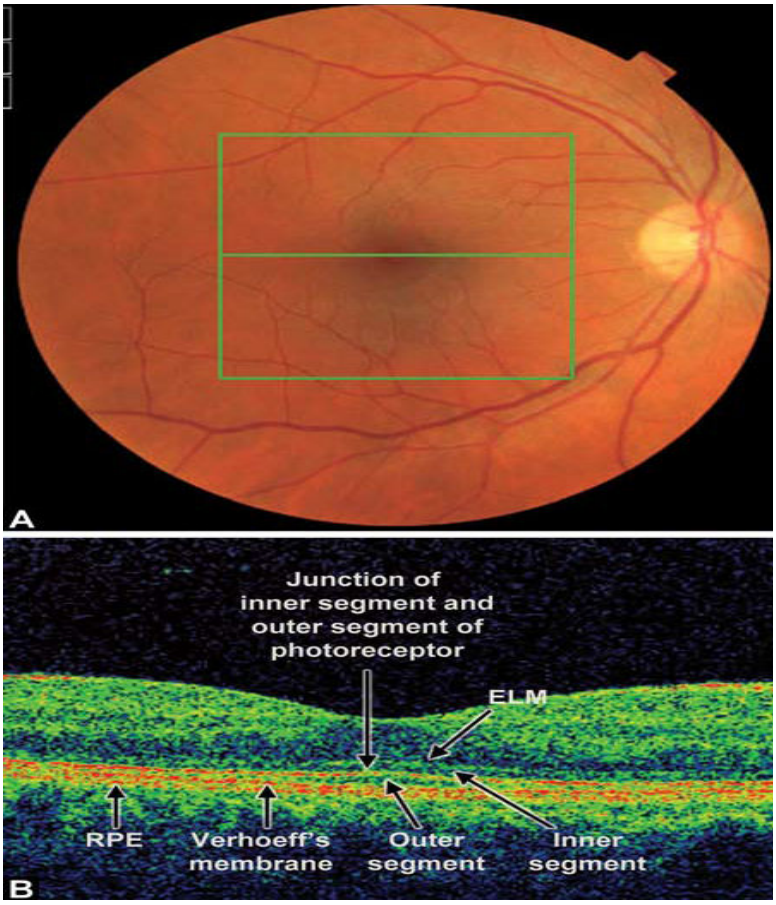


Figure (6): Morphological organization of fovea: **(A)** Color photograph of retina showing line scan on fovea.**(B)** The magnified image at the fovea shows three lines over the retinal pigment epithelium (RPE), that is, the external limiting membrane (ELM) ***(Quoted from Dacosta et al., 2011).***

Vascular supply of the macula:

The macula is divided into two layers according to blood supply:

i- Outer layer (RPE and photoreceptors): these layers are supplied by transudation from choriocapillaris network. It is derived from posterior ciliary arteries (choroidal circulation).

ii- Inner layer: terminating externally at the outer border of the inner nuclear layer. These layers are supplied from capillary network of central retinal artery (CRA) which is the first branch of the ophthalmic artery (retinal circulation).

The choroidal circulation is derived primarily from the long and short ciliary arteries with some contribution from the anterior ciliary arteries. Histologically, the choroid is divided into five layers. Starting from the retinal side, these include Bruch's membrane, three vascular layers (the choroicapillaries, Sattler's layer and Haller's layer) and the suprachoroidea. Haller's layer includes large arteries and veins, while Sattler's layer is composed of medium and small arterioles that feed the capillary network of the choriocapillaris and venules. The choroidal arteries arise from the long and short posterior ciliary arteries and branches of Circle of Zinn (around the optic disc). The choriocapillaris is a highly anastomosed network of capillaries (with little or no basement membrane material),

forming adense capillary network opposed to Bruch's membrane ***(Kur et al., 2012).***

Drainage of blood from the choroid is thought to occur exclusively through the vortex veins that ultimately merge with the ophthalmic vein ***(Kur et al., 2012).***

The retinal circulation is derived from the central retinal artery a branch from the ophthalmic branch of the internal carotid artery, entering the optic nerve within the orbit approximately 12 mm behind the globe and subsequently coursing through the lamina cribrosa to access the retina. On the inner surface of the retina, superior and inferior branches immediately give rise to temporal and nasal arcades, which supply the 4 quadrants of the retina. Corresponding retinal veins drain these quadrants and meet at the optic nerve head as the central retinal vein, which drains into the cavernous sinus both directly and via the superior ophthalmic vein ***(Bharadwaj et al., 2013).***

The retinal arteries and veins lie in the nerve fiber and ganglion cell layers. Arteriolar branches give rise to capillary networks, which exist in trilaminar form at the posterior pole. The layers include: radial peripapillary capillaries in the inner nerve fiber layer, mostly in a "long chain" pattern; an inner capillary plexus in the nerve fiber and ganglion cell layers; and a deep capillary plexus in the inner plexiform layer and inner nuclear layer. These layers reduce to 2 at the equator and only 1