INTRODUCTION

Diabetes Mellitus (DM) is a chronic metabolic disease with considerable morbidity and mortality ***(WHO, 2008).***

The prevalence of DM is projected to approach 600 million people worldwide by 2035. Such increase is thought to be the result of population growth, aging, obesity, and sedentary lifestyles ***(Chan et al., 2009).***

DM is classified into two distinct types: Type I diabetes (insulin dependent or juvenile onset), type II diabetes (noninsulin dependent, adult onset). The latter is characterized by insulin resistance in peripheral tissues and a secondary insulin secretory defect. Between 70 and 90% of diabetic patients have type II DM ***(Zhivov et al., 2013).***

DM can affect many ocular structures ,including the cornea, tear film, lens, choroid & retina ***(He and Bazan, 2012; Congdon et al., 2003).***

Diabetic retinopathy (DR), a complication of DM, affects a third of diabetics and is the principal cause of vision loss among the working age group in developed countries ***(Cheung et al., 2010).*** It remains a leading cause of preventable blindness ***(Yau et al., 2012).***

Diabetic macular edema (DME), characterized by increased vascular permeability and the deposition of hard exudates at the central retina, can develop at any stage of DR and affects 21 million people globally ***(Stewart, 2017).***

Through regular eye examinations and adequate diabetic management, diabetes-related vision loss can be prevented in 98% of cases ***(Kiire et al., 2013).*** Proper early interventions can reduce the incidence and progression of DR and DME, and hence may prevent development and progression of vision loss ***(Fong et al., 2007; Pershing et al., 2014; Wells et al., 2015; Wells et al., 2015; Gross eet al., 2015; Kroenke, 2015).***

Therefore, early detection of DR and DME through screening programs and appropriate referral for therapy are essential for preserving vision in individuals with DM ***(Chasan et al., 2014).***

Aim of the Work

The aim of this work is to correlate between OCT findings and VA in controlled type II diabetic patients with DME.

CHAPTER (1):
ANATOMY OF THE RETINA

The retina is a translucent tissue, forming the innermost coat of the globe. It extends from the macula posteriorly to the ora serrata anteriorly .The retina is attached to the vitreous at the optic nerve, macula, retinal vessels, and vitreous base ***(Stewart, 2017).***

Figures 1 and 2 show the microscopic structure of the retina, with the outermost being the retinal pigment epithelium (RPE), while the innermost is the internal limiting membrane.

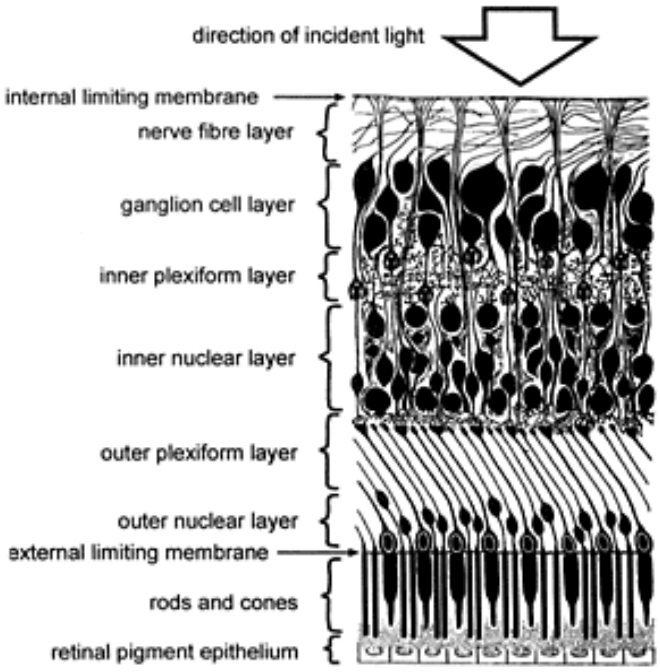

Figure (1): Diagram showing layers of the retina ***(Kaura et al., 2008)***

The macula lutea (Figure3)

It`s a circular area of diameter 5.5 mm, with the center located 4.0-5.0 mm temporal, and 0.53 - 0.8mm inferior to the center of the optic disc. It is the only region of the retina with more than one layer of ganglion cells, and called so because it contains high concentration of xanthophyll pigment in the ganglion and bipolar cell layers, giving the retina its characteristic yellow color, Xanthophyll decreases chromatic aberrations, absorbs potentially toxic blue light, and gets rid of active free oxygen radicals ***(Kanski, 2016) (Stewart, 2017).***

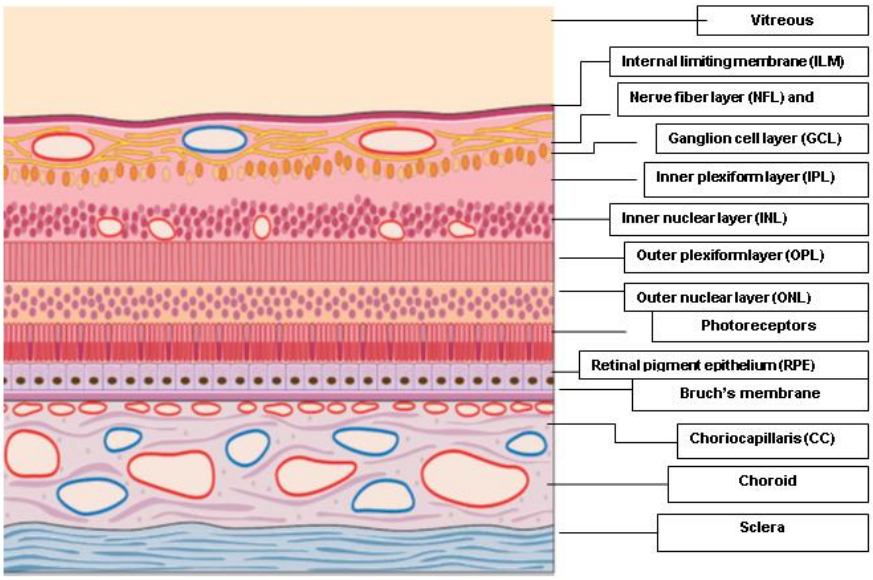

Figure (2): Modified schematic drawing of a microscopic section of retina, RPE, and choroid ***(Srinivas and Sadda, 2016)***

The Fovea:

It`s a depression in the inner retinal surface at the center of the macula, with a diameter of 1.5 mm (about one disc). It contains long and slender red and green (no blue) cones that are aligned perpendicular to the RPE, with maximum sensitization to incoming photons. Light scatter is minimized, because the fovea lacks the INL, IPL, GCL, and NFL ***(Kanski, 2016).***

The Foveola:

It forms the central floor of the fovea and has a diameter of 0.35 mm. It is the thinnest part of the retina, being devoid of ganglion cells and consists only of cones and their nuclei ***(Kanski, 2016).***

The Umbo

Is a tiny depression in the very center of the foveola, which corresponds to the foveal reflex, loss of which may be an early sign of damage ***(Kanski, 2016).***

The foveal reflex appears to lie just in front of the center of the foveola, and therefore overlies the anatomic umbo ***(Penfold et al, 2001; Tasman et al, 2006).***

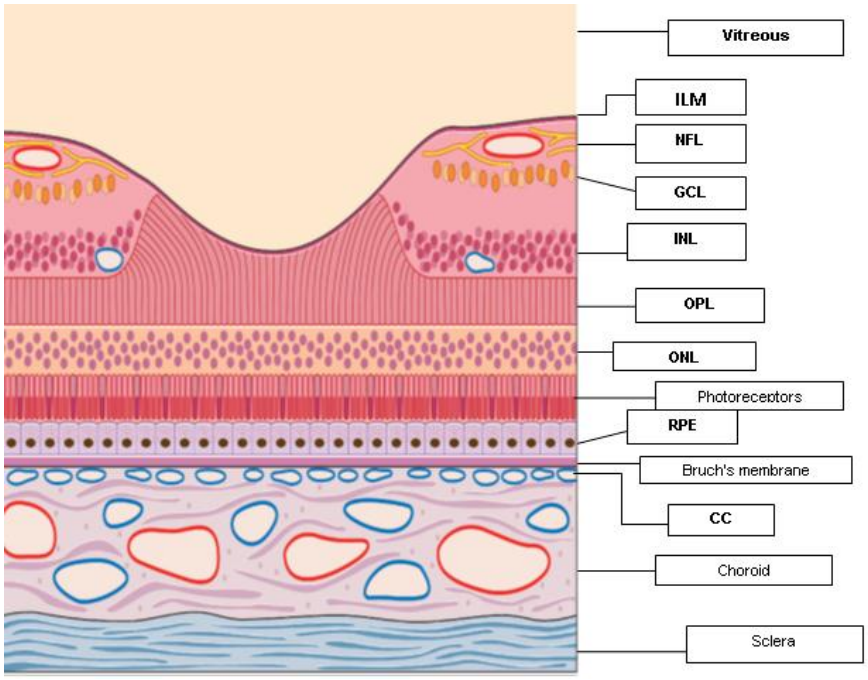

Figure (3): Modified schematic drawing of a microscopic section of the macula ***(Srinivas and Sadda, 2016)***

The Parafovea and Perifovea (Figure 4)

Two terms used in clinical practice. The parafovea is a 0.5 mm ring of retina that surrounds the fovea, and is characterized by an accumulation of ganglion and inner nuclear cells with a thickened Henle's layer. The density of cones in the parafovea is lower than within the fovea and rods start to be found. The perifovea is the outermost ring of the retina centralis, between 1.25 and 2.75 mm from the foveal center. The perifovea begins where the GCL is four nuclei thick and ends where it thins to a single layer ***(Stewart, 2017).***

Ophthalmoscopically, the anatomic subdivisions of the macula are ill defined ***(Penfold et al., 2001; Tasman et al., 2006).***

In healthy subjects**,** foveal thickness and central foveal thickness on the OCT are 212 ± 20 and 182 ± 23 μm, respectively. Macular thickness measurements are thinnest at the center of the fovea, thickest within 3-mm diameter of the center, and diminished toward the periphery of the macula. The temporal quadrant is thinner than the nasal quadrant. Central foveal thickness also is manually determined as 170 and 174± 18 μm, approximately 12 μm less than the value automatically obtained from the OCT software ***(Hee et al., 1998; Chan et al., 2006)***

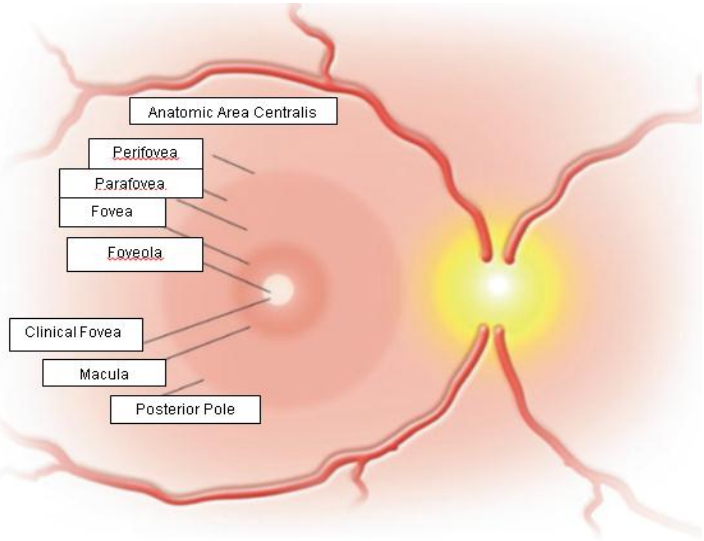

Figure (4): This drawing shows the anatomic and clinical areas of the macula. Despite being referenced more frequently by anatomists, the terms parafovea and perifovea are often used in clinical practice to describe the locations of macular pathology ***(Stewart, 2017).***

Blood Supply of the Retina

The retinal demand for oxygen is higher than that of any other tissue in the body. To meet this high metabolic demand, it has dual blood supply. The retinal blood vessels provide nourishment for the inner retinal layers and carry out waste products from them, while the outer retinal layers, containing the RPE and the photoreceptors, are avascular and are supplied by diffusion from the CC ***(Stewart, 2017).***

1- Inner retinal circulation:

The arterial supply of the inner retina is derived from the central retinal artery branch of the ophthalmic artery ***(Stewart, 2017).***

The retinal capillary network is spread throughout the retina, diffusely distributed between the arterial and venous systems. There are three specific areas of the retina that are devoid of capillaries; the ora serrate ridges (ora teeth), the 350-750 μm wide capillary-free region centered on the fovea is another area lacking retinal capillaries (foveal avascular zone (FAZ)) ,the retina adjacent to the major arteries and some veins lacks a capillary bed ***(*Besharse *and Dean, 2011).***

The retinal veins (mainly venules) are present in the inner retina, where they occasionally interdigitate with their associated arteries. When two vessels cross, the artery usually lies anterior to the vein, and the two vessels share a common adventitial sheath ***(Hayreh, 2011).***

2- Outer retinal circulation:

By two separate arterial systems; two long posterior ciliary arteries, and about 16–20 short posterior ciliary arteries that penetrate the sclera in a circular pattern surrounding the optic nerve ***(*Besharse *and Dean, 2011).***

Retinal pigment epithelium (RPE): (figure 5)

The RPE consists of a monolayer of cuboidal-shaped cells derived from neuroectoderm. The RPE extends from the margin of the optic disc to the ora serrata, where it is contiguous with the pigmented epithelium of the pars plana. The RPE has several features: tight junctional complexes including zonula occludens and zonula adherens; apical microvilli; basement membrane infoldings; melanin granules; and phagosomes.

The functions of the RPE include maintaining the outer blood-retinal barrier; promotion of retinal adhesion; synthesis of extracellular matrix; degradation of photoreceptor outer segments; retinol uptake and transport;

melanin absorption of scattered light;blocking external light from reaching the retina through the sclera directly; supporting the nutritional requirements of outer retina; and response to disease (atrophy, hyperplasia). Via secretion of a large number of local growth factors and immunomodulatory cytokines, including vascular endothelial growth factor (VEGF), ciliary neurotrophic factor, fibroblasts, and platelet-derived growth factors. It also contains superoxide dismutase, catalase, glutathione, melanin, ascorbate, and other antioxidants that protect the RPE against the effects of oxidative damage ***(Strauss, 2005; Thumann et al., 2006; Besharse and Dean, 2011).***

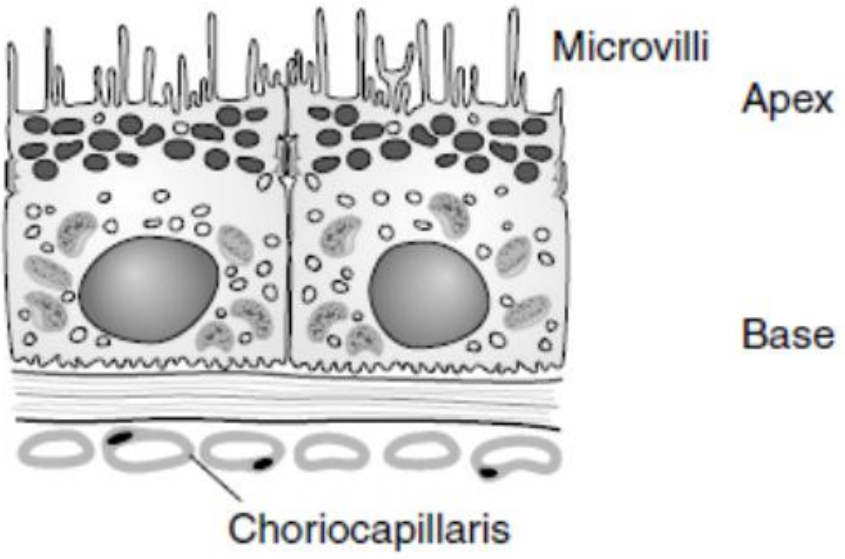

Figure (5): The RPE is a monolayer of cuboidal-shaped cells derived from neuroectoderm ***(Hayreh, 2011)***

Blood-retinal barrier (BRB): (Figure 6)

The BRB has two components: the inner and outer BRBs. The inner BRB is composed of tight junctions between the retinal vascular endothelial cells and pericytes, while the outer BRB is the result of tight junctions between RPE cells. Both the inner and outer BRBs contribute to the normal retinal homeostasis by restricting various permeabilities from the plasma. The BRBs may be disrupted by a variety of conditions, including ischemia and inflammation. The outer BRB is important in the pathogenesis of diffuse DME ***(Nitta et al, 2003; Felinski and Antonetti, 2005).***

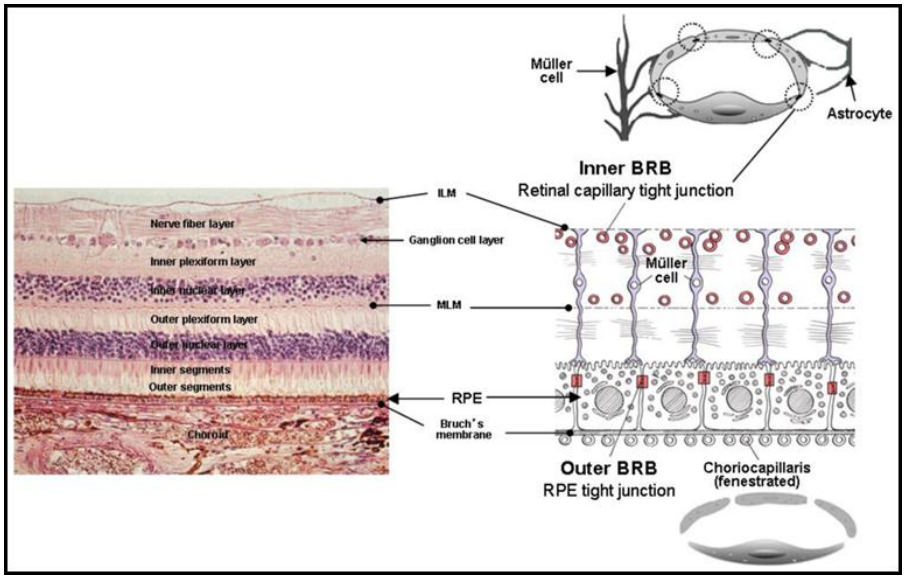

Figure (6): Blood retinal barrier ***(Kuno and Fujii, 2011).***

Chapter (2): Diabetes Mellitis &Diabetic Retinopathy (DM & DR)

DM is a chronic metabolic disease with considerable morbidity and mortality, with approximately 347 million persons worldwide (approximately 8.3% of the adult population) suffering from it. Such increase is thought to be the result of population growth, aging, obesity, socioeconomic conditions and sedentary lifestyles ***(Colagiuri et al., 2014; Tao et al., 2015).***

The prevalence of DM for all age groups is expected to be 4.4% by 2030; this makes DR a leading cause of vision loss in many developed countries ***(Congdon et al., 2003; Fong et al., 2004)***.

DM is classified into two distinct types. Type I DM (insulin dependent or juvenile onset) is characterized by destruction of the insulin secretory pancreatic β-cells of the islets of Langerhans caused by an autoimmune process, usually leading to absolute insulin deficiency. Type II DM (noninsulin dependent, adult onset) is characterized by insulin resistance in peripheral tissues, impaired regulation of hepatic glucose production, and declining ß-cell function that eventually leads to ß-cell failure and dependence on exogenous insulin. Between 70 and 90% of diabetic patients have type II DM ***(Tao et al., 2015).***

The development of DM increases the risk of developing irreversible complications that can be divided into macrovascular and microvascular complications. The former includes cerebrovascular, coronary, and peripheral vascular disease, while the latter includes diabetic neuropathy (vasa nervorum of the peripheral nerves, DR, and diabetic nephropathy (renal glomeruli). The prevalence of these complications is strongly related to the type and duration of DM ***(Donnelly et al, 2000; Brownlee, 2001; Klein et al, 2001; Kato et al, 2002).***

DM affects all parts of the ocular adnexae, neurosensory pathway, and ocular motility system, but most DM-related vision loss stems from retinopathy due to microvascular complications. DR and cataract, represent the leading cause of visual impairment and vision loss in adults younger than 75 years. Of the 246 million people with diabetes, about a third has signs of DR, and a third of these might have vision-threatening retinopathy, defined as severe retinopathy or ME ***(Saaddine et al., 2008).***

In many countries, DR is the most frequent cause of preventable blindness in working-aged adults (20–74 years) ***(Mohamed et al., 2007).***

Retinopathy was considered a vasculopathy that results from breakdown of the BRB and closure of retinal

capillaries. Recent studies suggest that DR is a neuro-retinopathy and that vascular changes occur later in the course of the disease ***(Stewart, 2017).***

Visual impairment due to DR and DME has an impact on patients' quality of life, and their ability to manage the disease, which affects the incidence of other diabetic complications and overall quality of life ***(McKean-Cowdin et al, 2007; McKean-Cowdin et al, 2008).***

Diabetic retinopathy

An estimated 50,000 new cases of retinal neovascularization and diabetic macular edema (DME) occur every year, and about half of the patients who would benefit from treatment remain undiagnosed The number of people worldwide with DR will increase from 126.6 million in2010 to 191.0 million by 2030, and the number with vision-threatening diabetic retinopathy (VTDR) is estimated to increase from 37.3 million to 56.3 million. The overall prevalence of DR was 34.6% for any DR, 6.96% for proliferative DR, 6.81% for DME, and 10.2% for VTDR ***(Kempen et al., 2004; Zheng et al., 2012).***

The presence of Clinically Significant Macular Edema (CSME) increases the risk of moderate visual loss to about 30—50% depending on the level of baseline Visual Acuity (VA) ***(Fong et al., 1999).***