Acknowledgment

Praise to ***Allah*** *who gave me everything, keep me guided and who allowed this work to be done.*

It is indeed an honor to me to be supervised by ***Prof. Dr./ Hoda M. Saber Naeim,*** *Professor of Ophthalmology, Faculty of Medicine, Ain Shams University, who was really so supportive & helpful to me in this study.*

And I'm really grateful to ***Dr./ Raafat Ali Rihan****, Assistant Professor of Ophthalmology, Faculty of Medicine, Ain Shams University, for his valuable advices and continuous efforts and his guidance to me throughout this study.*

And of course, I can't find enough words to thank my parents, my family and all my professors for their endless support.

Intravitreal Drugs in Diabetic Macular Oedema

Essay

Submitted for Partial Fulfillment of Master Degree in

Ophthalmology

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٢٠٠٧

استخدام الحقن بالأدوية داخل الجسم الزجاجي في تورم المقولة بسبب مرض البول السكري

رسالـــة

مقدمة توطئة للحصول على درجة الماجستير

في طب وجراحة العين

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٢٠٠٧

List of Abbreviation

AGES : Advanced glycation end products

ALT : Argon laser trabeculoplasty

ARI : Aldose reductase inhibitor

BCVA : Best corrected visual acuity

BDR : Background diabetic retinopathy

BRB : Blood retinal barrier

BRVO : Branch retinal vein occlusion

CAI : Carbonic anhydrase inhibitor

CFT : Central foveal thickness

CI : Confidence interval

CME : Cystoid macula edema

CRVO : Cetral retinal vein occlusion

CSME : Clinicaly significant macular edema

DAG : Diacylglecrol

DM : Diabetes mellitus

DR : Diabetic retinopathy

ETDRS : Early treatment diabetic retinopathy study

FA : Fluorescein angiography

FAZ : Foveal avascular zone

FFA : Fundus fluorescein angiography

GH : Growth hormone

HBP : High blood pressure

HLA : Human leukocyte antigen

IDDM : Insulin dependent diabetes mellitus

IGF **:** Insulin growth factor

ILM **:** Internal limiting membrane

INL **:** Inner nuclear layer

IOP **:** Intraocular pressure

IRMA **:** Intraretinal microvascular abnormality

IVTA **:** Intravitreal triamcinolone acetinoid

LDL **:** Low density protein

NFL **:** Nerve fiber layer

NIDDM **:** Non insulin dependent diabetes mellitus

NPDR **:** Non proliferative diabetic retinopathy

NV **:** Neovascularization

NVG **:** Neovascular glaucoma

OCT **:** Optical coherence tomography

ONL **:** Outer nuclear layer

OPL **:** Outer plexiform layer

PDR **:** Proliferative diabetic retinopathy

PEDF **:** Pigment endothelial deraived factor

PKC **:** Protein kinase C

PRP **:** Panretinal photocoagulation

ROS **:** Reactive oxygen species

SCMT **:** Standrised change in macular theckining

SLT **:** Selective laser trabeculoblasty

VEGF **:** Vascular endothelial growth factor

VMT **:** Vitreo-macular traction

CONTENTS

Aim of the Work

The aim of this work is to highlight and evaluate the role of intravitreal drugs in diabetic macular edema.

Anatomy of the Macula

Macroscopic anatomy:

Retina or nervous coat of the eye is a delicate diaphanous tissue that varies in thickness: ٠,١٣ mm at the umbo, ٠,٥٦mm at the foveal margin and adjacent to the optic nerve head (ONH), ٠,١mm at the ora serrata and ٠,٢mm at the equator.

The macula (macula lutea or central retina)*:** is defined anatomically as that portion of the posterior retina that contains xanthophyll and two or more layers of ganglion cells. It measures approximately ٥,٥mm in diameter and is centered approximately ٤mm temporal to and ٠,٨mm inferior to the center of the optic disc. It corresponds to approximately ١٥ degrees of the visual field ***(Gass, ١٩٩٧).

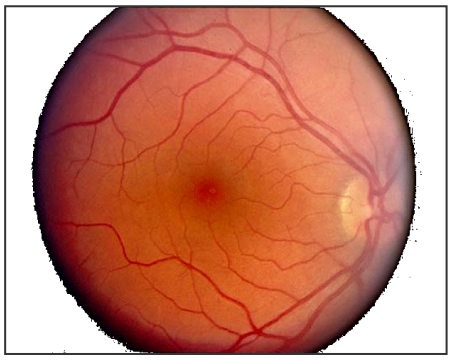

Fig. (١): Ophthalmoscopic appearance of the retina to show the macula lutea (yellow around fovea).[١]

The fovea (fovea centralis): is a depression in the inner retinal surface at the center of the macula with a diameter of ١,٥

mm (about ١ disc diameter). Ophthalmoscopically it gives rise to an oval light reflex because of the increased thickness of the retina and internal limiting membrane at its border.

The foveola (foveal pit): forms the central floor of the fovea and has a diameter of ٠,٣٥ mm. It is the thinnest part of the retina.

The foveal avascular zone (FAZ): is located within the fovea but extends beyond the foveola. The exact diameter is variable and its location can be determined with accuracy only by fluorescein angiography.

The umbo: is a tiny depression in the very center of the foveola which corresponds to the foveolar reflex, loss of which maybe an early sign of damage ***(Jack J Kanski, ٢٠٠٣)***.

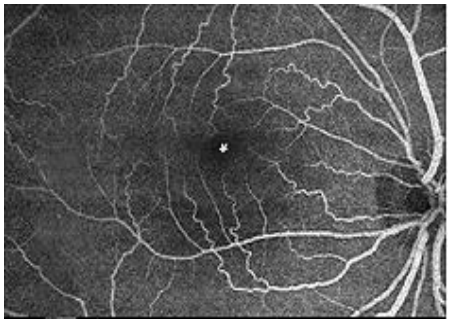

Fig. (٢): Foveal avascular zone (FAZ) determined by fluorescein angiography.[٢]

Microscopic anatomy:

The retina is composed of ١٠ layers, from the outside (nearest the blood vessel enriched choroid) to the inside (nearest the gelatinous vitreous body) they are:

١- Retinal pigmented epithelium (RPE): a single layer of cubical cells which are supporting cells for the neural portion of the retina. It is also dark with melanin which decreases light scatter within the eye. The cells are in close contact with Bruch's membrane ***(Kolb et al, ١٩٩٢).***

Macular RPE cells are characterized by being narrower, taller and more highly uniform than cells of RPE elsewhere. Pigment granules are present throughout cytoplasm of macular RPE where they are present mainly in apical cytoplasm of extra-macular RPE. So more pigment granules per unit area are present in the macula than elsewhere. Also pigment granules are different in extramacular RPE (melanin granules) than macular RPE (pure lipofuscin granules and mixture of lipofuscin and melanin granules).

Many growth factors are released from the RPE like pigment epithelial derived factor (PEDF), platelet derived growth factor (PDGF), vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF) and transforming growth factor (TGF) ***(Yanoff and Duker, ٢٠٠٣).***

٢- Photoreceptors (bacillary) layer: contains the outer and inner segments of cone and rod photoreceptors.

Rods are about ١٢٠ millions and are responsible for the light sense, light movement and scotopic vision. While cones are about ٦ million with the maximum concentration at the

center of the retina and are responsible for the color sense and photopic vision. The fovea contains only cones.

٣- External (outer) limiting membrane: widely fenestrated membrane that contains holes through which cones and rods pass.

٤- Outer nuclear layer (ONL): contains the cell bodies of cones and rods.

٥- Outer plexiform layer (OPL): contains the cone and rod axons, horizontal cell dendrites, bipolar dendrites ***(Kolb et al, ١٩٩٢)***.

Henle fiber layer is the portion of OPL in the central retina in which photoreceptors axons (inner fibers) course obliquely roughly parallel to ILM. These are fibers of cones diverted from the center of the fovea. They assume steeper slope towards the periphery so they are practically vertical at the margin of the central area. This arrangement of inner fibers creates a large potential space allowing pathological accumulation of edema fluid and exudates. This is clinically seen as radially oriented cystoid spaces of macular star with lipid exudation ***(Gass, ١٩٩٧).***

٦- Inner nuclear layer: contains the nuclei of horizontal cells, bipolar cells, amacrine cells, and Müller cells.

٧- Inner plexiform layer: shows the synapse between the axons

of bipolar cells, amacrine cells and dendrites of ganglion cells.

٨- Ganglion cell layer: contains the nuclei of ganglion cells which are the second order neuron in the visual pathway ***(Kolb et al, ١٩٩٣).***

The ganglion cell layer in the macula is characterized by being greater than one cell in thickness. Outside of the macula, the ganglion cell layer consists of a single row of continuous cells ***(Gass, ١٩٩٧)***.

٩- Axons (nerve fibers) layer: contains the nerve fibers from ganglion cells traversing the retina to leave the eye at the optic disk.

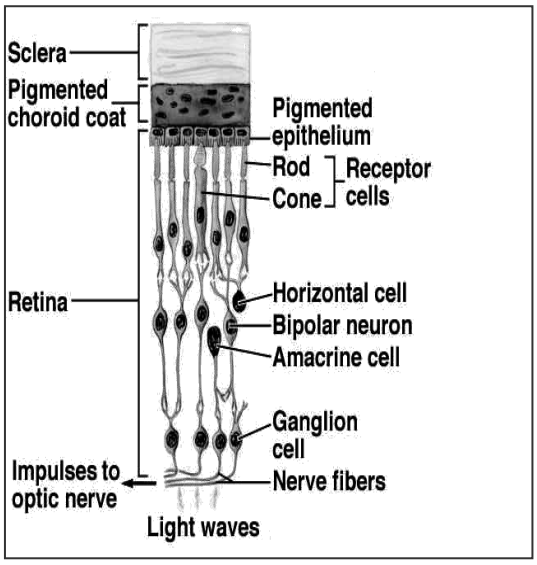

Fig. (٣): Layers of the retina.[٢]

١٠- Internal limiting membrane: separates the retina from the vitreous ***(Kolb et al, ١٩٩٢).***

Macula is further defined by high concentration of cones among photoreceptors, thick ILM and obliquely oriented fibers of OPL (Henle fibers) ***(McDonel, ١٩٩٤).***

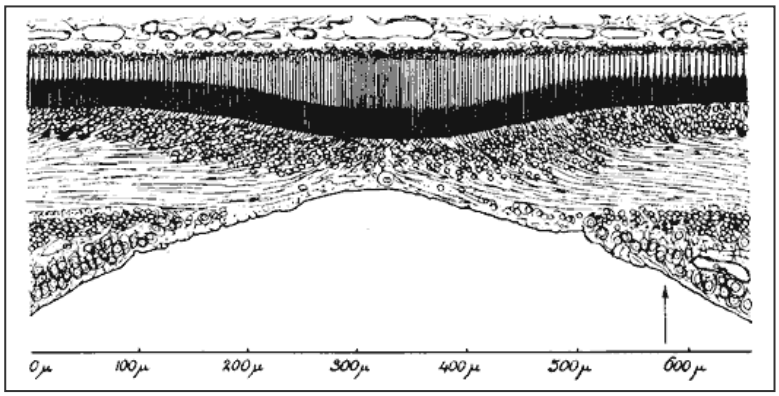

Fig. (٤): Central fovea of the human retina.[٣]

Blood supply of the macula:

The macula is divided into ٢ layers according to blood supply:

Outer layer:

RPE, photoreceptors (especially the foveal cones) and OPL are supplied by transudation from chorio-capillaris network which is derived from posterior ciliary arteries (choroidal circulation).

The choriocapillaris is thicker over the posterior pole than the periphery and it is thicker over the macular area than any other part. The choroidal capillaries are larger in diameter