

# Acknowledgement

*At first and foremost thanks to “Allah” who gave me the power to finish this work*

*I find no words by which I can express my deepest thanks and profound respect to my honored professor, **Professor Dr. Omar Mohamed Rashed**, Professor of ophthalmology, faculty of Medicine, Ain Shams University for the continuous kind encouragement, guidance and support he gave me throughout the whole 'Work. . It has been an honour and a privilege to work under his generous supervision.*

*Also, I would like to express my deepest thanks and appreciation to **Professor Dr. Sherif Zaki Mansour**, Professor of ophthalmology, faculty of Medicine, Ain Shams University, for his great support, valuable time, kind supervision and continuous advices 'which helped me to over come many difficulties.*

*I am also deeply grateful and would like to express my sincere thanks and gratitude to **Professor Dr. Khalid Abd-Elwahab Eltagory**, Professor of ophthalmology, faculty of Medicine, Ain Shams University, for his great help, valuable advice and criticism.*

*I would like to express my deepest gratitude to **Dr. Tarek S Hassan**, Vice-president of Associated Retinal Consultants, William Beaumont Hospital, Michigan, USA for his careful supervision, continuous contributions in the practical part of this 'Work and mastery teaching.*

*I' am greatly indebted to all my staff members in the ophthalmic department and colleagues, for the great support and help offered throughout this study.*

*Also I would like to thank my wife, son, parents, all my relatives who participated in a way or another in this work; I owe my thanks and appreciation.*

*Last but not least, I would like to express my endless gratitude to my dear patients who were the corner stone of this 'work, wishing them a rapid and complete recovery.*

*Tamer Fahmy Eliwa*

## List of Abbreviations

ACE	: Angiotensin converting enzyme .
a FGF	: Acidic fibroblast growth factor
AGE	: Advanced glycation end product
Ang II	: Angiotensin II
Ang2	: Angiopoietin2
ANP	: Atrial natriuretic peptide
AR	: Aldose reductase
ARBs	: Angiotensin receptor blockers
AT1-R	: Angiotensin II type 1 receptor.
AT-II	: Angiotensin II
bFGF	: Basic fibroblast growth factor
CF	: Counting fingers
CFZ	: Capillary free zone
CLBM	: Contact lens slit lamp biomicroscopy
CME	: Cystoid macular edema
CMT	: Central macular thickness
CSME	: Clinically significant macular edema
DAG	: Diacylglycerol
DCCT	: Diabetic control and complication trial.
DHAP	: Dihydroxyacetone phosphate
DME	: Diabetic macular edema
DRS	: Diabetic Retinopathy Study Research Group
ELM	: External limiting membrane.
eNOS	: Endothelial nitric oxide synthase
EPC	: Endothelial progenitor cells
ET-1	: Endothelin-1
ETDRS	: Early treatment Diabetic Retinopathy Study Group
F-6P	: Fructose-6-phosphate
FAZ	: Foveal avascular zone.
FFA	: Fundus fluorescein angiography

## List of Abbreviations (Cont.)

FGF	: Fibroblast growth factor
G1cN	: Glucosamine
G1cN-6P	: Glucosamine-6-phosphate
G-6P	: Glucose-6-phosphate
GA-3P	: Glyceraldehyde-3 -phosphate
GA-3PD	: Glyceraldehyde-3 -phosphate dehydrogenase
GFAT	: Glucosamine-fructose-amidotransferase
GK	: Glucokinase
HGF	: Hepatocyte growth factor.
HIFs	: hypoxia-inducible factors
HM	: Hand Motion
HRE	: Hypoxia response element
ICAM-1	: Intercellular adhesion molecule-1
IL-6	: Interleukin-6.
ILM	: Inner limiting membrane
INL	: Inner nuclear layer
IPL	: Inner plexiform layer
IRMA	: Intraretinal microvascular abnormalities
IVFA	: Intravenous fluorescein angiogram
IVTA	: Intravitreal injection of triamcinolone acetonide.
K	: Hexokinase
MMP-9	: Matrix metal-proteinase-9
NO	: Nitric oxide
NPDR	: Non-proliferative diabetic retinopathy
NV	: Neovessels
NVI	: Neovessels at iris
OCT	: Optica coherence tomography
ONH	: Optic nerve head
ONL	: Outer nuclear layer
OPL	: Outer plexiform layer

## List of Abbreviations (Cont.)

PA	:	Plasminogen activator
PAI-1	:	Plasminogen activator inhibitor-1
PDGF	:	Platelet derived growth factor
PDGF	:	Platelet-derived growth factor
PDR	:	Proliferative diabetic retinopathy
PEDF	:	Pigment epithelial derived factor
PG	:	Prostaglandins
PHT	:	Posterior hyaloid traction.
PKC	:	Protein kinase C
PL	:	Perception of light
R-5P	:	Ribose-5phosphate
RAGE	:	Receptor for advanced glycation endproducts
ROS	:	Reactive oxygen species
RPE	:	Retinal pigment epithelium
SD	:	Sorbitol dehydrogenase
SDF-1	:	Stromal derived factor-1
SDM	:	Subthreshold diode micropulse
SLO	:	Scanning laser ophthalmoscope
TA	:	Triamcinolone acetonide
TGF	:	Transforming growth factor
TNF $\alpha$	:	Tumor necrosis factor $\alpha$
TX	:	Thromboxane
UKPDS	:	United Kingdom Prospective Diabetes Study
USA	:	United State of America
VA	:	Visual acuity
VCAM-1	:	Vascular cellular adhesion molecule-1
VEGF	:	Vascular endothelial growth factor
VEGFR2	:	VEGF-receptor 2
WESDR	:	Wisconsin Epidemiologic Study of Diabetic Retinopathy

## List of Figures

<b>Figure</b>	<b>Subject</b>	<b>Page</b>
1	Important anatomical landmarks at the posterior pole, quoted from <b>Kanski, 2004</b> .	5
2	Capillary free zone (foveal avascular zone), quoted from <b>Kanaski, 2004</b> .	6
3	Umbo and foveola, quoted from <b>Yanoff and Duker, 2003</b> .	7
4	Cross section of the retina quoted from <b>Kanaski, 2004</b>	9
5	Hyperglycaemia-induced biochemical and metabolic abnormalities quoted from <b>Mario and Pugliese, 2003</b>	20
6	Flow sheet depicting protein kinase C(PKC) upregulation and its consequences for vascular endothelial growth factor (VEGF) expression and action quoted from <b>Frank, 2002</b>	24
7	Hyperglycaemia-dependent abnormal expression pattern of mediators modulating altered vascular remodelling quoted from <b>Mario and Pugliese, 2003</b> .	31
8	Pathways of VEGF expression and effects on vascular cells quoted from <b>Ryan, 2006a</b>	32
9	Molecular effects of angiotensin II (Ang II) type 1 receptor (AT1-R) antagonism on retinal vascular cells and tissue quoted from <b>Takagi et al, 2004</b>	35
10	Role of renin/angiotensin system in diabetic retinopathy quoted from <b>Takagi et al, 2004</b>	35
11	Clinical significant diabetic macular edema quoted from <b>Kanaski, 2004</b>	43
12	Focal macular edema quoted from <b>Tranos et al., 2004</b>	45
13	Diffuse macular edema quoted from <b>Kang, Park and Ham, 2004</b>	46
14	Color photograph and fundus fluorescein angiography demonstrating petaloid pattern of fluorescein leakage in a diabetic patient with CME quoted from <b>Tranos et al, 2004</b> .	49
15	Fluorescein angiography showing ischemic maculopathy (quoted from <b>Tranos et al, 2004</b>	50
16	Retinal mapping protocol quoted from <b>Polito et al, 2006</b> .	56
17	OCT shows type 1 DME, quoted from <b>Kang et al, in 2004</b> .	57
18	Optical coherence tomography shows type 2A DME quoted from <b>Otani et al, 1999</b>	58

## List of Figures (Cont.)

<b>Figure</b>	<b>Subject</b>	<b>Page</b>
19	OCT shows cystoid macular edema with persistent PHT [Type 2B] quoted from <i>Gaucher et al, 2005</i> .	58
20	Optical coherence tomography demonstrates intraretinal edema with subretinal setachment with the posterior border of the detached retina as a line of high reflectivity quoted from <i>Otani et al, 1999</i> .	59
21	OCT shows Type 3B DME: intraretinal edema with foveolar detachment and apparent vitreofoveal traction (arrowhead), quoted from <i>Kang et al, in 2004</i>	59
22	OCT shows highly reflective hard exudates have accumulated in the inner portion of the neurosensory retina (yellow arrows) quoted from <i>Otani and Kishi, 2001</i> .	60
23	OCT shows subretinal plaque of hard exudates, quoted from <i>Otani and Kishi, 2001</i> .	60
24	Focal macular edema before and after laser photocoagulation, quoted from <i>Ryan, 2006b</i>	64
25	Effect of glucocorticoids on the inflammatory mechanism, quoted from <i>Reichle, 2005</i> .	73
26	Fluorescein angiograms of diffuse diabetic macular oedema. A, pretreatment. B, post triamcinolone injection with complete resolution of macular oedema ( <i>Brooks et al, 2004</i> ).	75
27	Fluorescein angiography and optical coherence tomography before, and 11 weeks after, intravitreal injection of triamcinolone acetonide, quoted from <i>Jonas et al, 2005a</i> .	75
28	Macular edema and serous macular detachment before and after TA, quoted from <i>Ozdemir, Karacorlu and Karacorlu, 2005</i>	76
29	Intravenous fluorescein angiogram (IVFA) in a patient with active high-risk proliferative diabetic retinopathy (PDR) before and after IVTA, quoted from <i>Brooks et al, 2004</i>	77
30	Hard exudates regression with IVTA, quoted from <i>Khairallah et al, 2005</i>	78
31	Structural formal of recombinant fragment of human monoclonal antibody directed against VEGF (rhuFAB), quoted from <i>Ryan, 2006a</i> .	87
32	Results of vitrectomy for diffuse diabetic macular edema combined with a taut thickened posterior hyaloid, quoted from <i>Massin et al, 2003</i>	89
33	The percentage of fluorescein leakage in group A	105

## List of Figures (Cont.)

<b>Figure</b>	<b>Subject</b>	<b>Page</b>
34	The percentage of fluorescein leakage in group B	110
35	Difference in percentage of type of macular edema as diagnosed by FFA and OCT.	112
36	Visual outcome following laser photocoagulation.	113
37	Visual gain in laser group through out the follow up period	114
38	Distribution of Snellen's visual changes in the laser group at different intervals in comparison to the baseline.	115
39	Visual outcome following intravitreal injection of triamcinolone acetate	116
40	Visual gain in laser group through out the follow up period	117
41	Distribution of Snellen's visual changes in triamcinolone group at different intervals in comparison to the baseline	118
42	Visual outcome in both groups along the follow up period.	119
43	Comparison of the mean visual gain of the two groups allover the follow up period { in relation to the baseline}.	121
44	Reduction of hard exudates with laser photocoagulation through out follow up period.	122
45	Regression of hard exudates with laser photocoagulation	123
46	Reduction of hard exudates with triamcinolone injection allover the time	124
47	Regression of subretinal plaque hard exudates with triamcinolone injection	124
48	Regression of intraretinal hard exudates with triamcinolone injection	125
49	Comparison of percentage of reduction of hard exudates in both groups	126
50	Distribution of fluorescein leakage allover the follow up period in laser group	127
51	FFA pictures of cystoid edema treated by laser photocoagulation,	128
52	FFA pictures of diffuse edema treated by laser photocoagulation,	128
53	Distribution of fluorescein leakage allover the follow up period in triamcinolone group.	129
54	FFA pictures of cystoid edema treated by intravitreal injection of triamcinolone acetate	130

## List of Figures (Cont.)

<i><b>Figure</b></i>	<i><b>Subject</b></i>	<i><b>Page</b></i>
55	The percentage of reduction of flouresciene leakage at different time intervals of follow up in the two groups.	131
56	Regression of neovessels following triamcinolone.injection.	132
57	Regression of neovessels with triamcinolone injection	133
58	The mean central macular thickness of laser group along the follow up period.	134
59	OCT pictures of cystoid edema treated by laser photocoagulation	136
60	The mean central macular thickness of triamcinolone group along the follow up period.	138
61	OCT pictures of cystoid edema treated by intravitreal injection of triamcinolone acetamide	138
62	Comparison of changes in CMT of the two groups [in relation to the baseline].	140
63	The mean IOP in laser group along the follow up period	141
64	The mean IOP in triamcinolone group along the follow up period	143
65	Cataract progression in Laser group	144
66	Cataract progression in triamcinolone group	145
67	Posterior subcapsular cataract in a case injected with triamcinolone	146
68	Comparison of cataract progression in both groups	147
69	Visual outcome of diffuse edema group treated by laser	149
70	Distribution of Snellen's visual changes in laser group treated diffuse edema type at different month interval in comparison to the baseline.	150
71	The mean central macular thickness in diffuse edema group treated by laser.	151
72	OCT pictures of diffuse edema treated by laser photocoagulation	151
73	Visual outcome of diffuse edema group treated by triamcinolone acetamide	153
74	Distribution of Snellen's visual changes in triamcinolone group treated diffuse edema type at different month interval in comparison to the baseline.	154
75	The mean central macular thickness in diffuse edema group treated by triamcinolone acetamide.	154



## List of Figures (Cont.)

<b>Figure</b>	<b>Subject</b>	<b>Page</b>
76	OCT pictures of diffuse edema treated by triamcinolone injection	155
77	Comparison of visual gain of the two groups in treatment of diffuse edema type [in relation to the baseline]	157
78	Comparison of changes in CMT of the two groups in treatment of diffuse edema type [in relation to the baseline]	158
79	Visual outcome of cystoid edema group treated by laser	160
80	Distribution of Snellen's visual changes in laser group treated cystoid edema type at different month interval in comparison to the baseline	161
81	The mean central macular thickness in cystoid edema type treated by laser.	162
82	OCT pictures of cystoid edema treated by laser photocoagulation	163
83	Visual outcome of cystoid edema group treated by triamcinolone acetamide.	164
84	Distribution of Snellen's visual changes in triamcinolone group treated cystoid edema type at different month interval in comparison to the baseline.	166
85	The mean central macular thickness in cystoid edema type treated by triamcinolone acetamide.	168
86	OCT pictures of cystoid edema treated by triamcinolone injection	168
87	Comparison of visual gain of the two groups in treatment of cystoid edema type [in relation to the baseline]	170
88	Comparison of changes in CMT of the two groups in treatment of cystoid edema type [in relation to the baseline]	171
89	Visual outcome in mixed maculopathy group treated by laser.	172
90	Distribution of Snellen's visual changes in laser group treated mixed maculopathy at different month interval in comparison to the baseline.	174
91	The mean central macular thickness in mixed maculopathy treated by laser.	175
92	Visual outcome of mixed maculopathy treated by triamcinolone acetamide	177
93	Distribution of Snellen's visual changes in triamcinolone group treated mixed maculopathy at different month interval in comparison to the baseline.	178

## List of Figures (Cont.)

94	The mean central macular thickness in mixed maculopathy treated by triamcinolone acetonide	179
95	Comparison of visual gain of the two groups in treatment of mixed maculopathy [in relation to the baseline]	181
96	Comparison of changes in CMT of the two groups in treatment of cystoid edema type [in relation to the baseline]	182
97	Combined therapy in treatment of refractory cystoid edema.	207

## *AIM OF THE WORK:*

To study, evaluate & compare the efficacy of retreatment by laser photocoagulation versus intravitreal injection of triamcinolone acetonide in treatment of refractory diabetic macular edema.

## *INTRODUCTION*

Diabetic retinopathy is one of the most common causes of macular edema. The prevalence of macular edema is 3% in people with mild non-proliferative diabetic retinopathy (NPDR); 38% in those with moderate to severe NPDR; and 71% in those with PDR (*Klein et al, 1984b*).

Diabetic macular edema (DME) is the result of retinal microvascular changes that occur in diabetic patients. Thickening of the basement membrane of retinal capillaries and reduction in the number of pericytes are believed to lead to increased permeability and incompetence of retinal vasculature. This compromise of blood-retinal barrier leads to the leakage of plasma constituents in the surrounding retina, resulting in retinal edema (*Khan & Wai-Ching, 2001*).

Diabetic patients with macular edema usually complain of blurring of vision. 25-30% of patients with clinically significant macular edema (CSME) exhibit doubling of the visual angle within 3 years. Diabetic macular edema is best diagnosed by slit-lamp biomicroscopy which appears either as focal edema due to leakage from microaneurysms or as diffuse edema due to breakdown of blood-retinal barrier

with leakage from micro aneurysms, retinal capillaries, and arterioles (*Khan & Wai-Ching, 2001*).

Imaging studies are useful in confirming macular edema like fluorescein angiography, which is used to distinguish and localize areas of focal versus diffuse leakage, thereby guiding the placement of laser photocoagulation. It is helpful to exclude ischemic macular edema (*Kylstra et al, 1999*).

Optical coherence tomography (OCT) has been able to measure central macular thickness, and also demonstrate 3 basic structural changes of the retina in DME, i.e., retinal swelling, cystoid edema, and serous retinal detachment (*Otani et al, 1999*).

Laser treatment is clearly the first-line treatment of DME in order to reduce progression & the risk of doubling the visual angle from 24% to 12%, over all levels of visual acuity, over a period of 3 years (*ETDRS, report no.1, 1985*). Unfortunately, even with well-timed and adequate laser treatment, many patients continue to lose vision (*Martidis et al, 2002*).

Recent research in pharmacotherapy for diabetic retinopathy and macular edema offers new hope for these difficult situations. Steroids are a class of medications

being studied with intense interest for the treatment of diabetic macular edema. They are known to be effective for the treatment of inflammatory types of macular edema, such as uveitis or pseudophakic cystoid macular edema (CME) (*Martidis et al, 2002*).

Steroids are potent anti-inflammatory agents. They are thought to inhibit production of vascular endothelial growth factor and have been shown to decrease the breakdown of the blood-retinal barrier. These qualities make steroids a potential treatment in diabetic retinopathy (*Wilson et al, 1992 & Martidis et al, 2002*).

*Martidis & his associates in 2002* did a prospective study on intravitreal injection of triamcinolone acetonide in refractory diabetic macular edema & their results were satisfactory. These findings are confirmed by significant decrease in fluoresceine leakage within the macula & leakage from retinal neovascularization (*Brooks et al, 2004 and Avci, Kaderli and Akalp, 2006*).

## *ANATOMY OF THE MACULA*

### **THE RETINA:**

Retina or nervous coat of the eye is a delicate diaphanous tissue that varies in thickness: 0.13mm at the umbo, 0.56mm at the foveal margin and adjacent to the optic nerve head (ONH), 0.1mm at the ora and 0.2mm at equator (*Gass, 1997*).

As seen in the cross-section by light microscopy, the retina is represented by 10 layers from outside inward they are: RPE, photoreceptor layer of rods and cones, external limiting membrane, outer nuclear layer(ONL), outer plexiform layer(OPL), inner nuclear layer(INL), inner plexiform layer(IPL), ganglion cell layer, nerve fiber layer and internal limiting membrane (*Yanoff and Duker, 2003*).

### **THE HUMAN MACULA:**

#### ▪ *Anatomical consideration:*

Anatomically, the macula (macula lutea or central retina) is defined as that portion of the posterior retina that contains xanthophyll and two or more layers of ganglion cells. It measures approximately 5.5mm in diameter and is centered approximately 4mm temporal to and 0.8mm inferior to the center of the optic disc. It corresponds to approximately 15 degree of the visual field (*Gass, 1997*).