

Updates in Diagnosis and Treatment of Low Tension Glaucoma

Essay

**Submitted for Partial Fulfilment of
M.SC. Degree in Ophthalmology**

Presented By

Ali Ibrahim Ali Hassan

M.B., B.Ch

Under supervision of

Prof. Dr. Fatma El Hennawi

Professor of Ophthalmology

Ain Shams University

Dr. Amr El Awamry

Assistant Professor of Ophthalmology

Ain Shams University

Faculty of Medicine

Ain Shams University

2016

أحدث التطورات في تشخيص وعلاج الجلوكوما ذات الضغط المنخفض

رسالة توطئة للحصول على درجة الماجستير في
طب وجراحة العيون

مقدمة من

الطبيب/ علي ابراهيم علي حسن

بكالوريوس الطب والجراحة

تحت إشراف

ا.د/ فاطمة الحناوي

أستاذ طب وجراحة العيون

جامعة عين شمس

د/ عمرو العوامري

أستاذ مساعد طب وجراحة العيون

جامعة عين شمس

كلية الطب

جامعة عين شمس

2016

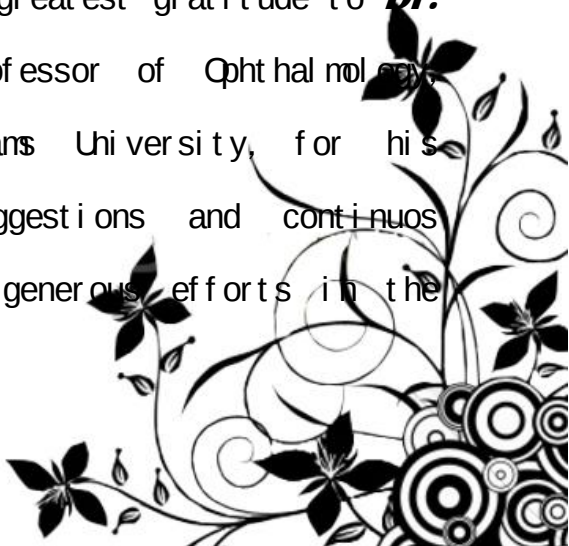


Acknowledgment

First of all I thank Allah for helping me to accomplish this research and for providing me with such very encouraging and supportive supervisors.

I wish to express my deepest gratitude **Prof. Dr. Fatma El Hennawi**, Professor of Optalmology, Faculty of Medicine, Ain Shams University, who suggested this topic and supervised this work. I appreciate her close enthusiastic co-operation and advise as well as her generous efforts in the evaluation of this work.

I would like to express my greatest gratitude to **Dr. Amr El Awamry**, Assistant Professor of Optalmology, Faculty of Medicine, Ain Shams University, for his valuable advice, fruitful suggestions and continuous encouragement as well as his generous efforts in the evaluation of this work.





LIST OF CONTENTS

Chapter	Page
ACKNOWLEDGMENT -----	i
LIST OF CONTENT -----	ii
LIST OF TABLES -----	vi
LIST OF FIGURES -----	vii
LIST OF ABBREVIATION -----	x
INTRODUCTION -----	1
Chapter 1: Anatomy of the Anterior Chamber -----	5
- Trabecular meshwork and site of aqueous resistance -----	7
- Morphology of the trabecular lamellae -----	8
- Schlemm's canal -----	11
- Schwalbe's line cells -----	15
- Physiology of Aqueous Humor -----	15
- Formation and secretion of aqueous humor -----	16
- Diffusion -----	17
- Dialysis and ultrafiltration -----	17
- GIBBS-DONNAN Equilibrium -----	18
- Secretion -----	19
- Aqueous flow -----	21
- Aqueous drainage -----	21
- Trabecular pathway -----	22
- Uveoscleral pathway -----	24
Chapter 2: Definitions of Glaucoma -----	27
- Pathophysiology of Glaucoma -----	28
- Early effects of glaucoma on the optic disc -----	32
1. Neuroretinal rim size and shape -----	32
2. Optic cup size, shape and depth -----	33

3. Cup\ Disc ratio -----	34
4. Optic disc hemorrhages -----	34
5. Retinal nerve fiber layer defects-----	35
6. Retinal vessels-----	35
7. Parapapillary chorioretinal atrophy -----	36

Chapter 3: Conventional and Novel Ways for Diagnosis of Low Tension Glaucoma -----

- Risk factors -----	38
1. Trans-cribrosal and cerebro-spinal fluid (CSF) pressure -----	38
2. IOP fluctuation -----	38
3. Genetic mutations -----	39
- Differential diagnosis -----	39
1. Other types of glaucoma -----	39
2. Thin central corneas -----	39
3. Other disorders of the optic nerve -----	40
4. Systemic disorders -----	40
5. Systemic drugs -----	40
- History -----	40
- Examination -----	41
- Investigations -----	41
A. Evaluation of glaucomatous structural damage -----	41
1. Optic disc photography -----	41
2. Confocal scanning laser ophthalmoscopy (CSLO) -----	43
3. Optical coherence tomography (OCT) -----	46
4. Doppler optical coherence tomography (OCT angiography) ---	48
5. Scanning laser polarimetry (SLP) -----	50
6. Ocular Response Analyzer (ORA) -----	53

B. Evaluation of functional damage -----	55
1. Standard automated perimetry (SAP) -----	55
2. Short-wavelength automated perimetry (SWAP) -----	58
3. Frequency-doubling technology perimetry (FDT) -----	60
Chapter 4: Conventional and Novel Ways for Treatment of Low Tension Glaucoma -----	62
- IOP reducing Medications -----	63
1. Prostaglandin analogs -----	64
2. Topical beta-adrenergic receptor antagonists -----	64
3. Alpha2-adrenergic agonists -----	65
4. Less-selective alpha agonists -----	66
5. Combined Medications -----	67
- Neuroprotection -----	68
1. Glutamate induced excitotoxicity -----	69
2. Nitric oxide -----	70
3. Neurotrophin withdrawal -----	71
- Gene therapy -----	73
- Laser applications -----	81
Chapter 5: Future trends for diagnosis and treatment of low tension glaucoma -----	83
- Future trends for diagnosis -----	83
1. DARC (Detection of Apoptotic Retinal Cells) -----	83
2. IOP telemetry (Sensimed Triggerfish) -----	83
- Future trends for treatment -----	85
1. Pharmacological agents -----	85
a. Rho kinase inhibitors -----	85
b. Future neuro-protective agents -----	86

2. Minimally-invasive glaucoma surgeries (Implants) -----	86
a. Devices designed to facilitate aqueous flow into Schlemm's canal (The Stegmann canal expander) -----	86
b. Another approach has been to find novel pathways for fluid to leave the eye(CyPass micro-shunt)-----	87
3. Non-invasive glaucoma surgeries -----	88
* Ultrasound therapeutic uses in glaucoma -----	88
a) Low-intensty frequency ultrasound -----	88
b) Deep-wave Trabeculoplasty (DWT) -----	89
c) High-intensty frequency ultrasound (HIFU)-----	90
- New methods of drug delivery -----	91
- Nano-medicine in glaucoma -----	94
1. Drug delivery vectors-----	94
2. Extraocular intraocular pressure sensors -----	95
3. Drainage devices -----	95
4. Intraocular pressure sensors -----	96
- Stem cells in glaucoma -----	98
SUMMARY -----	100
REFERENCES -----	103
ARABIC SUMMARY	

LIST OF TABLES

Table		Page
Table 1:	Pharmacological neuroprotection strategies -----	72
Table 2:	Potential target genes and tissues that could be used therapeutically to treat glaucoma -----	77
Table 3:	Glaucoma relevant tissues and available vector systems-----	80
Table 4:	Comparison between Argon Laser (ALT) and Selective Laser (SLT) Trabeculoplasty-----	82

LIST OF FIGURES

Figure	Page
Fig.1: Site and components of the anterior chamber-----	6
Fig. 2: Scanning electron micrograph of the human trabecular meshwork. Internal aspect from the chamber angle side ($\times 1,640$) -----	8
Fig.3: Electron micrograph of part of atrabecular lamella, after anterior chamber perfusion with cationized ferritin-----	9
Fig. 4: Structure of corneoscleral lamellae of the trabecular meshwork -----	10
Fig. 5: Electron micrograph of a tangential section through the inner wall of Schlemm's canal showing the subendothelial elastic-like fiber network of the cribriform layer ($\times 10,000$) ----	11
Fig.6: Structure of the inner wall endothelium of Schlemm's canal showing a transcellular pathway through a giant vacuole and a paracellular route labeled with cationized ferritin-----	13
Fig.7: Scanning electron micrograph of the outer wall of Schlemm's canal showing a group of openings that lead into collector channel -----	14
Fig.8: Different types of collector channels drawn after specimens injected by India ink-gelatin -----	15
Fig.9: Aqueous circulation system. Direction of aqueous flow -----	16
Fig.10: Dialysis: movement of small particles according to concentration gradient -----	18
Fig.11: Ultrafiltration: movement of small particles under pressure ----	18
Fig.12: Gibbs-Donnan effect: movement of particles according to electrical charges-----	19
Fig.13: Model for HCO_3^- formation and its linkage to Na^+ transport in the ciliary processes -----	20

Fig.14:	Possible secretory pathways in the ciliary processes-----	21
Fig.15:	Flow of aqueous through trabecular and uveoscleral pathways -----	24
Fig.16:	Flow of aqueous through trabecular and uveoscleral pathways -----	26
Fig.17:	Fundus photos show pale neuroretinal rim with loss of ISNT rule -----	33
Fig.18:	Fundus photo shows pale vertically oval optic cup -----	33
Fig.19:	Fundus photo shows asymmetrical C/D ratio-----	34
Fig.20:	Fundus photos show optic disc hemorrhages -----	34
Fig.21:	Fundus photos show optic disc hemorrhages -----	35
Fig.22:	Fundus and red free photos show sharp kinking of retinal vessels -----	36
Fig.23:	Fundus photos show peripapillary atrophy -----	37
Fig.24:	Schematic diagram of early optic disc changes in glaucoma ---	37
Fig.25:	Glaucomatous optic disc photo-----	42
Fig.26:	Front of Heidelberg Retina Tomograph -----	44
Fig.27:	Side of Heidelberg Retina Tomograph -----	44
Fig.28:	Example of HRT printout -----	46
Fig.29:	Example of OCT printout -----	48
Fig.30:	Disc photographs, optical coherence tomography (OCT) reflectance, whole-depth OCT angiograms, and cross-sectional angiograms -----	49
Fig.31:	To appreciate the ability of OCT angiography to detect blood flow within the various vascular beds, the 3-dimensional angiograms were separately projected into en face maximum projection in 3 layers, that is, retinal angiograms, choroidal angiograms, and scleral/lamina cribrosa angiograms -----	50

Fig.32:	GDx Nerve Fiber Analyzer -----	51
Fig.33:	Example of GDx printout -----	52
Fig.34:	Ocular Response Analyzer: the device, mechanism and illustrated printout -----	54
Fig.35:	Example of SAP printout -----	57
Fig.36:	Examples of SAP devices -----	57
Fig.37:	Example of SWAP device -----	59
Fig.38:	Example of SWAP printout-----	59
Fig.39:	Example of FDT device -----	61
Fig.40:	Example of FDT printout -----	61
Fig.41:	The glutamate-glutamine cycle-----	70
Fig.42:	SENSIMED Triggerfish (the contact lens and its related parts)-----	85
Fig.43:	Demonstration of The Stegmann canal expander -----	87
Fig.44:	Demonstration of CyPass micro-shunt in suprachoroidal space-----	87
Fig.45:	Deep wave trabeculoplasty device from ocutherix and its application to the limbus -----	90
Fig.46:	The Eyeopt 1 device showing the 6 transducers and its application to the eye -----	91

LIST OF ABBREVIATIONS

AAVs	:	Adeno associated viruses
ABPs	:	Atypical birefringence patterns
AC	:	Anterior chamber
Ads	:	Adenoviruses
ALT	:	Argon Laser Trabeculoplasty
BDNF	:	Brain-derived neurotrophic factors
BL	:	Borderline
CCT	:	Central corneal thickness
CE	:	Ciliary epithelium
CH	:	Corneal hysteresis
Cl ⁻	:	Chloride
CM	:	Ciliary muscle
CMV	:	Cytomegalovirus
CNS	:	Central neural system
CNTGS	:	Collaborative Normal Tension Glaucoma Study
CRF	:	Corneal resistance factor
CSF	:	Cerebro-spinal fluid
CSLO	:	Confocal scanning laser ophthalmoscopy
DARC	:	Detection of Apoptotic Retinal Cells
Db	:	Decibel
DWT	:	Deep-wave Trabeculoplasty
FDA	:	Federal Drug Administration
FDT	:	Frequency-doubling technology perimetry
FIV	:	Feline Immunodeficiency Virus
GAT	:	Goldmann Applanation Tonometry
GDx	:	Nerve Fiber Analyzer

List of Abbreviations

GDx-ECC	: Nerve Fiber Analyzer with enhanced corneal compensation
GDx-VCC	: Nerve Fiber Analyzer with variable corneal compensation
GFAP	: Glial fibrillary acidic protein
GPA	: Guided progression analysis
GPS	: Glaucoma Probability Score
GTPases	: Guanosine triphosphotases
HCO ₃ [–]	: Bicarbonate
HFA	: Humphrey Visual Field Analyzer
HIFU	: High-intensity frequency ultrasound
HIV	: Human Immunodeficiency Virus
HRT	: Heidelberg Retina Tomograph
HSP	: Heat shock proteins
HSVs	: Herpes simplex viruses
Hz	: Hertz
IgG	: Immunoglobulin G
IOP	: Intra-ocular pressure
IOPcc	: Corneal compensation intraocular pressure
IOPg	: Goldmann-corrected IOP value
iPSCs	: Induced pluripotent stem cells
K ⁺	: Potassium
LoGTS	: Low-tension Glaucoma Study
LPI	: Laser Peripheral Iridotomy
LPs	: Liposomes
LTG	: Low-tension glaucoma
LVs	: Lentiviruses
MCs	: Muller cells
MDLT	: Micropulse Diode Laser Trabeculoplasty
MHRA	: Medicines and Healthcare regulatory agency

List of Abbreviations

MIGS	:	Minimally-invasive glaucoma surgeries
Mm Hg	:	Millimeter mercury
Mm	:	Millimeter
MMPs	:	Metalloproteinases
MRA	:	Moorfields Regression Analysis
Na ⁺	:	Sodium
NGF	:	Nerve growth factors
NIGS	:	Noninvasive glaucoma
NMDA	:	N -methyl-D-aspartate
NO	:	Nitric oxide
NT-3	:	Neurotrophin-3
NT-4	:	Neurotrophin-4
NTG	:	Normal-tension glaucoma
OCT	:	Optical Coherence Tomography
ONH	:	Optic nerve head
ONL	:	Outside normal limits
ORA	:	Ocular Response Analyzer
POAG	:	Primary open-angle glaucoma
RGC	:	Retinal ganglion cell
ROCK	:	Rho associated coiled coil-forming protein kinase
SAP	:	Standard automated perimetry
SITA	:	Swedish interactive thresholding algorithm
SLP	:	Scanning laser polarimetry
SLT	:	Selective Laser Trabeculoplasty
SSADA	:	Split-spectrum amplitude-decorrelation angiography
SWAP	:	Short-wavelength automated perimetry
TCA	:	Topographic Change Analysis
TCPD	:	Trans-cribrosal pressure differential