

**SIGNIFICANCE OF RETINAL
NERVE FIBER LAYER ASSESSMENT
IN OPHTHALMOLOGY**

Essay

Submitted for Complete Fulfillment of
The Master Degree (M.Sc.) in
Ophthalmology

By

Yomna Amr Abd-Elwahab Ali
(M.B.; B.Ch.)

Under supervision of

Prof. Dr. BESHAR AHMED ATTEF KENAWY
*Professor of Ophthalmology,
Faculty of Medicine, Cairo University*

Prof. Dr. MAGDA SALAHELDIN ABDELAZIZ
*Professor of Ophthalmology,
Faculty of Medicine, Cairo University*

Prof. Dr. AHMED MOSTAFA ABDEL RAHMAN
*Professor of Ophthalmology,
Faculty of Medicine, Cairo University*

**Faculty of Medicine,
Cairo University
2010**

ACKNOWLEDGMENT

Thanks God, the most kind and the most merciful, for this would have never been put together to become finally real but by God's providence.

*I would like to express my deepest gratitude and respect to Prof. Dr. **Beshr Kenawy**, Professor of Ophthalmology, Faculty of Medicine, Cairo University, for helping me, encouraging me, giving me the chance and the facility to launch into new fields and granting me the honour of supervising this work.*

*Much gratitude mixed with respect go to Prof. Dr. **Magda Salah**, Professor of Ophthalmology, Faculty of Medicine, Cairo University for her generous supervision, sincere support, and careful revision throughout this work step by step.*

*My true thanks and gratitude are directed to Prof. Dr. **Ahmed Mostafa**, Professor of Ophthalmology, Faculty of Medicine, Cairo University, for his continuous support and fruitful advice during this work.*

Last but not least no acknowledgment would be complete without thanking my family. To them I owe this work and everything I have achieved.

CONTENTS

	Page
▪ Introduction	1
▪ Chapter One: Anatomy of the Retinal Nerve Fiber Layer	3
▪ Chapter Two: Clinical Assessment of Retinal Nerve Fiber Layer	13
▪ Chapter Three: Imaging Modalities for Measurement of RNFL Thickness. 26	
▪ Chapter Four: Retinal Nerve Fiber Layer Assessment in Glaucoma	38
▪ Chapter Five: Retinal Nerve Fiber Layer Assessment in Non Glaucomatous Disorders	58
▪ Summary	109
▪ References	112
▪ Arabic Summary	

LIST OF FIGURES

No.	Title	Page
1	A diagram showing the ten layers of the retina from innermost to outermost.	3
2	Retinotopic organization of the ganglion cell axons in the retina and optic nerve.	6
3	Histological section of the optic nerve head and peripapillary retina, including the retinal nerve fiber layer and a Similar section obtained by optical coherence tomography.	9
4	Red free fundus photography of normal fundi.	18
5	Red free photography of normal NFL and vessels of the superior temporal archade.	18
6	Red free fundus photography showing diffuse degeneration and thinning of RNFL.	19
7	Red free fundus photography shows slit like defects in RNFL.	21
8	Red free fundus photography with wedge defect in RNFL.	21
9	Red free fundus photography showing pseudodeflects.	22
10	A 2-dimentional Gabour filter.	23
11	Erasing" blood vessels in the retinal fundus images.	23
12	Transformation of retinal fundus image into rectangular array	24
13	NFLD regions in the transformed image enhanced after the application of Gabor filtering.	24
14	long vertical dark regions ,the candiate regions for NFLDs.	24
15	Diagram of a Michelson interferometer.	28
16	Optical slices.	32
17	confocal section images all at different focal planes .	32
18	Color scale of HRT.	33
19	Topography image and reflectance image of HRT.	33
20	The glaucoma continuum.	38
21	Fundus photography of bean pot appearance of optic disc in glaucoma.	40
22	Fundus photography of glaucomatous optic disc with inferior rim notch.	40

No.	Title	Page
23	Fundus photography with peripapillary changes in glaucoma.	41
24	RNFL thickness average analysis report.	45
25	The Stratus OCT ‘Optic Nerve Head Analysis’.	46
26	RTVue Nerve Head/RNFL Analysis and Cirrus RNFL Thickness Map.	47
27	RNFL thickness change analysis.	49
28	Advanced Serial Analysis Report of GDx VCC Scanning Laser Polarimeter.	51
29	RTA clinical printout of Glaucoma Analysis.	52
30	Topography and reflectance images of a normal optic nerve head and of a glaucomatous optic nerve head.	53
31	Contour line drawn around the optic disc in normal and glaucomatous eye and their stereometric parameters.	54
32	Retinal photographs of a control subject and a patient with Alzheimer’s disease showing that the retinal veins in the patient appear narrower than those in the control subject.	64
33	Superior temporal quadrant of fundus of an AD patient showing diffuse loss in retinal nerve fiber layer.	65
34	Superior temporal quadrant of fundus of an AD patient showing several slit defects in retinal nerve fiber layer.	66
35	Fundus photography from a patient with autosomal-recessive cone–rod dystrophy.	72
36	Optical coherence tomography and optic nerve head photographs from a patient with NAION.	89
37	A colored fundus photography of Leber’s optic neuropathy.	98
38	Red free fundus photographs of normal, congenitally crowded optic disc and mild papilloedema.	102
39	OCTs from the same eyes shown in figure 38.	102
40	Optic nerve photograph showing dense optic nerve head drusen, dense inferior arcuate scotoma and corresponding optical coherence tomography.	106

LIST OF ABBREVIATIONS

AAION:	Arteritic anterior ischemic optic neuropathy
AD:	Alzheimer's disease
AION:	Anterior ischemic optic neuropathy
AON:	Acute optic neuritis
CAD:	Computer aided detection
CMO:	Cystoid macular oedema
CMV:	Cytomegalovirus
CRD:	Cone rod dystrophy
CSLO:	Confocal scanning laser ophthalmoscopy
DR:	Diabetic retinopathy
FCC:	Fixed corneal compensation
FPs:	False positives
GON:	Glaucomatous optic neuropathy
HIV:	Human immunodeficiency disease
HRT:	Heidelberg retina tomograph
INO:	Internuclear ophthalmoplegia
IOP:	Intraocular pressure
LASIK:	Laser Assisted In-situ Keratomileusis
LHON:	Leber's hereditary optic neuropathy
MS:	Multiple sclerosis
NAA:	N-acetyl aspartate
NAION:	Non arteritic anterior ischemic optic neuropathy
NFA:	Nerve fiber layer analyzer
NFL:	Nerve fiber layer
OCT:	Optical coherence tomography
ON:	Optic neuritis
ONH:	Optic nerve head
ONHD:	Optic nerve head drusen
OSAS:	Obstructive sleep apnea syndrome

PD:	Parkinson's disease
PERG:	Pattern electroretinogram
PRP:	Pan retinal photocoagulation
PS-OCT:	Polarization sensitive OCT
RGC:	Retinal ganglion cells
RNFL:	Retinal nerve fiber layer
RNFLD:	Retinal nerve fiber layer defect
RP:	Retinitis pigmentosa
RTA:	Retinal thickness analyzer
SDOCT:	Spectral domain OCT
SLP:	Scanning laser polarimetry
TDOCT:	Time domain OCT
TSINT:	Temporal, superior, inferior, nasal, temporal.
UHR-OCT:	Ultra-high resolution OCT
VA:	Visual acuity
VCC:	Variable corneal compensation
VEP:	Visual evoked potential
VF:	Visual field
XLRS:	X- linked retinoschisis

ABSTRACT

Retinal nerve fiber layer is the innermost layer of the retina, it is formed of the axons of ganglion cells. Attrition of nerve fibers in the anterior visual pathways is reflected directly in the nerve fiber layer of the retina. These retrograde degenerative changes are subtle but they can be seen with an ophthalmoscope and can be photographed with a fundus camera. So, the importance of the new objective quantitative technologies for RNFL assessment which are the optical coherence tomography, the confocal scanning laser ophthalmoscopy, the scanning laser polarimetry and the retinal thickness analyzer had been proved. Glaucoma is a multi-factorial optic neuropathy characterized by irreversible progressive loss of the retinal ganglion cells (RGCs) and thinning of the retinal nerve fiber layer (RNFL), leading to visual field loss and eventually, total loss of vision. 40% to 50% of the RNFL could be lost before visual field defects are detected by conventional perimetry. Thus, RNFL assessment had emerged as an important parameter for pre-perimetric diagnosis of glaucoma. Diabetic retinopathy (DR) is the fifth most common cause of blindness worldwide. In addition to typical retinopathies, neuro-visual impairments had been reported. Focal retinal nerve fiber layer loss in diabetic patients with preclinical DR was detected. In vitro studies had demonstrated that diabetes affects both retinal neurons and glial cells. Panretinal photocoagulation causes a sequential decrease in the peripapillary retinal nerve fiber layer (RNFL) thickness. On the other hand, some diseases had been thought to change RNFL, but studies had proved the opposite and that aided in the true understanding of these pathologies as in amblyopia in which RNFL assessment was insignificant.

Keywords:

Retinal nerve

Fiber layer assessment

Ophthalmology

Diabetic retinopathy

INTRODUCTION

INTRODUCTION

Retinal nerve fiber layer (RNFL) assessment had proved to be an important clue to many ophthalmological disorders, especially after the recent developments in computer- based imaging technologies, besides the clinical examination, which provided a means of obtaining quantitative measurements of retinal nerve fiber layer thickness (**Blumenthal *et al.*, 2001**).

Glaucoma is a multi-factorial optic neuropathy characterized by progressive loss of retinal ganglion cells and their nerve fibers, which leads to characteristic loss of visual function. Although the exact cause for RNFL damage is not known, major risk factors for glaucoma had been identified, including intraocular pressure, heredity, and possibly vascular dysfunction. Humans have a large reserve of retinal nerve fibers, and redundancy in the system may prevent detection of early functional damage. It had been estimated that up to 50% of fibers may be lost before a visual field defect is detectable with white on white perimetry. Furthermore, intraocular pressure and cup to disc ratio may not be sensitive or specific enough as indicators for the presence of glaucomatous optic neuropathy. Many people with large cup to disc ratio do not have glaucoma (physiologic cupping) (**Sommer *et al.*, 1991**).

Visual field testing may miss defects especially early in the disease (now called pre-perimetric glaucoma). It makes sense therefore, to evaluate the RNFL for the diagnosis and follow up of glaucomatous disease, at least prior to the development of characteristic visual field loss. In the near future, perhaps we will characterize glaucoma by the technology used to detect RNFL

damage. We may have terms such as topographic, interferometric or polarimetric glaucoma (**Sommer *et al.*, 1991**).

A number of techniques are available for evaluation of the RNFL. These include red-free ophthalmoscopy and photography, retinal thickness analyzer, optical coherence tomography, confocal scanning laser ophthalmoscopy and scanning laser polarimetry (**Blumenthal *et al.*, 2001**).

The effect of diabetic retinopathy and degree of blood glucose regulation on RNFL thickness can be assessed using scanning laser polarimetry. RNFL thickness was seen to decrease with development of diabetic retinopathy. This issue should be taken into account while assessing RNFL in diabetic glaucomatous patients (**Chihara *et al.*, 1993**).

Axonal loss was detected not only in multiple sclerosis with a previous attack of optic neuritis, but also in MS eyes with no previous episode of optic neuritis (**Henderson *et al.*, 2007**).

Patients with retinitis pigmentosa and other retinal dystrophies have abnormal thinning of RNFL (**Walia *et al.*, 2007**).

CHAPTER ONE

ANATOMY OF THE RETINAL NERVE FIBER LAYER

CHAPTER ONE

ANATOMY OF THE RETINAL NERVE FIBER LAYER

The retina is a complex, layered structure with several layers of neurons interconnected by synapses. The retina has ten distinct layers (Fig. 1). They include from innermost to outermost (**Radius and Anderson, 1979**):

1. Inner limiting membrane - Müller cell footplates
2. Nerve fiber layer - Essentially the axons of the ganglion cell nuclei.
3. Ganglion cell layer - Layer that contains nuclei of ganglion cells and gives rise to optic nerve fibers.
4. Inner plexiform layer
5. Inner nuclear layer contains bipolar cells.
6. Outer plexiform layer - In the macular region, this is known as the Fiber layer of Henle.
7. Outer nuclear layer
8. External limiting membrane - Layer that separates the inner segment portions of the photoreceptors from their cell nucleus.
9. Photoreceptor layer - Rods / Cones
10. Retinal pigment epithelium (**Radius and Anderson, 1979**).

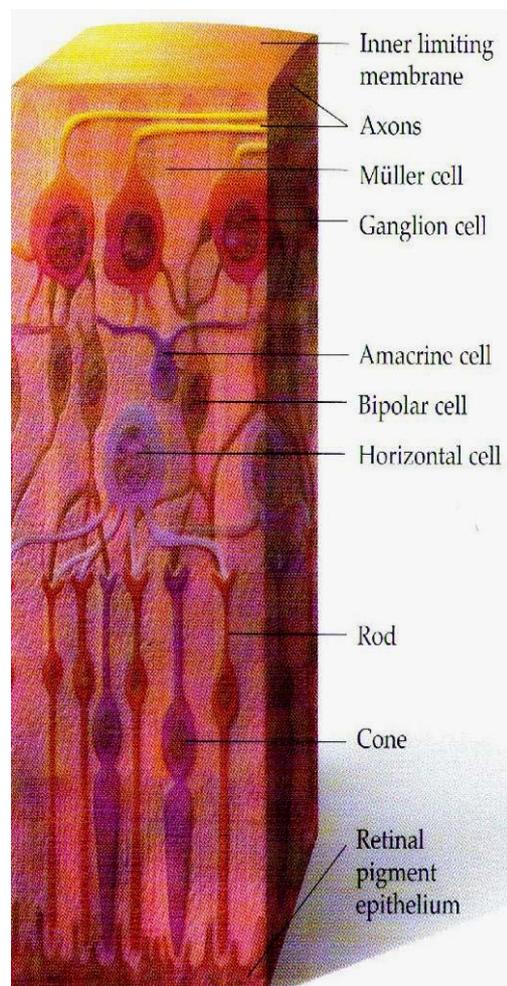


Fig (1): A diagram showing the ten layers of the retina from innermost to outermost (www.eyedesignbook.com).

The retinal nerve fiber layer (stratum opticum, RNFL) is the innermost layer of the retina packed between the inner limiting membrane and the retinal ganglion cell layer, it is visible to the examiner using direct or indirect ophthalmoscopy (**Radius and Anderson, 1979**).

The RNFL is composed of axons of ganglion cells, astrocytes, retinal vessels and Muller cell processes forming the internal limiting membrane as their basal lamina covering the surface of the nerve fiber layer. There are an estimated 700, 000 to 2 million ganglion cells in the human retina and a similar number of nerve fibers found in the optic nerve (**Mikelberg et al., 1989**).

The ganglion cells are arranged in layers of four to six cells in the macula, and are only two cells thick in the retinal periphery. Three types of ganglion cells are identified P cells, M cells and W cells. There had been some work in trying to distinguish if certain types of ganglion cells are preferentially damaged in glaucoma (**Quigley et al., 1987**).

Astrocytes and Muller cells comprise a neuroglial system which surrounds the nerve fibers and provides a structural framework supporting the neural elements. The Muller cells occupy nearly all the intercellular retinal space and form by their basal lamina the internal limiting membrane covering the nerve fiber layer. The astrocyte processes envelop all nerve fibers, giving structural and nutritional support, and in combination with the pericytes they cover the retinal capillaries isolating the retinal ganglion cells and their axons from the retinal blood flow. This complex of astrocytes and Muller cells channels, established in embryogenesis, may play a role in the