Correlation between lamina cribrosa morphology and glaucoma severity in patients with primary open-angle glaucoma

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CORRELATION BETWEEN LAMINA CRIBROSA MORPHOLOGY AND GLAUCOMA SEVERITY IN PATIENTS WITH PRIMARY OPEN-ANGLE GLAUCOMA

BY

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In partial fulfillment of the requirement for the degree of
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LIST OF ABBREVIATIONS

S no.	ABBREVIATION	FULL FORM
1	DALY	Disability adjusted life years
2	WHO	World health organization
3	RPE	Retinal pigment epithelium
4	ONH	Optic nerve head
5	IOP	Intraocular pressure
6	LC	Lamina cribrosa
7	POAG	Primary open-angle glaucoma
8	SD-OCT	Spectral domain ocular coherence tomograph
9	EDI	Enhanced depth imaging
10	ALCD	Anterior lamina cribrosa depth
11	LCT	Lamina cribrosa thickness
12	VF-MD	Visual field mean deviation
13	VF-PSD	Visual field pattern standard deviation
14	PPA	Parapapillary atrophy
15	ONHH	Optic nerve head hemorrhage
16	GON	Glaucomatous optic neuropathy
17	VF	Visual field
18	RNFL	Retinal nerve fiber layer
19	RNFLT	Retinal nerve fiber layer thickness
20	RNFLD	Retinal nerve fiber layer defect

21	RGC	Retinal ganglion cell
22	ERC	Ethical review committee
23	FRC	Faculty review committee
24	AXL	Axial length of eye
25	VCDR	Vertical cup-to-disc ratio
26	NRR	Neuroretinal rim
27	SPSS	Statistical package for social sciences

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ABSTRACT

Objectives: The objectives of the study are

1) To determine the morphological parameters of lamina cribrosa (LC), lamina cribrosa thickness (LCT) and anterior lamina cribrosa depth (ALCD) in patients with primary open angle glaucoma (POAG) and normal healthy controls.

2) To compare the lamina cribrosa thickness (LCT) and anterior lamina cribrosa depth (ALCD) in POAG cases and controls.

3) To correlate LCT and ALCD with retinal nerve fiber layer (RNFL) thickness and visual field (VF) changes in patients of primary open angle glaucoma (POAG)

Methods: The study was conducted from August 2018 to April 2019. A total of 103 subjects (57 POAG cases and 46 age-matched healthy controls) were assessed for general ophthalmological investigations including intraocular pressure (IOP), axial length (AXL), steroesopic ophthalmoscopy, slit-lamp biomicroscopy, and visual field (VF) testing deducing mean deviation (VF-MD) and visual field pattern standard deviation (VF-PSD) testing utilizing enhanced depth imaging (EDI) spectral domain ocular computed tomography (SD-OCT).

Results: The mean age of subjects was 65 years (65 ± 22) with more male participants. We obtained statistically significant results for intraocular pressure [IOP (20.05 ± 2.47)], AXL (24.23 ± 1.99) and VCDR (0.86 ± 0.24). We also assessed highly significant statistical values for the POAG clinical parameters of laminar dots (P-value 0.000), optic nerve head hemorrhages [ONHH P-value 0.000], parapapillary atrophy [PPA P-value 0.000] and retinal nerve fiber layer sectorial defects [RNFLD P-value 0.000]. While calculating the functional parameters of lamina cribrosa defects, significant results were procured for VF-MD and VF- PSD. The values of VF mean deviation in POAG cases were (-2.92 ± 2.52) and visual field pattern standard deviation (7.54 ± 4.69). Structural

variables of RNFLT (73.21 ± 13.63) and LCT (218.07 ± 79.80) were statistically significant in POAG cases as compared to the controls. We aimed for statistically significant results for deeper ALCD and thinner LCT with presence of laminar dots, PPA, ONHH, VF-MD and VF-PSD in POAG cases, in which the ALCD result was not found statistically significant.

Conclusion: A thinner lamina cribrosa, quantified by lamina cribrosa thickness (LCT) in primary open-angle glaucoma (POAG) correlated significantly with the decrease in retinal nerve fiber layer thickness (RNFLT) and visual field (VF) mean deviation (VF-MD) and visual field pattern standard deviation (VF-PSD) defects. Lamina cribrosa parameters were also significantly associated with a greater axial length of the eyes (AXL), raised intraocular pressure (IOP), superior and superior-inferior sectorial retinal nerve fiber layer defects (RNFLD) and a greater vertical cup-to-disc ratio (VCDR). Laminar defects were significant in myopics.

Anterior lamina cribrosa depth (ALCD) and lamina cribrosa thickness (LCT) can be estimated with precision using enhanced depth imaging spectral domain ocular coherence tomography (EDI SD-OCT). Timely evaluation and monitoring of lamina cribrosa morphology can prove prophylactic and prognostic against the deleterious effects of glaucomatous optic neuropathy (GON).

KEYWORDS: Lamina cribrosa thickness, Lamina cribrosa depth, Visual field defects, Primary open angle glaucoma, SD-OCT

CHAPTER 1

INTRODUCTION

1.Living beings are bestowed by special senses of vision, smell, acoustic sense and taste. Humans are fortunate and unique to have them all; and that too in the most supreme form. It is not wrong to state that vision is the prime special sense modality. From appreciation of nature to keeping warmth up in relations with positive social interactions (Grossmann 2017), working for the living, contact with external world and the sense to adapt to changes is all very much dependent upon vision that is the eyes and accessory visual apparatus. Eyes are the magnificent organs that perceive the light, its convergence, scattering, processing into the formation of image and thus imparting the ability to visualize. Eye is sophisticated enough to make us see both in luminance and dark. The eyes are highly specialized for comprehension of the stimuli related to the general form and colors. Many endocrine functions; like circadian and diurnal rhythms (Nickla and Totonelly 2016), production and release of certain vital hormones and melatonin is all based on the perception of light through our eyes. All these vital physiological functions are regulated via upholding visual connection with the outside world with the eyes; aided by its auxiliary structures.

Flaxman et al., (2017) addressed an issue of compiling the global causative factors of blindness. According to them in the year 2015, a massive 216.6 million people across the globe were suffering from moderate to severe visual impairment, with a thick figure of 36.0 million cases of blindness in the year 2015. The causes of blindness in which the better eye had visual acuity of <3/60, were listed to be cataract, glaucoma, age-related macular degeneration, diabetic retinopathy, corneal opacities, some infective states like trachoma and uncorrected visual errors.

Glaucoma is the third leading cause of blindness worldwide. For better understanding of glaucoma and hence preventing millions from the deleterious complication of blindness, we need to research more towards the modifiable aspects of the disease and for it a sound knowledge of eyes is mandatory.

The eyes are delicate and need to be housed within the protective encasement offered by the skull; known as the orbital cavity (Figure 1). It is in the interior of the orbital cavity, the eyes along with the accessory organs like extraocular muscles, lacrimal apparatus,

nerves, vessels, fascia and fat are lodged. The visual natural system of the body is present in the eyeball, occupying the anterior 2/3rd of the orbit, which itself is surrounded by the extraocular muscles that maintain the movement of eyes; the lacrimal apparatus which maintains its lubrication and prevent drying; nerves which make it sensitive enough for the image processing, vessels for the nourishment and fascial sheaths serving as suspensory apparatus, as is explained by Moore, Dalley and Agur (2013).

Aqueous humor is produced by the ciliary apparatus and is drained through the canal of Schlemm. A balanace in the production and drainage maintains the normal IOP of the eye, and any imbalance creates the condition known as glaucoma. Glaucoma is the chronic sustain in the IOP (Sinnatamby, 2011)

The axial length of the eyeball measures about 25mm (Kim et al 2016). The eyes have a fibrous layer for its protection; a vascular layer to nourish it, a lens with refractive system for focusing, and a photosensitive part that responds to the light; all arranged in a circular manner. Sinnatamby (2011) stated that the Tenon's capsule or bulbar fascia is a separate layer enveloping the eye inside the orbit, separating it only from the orbital fat and also contributes in the formation of the suspensory ligament of Lockwood.

Besides the strategic alignment of layers of the eyes, eye ailments are the top contributory factors for the nonfatal disabling conditions; calculated in the prevalence studies as the disability-adjusted life years (DALY) in both high and low income countries (Ono, Hiratsuka and Murakami 2010), it can be observed that the highest proportion of DALYs is present in the middle and low economic groups of Asia, with 4% of DALYs amounting to 61.4 million DALYs due to eye diseases. According to WHO, 285 million people are visually impaired worldwide, with more alarming 38 million of them are blind. While looking at the top causative elements of these distressing facts, Sutradhar et al (2019) found glaucoma to be one of the major contributors, amounting to 4.7 million DALYs. Glaucoma not only add to the disability struck years; if left untreated it may result in the catastrophic result of blindness. Any measures taken for prevention from

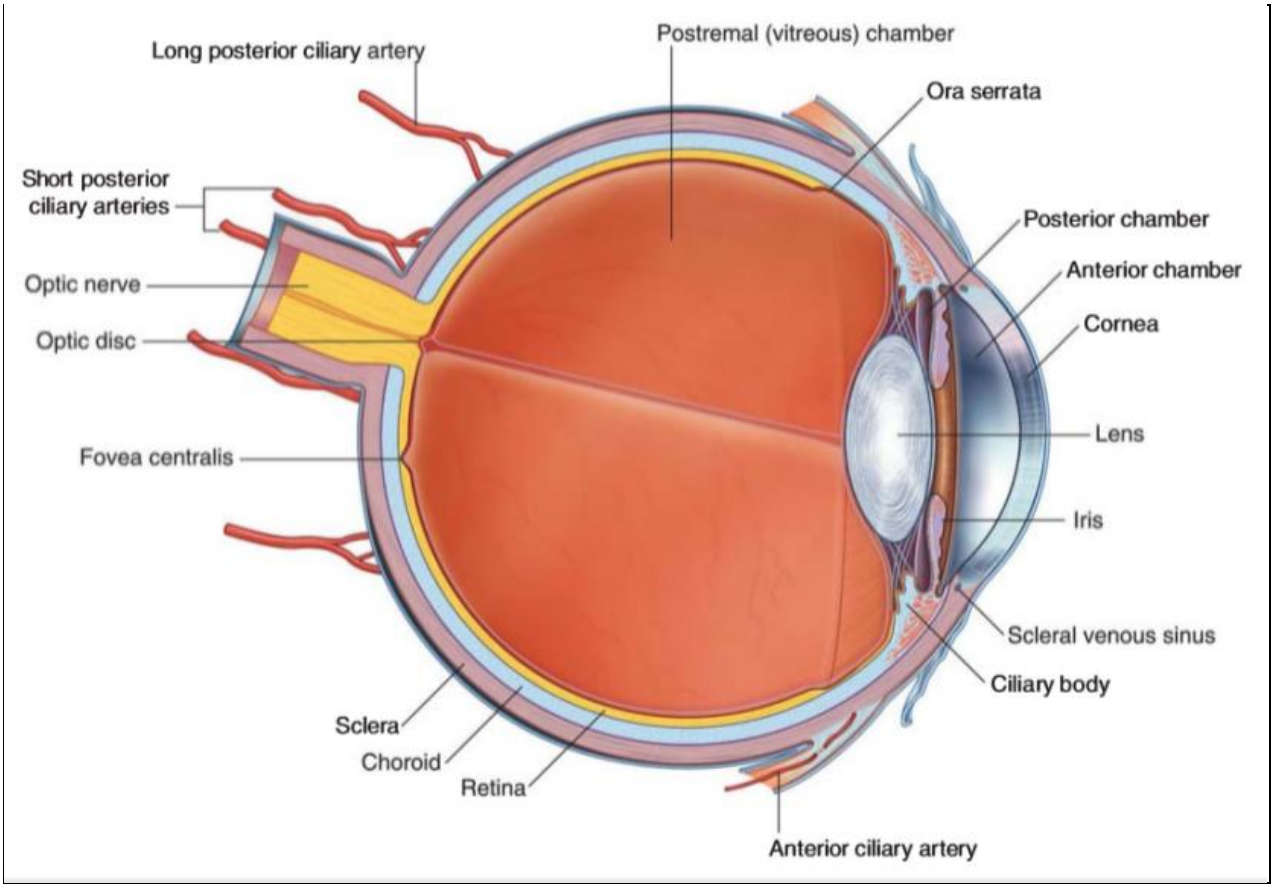


Figure 1.Gross anatomical structure of Eye (Moore, K. L., Dalley & Agur. 2013)

the deleterious effects of glaucoma would prove substantial and will in due course be reducing the DALYs.

Finding out ways to minimize global burden of blindness due to glaucoma, the anatomy of eyes and understanding of the normal physiology and pathogenesis of glaucoma needs to be given due consideration.

1.1 LAYERS OF THE EYE

1.1 (A) RETINA

Fascinating is the fact that a sequence of patterned light is being converted into an image, and even more fascinating is the inner most layer of eye the retina.. Taking a look into the morphology of retina at:

1.1 (A i) Macroscopic level

Macroscopically, the sensory layer can be divisible into two functional parts, the optic part and the non-optic part.

According to Moore et al., (2013), the optic part of the retina is composed of two strata, a sensitive neural layer or retina proper and a color containing pigmented layer. As the names suggest, the neural layer is light sensitive and the pigmented one enhances the light capturing capability of the choroid and thus prevents the light scattering effect.

The non-optic part of retina starts at the termination of the neural part, known as the dentate line or ora serrata. The non-optic part is an elongation of the retinal pigment epithelial (RPE) layer, coating the ciliary body and iris as the ciliary and iridial parts of non-optic retina. RPE is bound to the Bruch's membrane and through it to the choriocapillary layer of choroid. At the posterior pole, the retina has a central depressed area, where optic nerve leaves the eye, known as the optic disc, 1.5 mm in diameter. This optic disc overlies the lamina cribrosa, also referred to as the optic nerve head (ONH), and is most susceptible part of the corneo-scleral shell to get deformed in glaucoma (Laxmikanth and Girkin (2011). Moreover as stated by Sinnatamby (2011), the central depression of the optic disc extends to a variable degree, known as physiological cup; this

light insensitive component has no visual receptors within it, and functionally called as physiological blind spot or scotoma.

Area centralis is 3 mm lateral to the optic disc at the posterior pole of the eye (Grossniklaus, Geisert and Nickerson 2015). Within the area centralis in the middle of the superior and inferior temporal branches of the central retinal artery, is a low yellow excavation, macula lutea. Macula appears darker in appearance due to the more prevalence of photoreceptors and more pigments behind them, and it also contains xanthophyll pigment imparting the color. The very center of the macula is aligned with the optical axis, and is known as the fovea or fovea centralis, which is the thinnest part of retina, the area is devoid of blood vessels and rods presence; and is the most preponderant site for cones composed of inner limiting membrane and cones only, 500 µm in diameter. Fovea centralis is the area for most acute vision and gives the best resolved images.

The RPE is attached with the overlying choroid, but the layer of rods and cones is not that adherent to it, and here lies a potential space. Hence in cases of retinal histological preparations or retinal detachment, the layers from within the RPE displace inwards.

1.1 (Aii) Microscopic structure

In the histological features of retina, the cell types present within it would help in understanding of the normal circuitry of the layer (figure 2)

Photoreceptor cells: rods and cones

Conducting neurons: bipolar and ganglion cells

Association neurons: horizontal, centrifugal, interplexiform and amacrine cells

Supporting cells: Muller cells, microglia and astrocytes

The interplay within these above described cell types have the regular and sequential arrangement of the 10 layers of retinal histology.

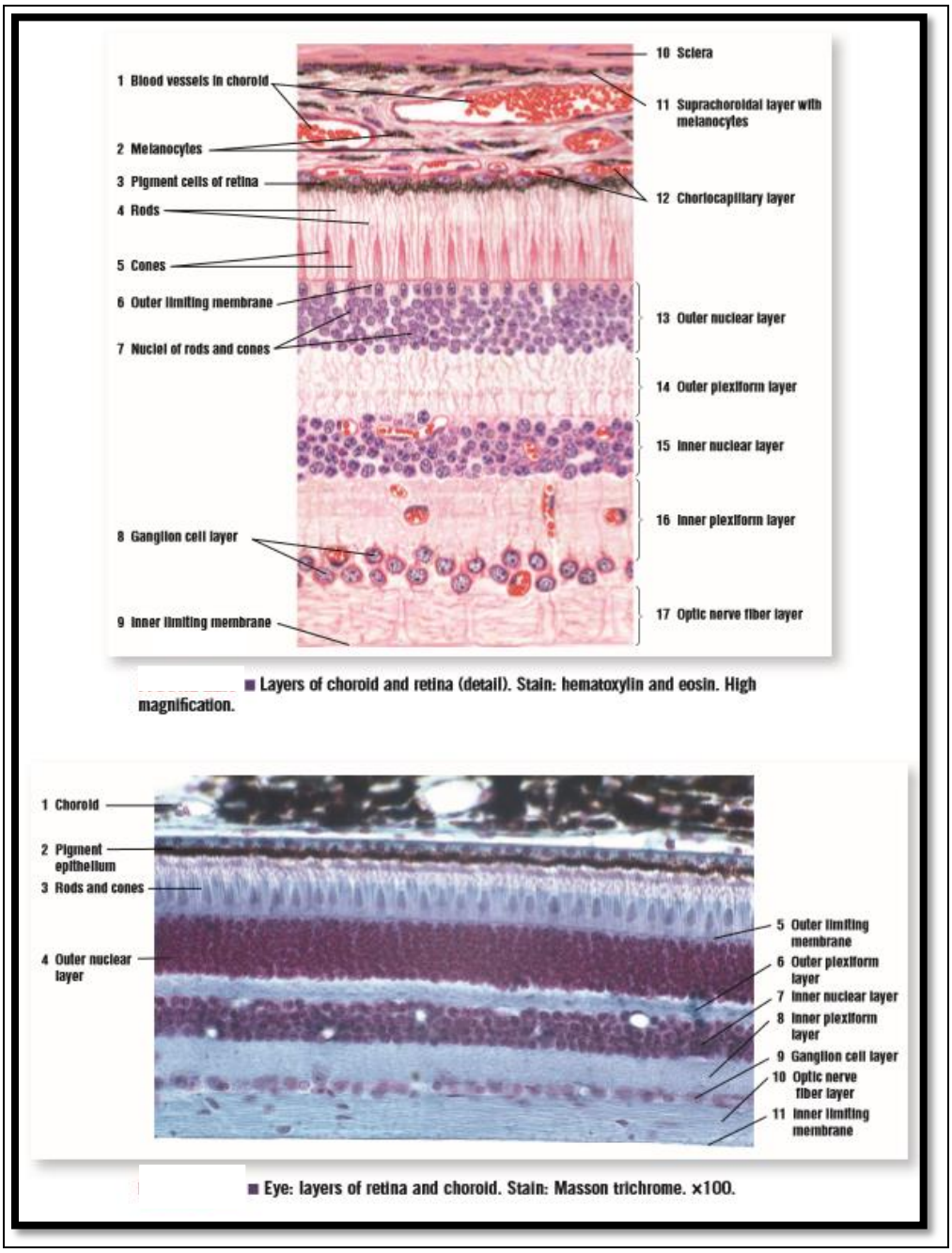


Figure 2: Microscopic features of choroid and retina (Eroschenko & Di Fiore. 2013)

1. Retinal pigment epithelium (RPE)
2. Layer of rods and cones: they are the photoreceptors containing opsins of different kinds, also explained by Klooster and Kamermans (2016)
3. Outer limiting membrane contains the outer processes of Muller cells
4. Outer nuclear layer, composed of the somata of photoreceptors
5. Outer plexiform layer, maintains the circuits between the photoreceptor cells and horizontal and bipolar cell processes
6. Inner nuclear layer, consists of somata of horizontal, amacrine and bipolar cells
7. Inner plexiform layer: processes of horizontal, amacrine and bipolar cells make nexuses
8. Ganglion cell layer, have the cell bodies of ganglion cells
9. Layer of optic nerve fibers, contains processes of the ganglion cells
10. Inner limiting membrane, contains the inner processes of Muller cells

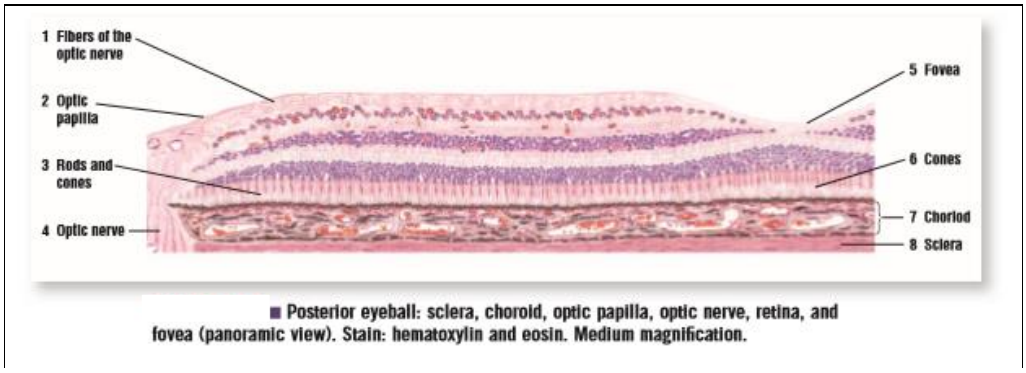


Figure 3: Microscopic features of optic disc (Eroschenko & Di Fiore. 2013)

1.2 UVEA

The intermediary layer of the visual apparatus, consists of a series of vascular structures of choroid, ciliary apparatus and iris.

1.2 (A) CHOROID

The choroid is a dark, reddish brown pigmented layer, stretching from optic nerve posteriorly to the ora serrata anteriorly, externally separated by the sclera by suprachoroidal lamina. The outer surface of the choroid has a roughened appearance

where it is penetrated by the optic nerve, and at the entrance of ciliary neurovascular bundle. Its anterior extensions go into the ciliary body to the extent of the optic nerve posteriorly. RPE is firmly attached to it, whereas its finest vessels in the form of choriocapillaris nourish the photoreceptors housed within the retina. Venous return through the vena vorticosae make about 4 veins which exit just posterior to the equator of the eye via the choroid. On the internal aspect of choroid lies Bruch's (glassy) membrane, also known as lamina vitrea, an avascular and unstructured layer, delineating choroid from the retina (Malhotra 2011).

1.2 (B) CILIARY APPRATUS

Anteriorly iris and posteriorly choroid are the neighboring relations of ciliary apparatus. It is triangular in cross section, with one long side applied to the sclera externally and contains the ciliary muscles, whereas the other lies adjacent to the vitreous body. Internally ciliary apparatus is covered by two layers of epithelium, outer RPE and inner nervous part of the retina. More anteriorly this surface projects into 60-70 ciliary processes which elaborate the secretion of aqueous humor. The short anterior base at its middle has the attachment of iris. Ciliary smooth muscles and the zonular ligaments contract to make the lens bulge and help in near focusing. These ciliary muscles are supplied by the parasympathetic Edinger-Westphal part of the Oculomotor nerve (Sinnatamby 2011).

1.2 (C) IRIS

The posterior attachment of iris is at the ciliary body, and peripheral to it, lies the iridocorneal angle of the anterior chamber of the eye, where the canal of Schlemm is present. Iris is composed of vascular connective tissue, with epithelia surrounding it behind its stroma. The anterior epithelium contains few melanin granules, but the posterior one is packed them, thus imparting color to the eyes. Iris is centrally perforated by the pupil, controlling the trafficking of light. The iris contains sphincter pupillae muscle, supplied by the nerves emerging through Edinger-Westphal, a parasympathetic nucleus of Oculomotor nerve and the dilator pupillae muscles, supplied by the cervical sympathetics.

1.2 (D) MICROSCOPIC STRUCTURE OF UVEA

At the microscopic level, the choroid is seen to be present within the Suprachoroid lamina along with melanocyte, this layer is composed of collagen and elastic fibers with the melanocytes. The vascular layer is composed of the medium and the large sized blood vessels with interspersed melanocytes in between, bestowing it a colored appearance. The choriocapillary layer contains network of capillaries with large lumina, which nourish the photoreceptor cells of retina. The innermost part of the choroid, the Bruch's or glassy membrane lies attached to the RPE, intervening between the choroid and retina. Treuting et al (2012) described that the iris consists of five layers, anterior border layer, stroma, muscular layer, and anterior and posterior pigment epithelial layers.

According to Ross and Pawlina (2018), the iris is composed of a stroma rich of vascular tissue, enveloped posteriorly by an epithelium laden by pigment, called posterior epithelium. They further elaborated structure behind it, which is a layer of myoepithelial cells, called anterior pigment myoepithelium. In the anterior limit of the anterior myoepithelial cells are embedded stacks of melanin granules, whereas the posterior limits have contractile elements, extending into the dilator pupillae. The contractility of the iris is maintained by the sphincter pupillae muscles.

Ciliary body has the microarchitectural arrangement similar to the iris as explained by Ross and Pawlina (2018), with inner vascular and outer muscular layer and has three sets of muscles emerging from the scleral spur. They are the meridonial (longitudinal), radial (oblique) and circular (sphinteric). Ciliary processes are thickenings of the inner vascular layer of the ciliary body, covered by double fold of epithelium, the ciliary epithelium. This epithelium helps in the production of aqueous fluid, maintenance of blood-aqueous barrier and the suspension and generation of the zonular ligaments.

The non-pigmented epithelium faces towards the ciliary stroma, whereas the pigmented epithelium continues with the RPE posteriorly and becomes the posterior pigment epithelium and anterior myoepithelium over the iris

1.2 (E) AQUEOUS SECRETION

The non-pigmented ciliary epithelium has the properties of fluid-transportation, with appropriate cell junctions for the purpose, and Na^+ K^+ ATPase. According to Keil et al., (2011), aqueous is produced by the ciliary processes from the posterior chamber under the iridocorneal junction. Production spans over two processes as is explained by Quaranta et al., (2013), first the plasma that reaches the ciliary vessels passes through the fenestrated capillaries and a filtrate is made in the interstitial space, situated between the capillary endothelium and ciliary epithelium, followed by a part of the filtrate's active secretion into the posterior eye chamber. The arterial supply is through the long posterior ciliary arteries, with the circulation of the ciliary apparatus segmenting into three zones. The fenestrated capillaries of the ciliary epithelium allow proteins to flow within them, and thus creating an oncotic pressure, important for aqueous production. A landmark work by Moses (1981) describes that the aqueous production at a certain level of perfusion becomes blood independent, and at some other level gets dependent over it. According to him with rising IOP the aqueous production slightly decreases, and when IOP equals the capillary pressure, than its production decreases markedly.

1.2 (F) AQUEOUS OUTFLOW

The production of the aqueous must balance its outflow (Kagemann 2011). Majority of aqueous humor exits through the angle of anterior chamber of the eye via the trabecular meshwork; canal of Schlemm. It drains via the multiple venous connections of deep, midlimbal and perilimbal scleral venous plexuses, and a second set of Ascher's aqueous veins bypassing this channel and ultimately ending up in scleral and episcleral veins. This is the convention outflow system of draining and is largely pressure dependent (Quaranta 2013). Outflow decreases in aged individuals, in subjects of ocular hypertension and in POAG (Liu 2011). The outflow also diminishes at night in aged individuals (Konstas et al 2013) and its production also occurs at a lesser pace in such people.

There is another system for the aqueous outflow, known as the unconventional or Uveoscleral pathway as stated by Quaranta et al., 2013, it is pressure independent, not related to the amount of the aqueous and constitutes about 50% of the outflow in normal human eyes. Uveoscleral pathway is also pressure-independent. Studies reflect no

evidence against the functionality of this pathway in glaucoma. Some researchers have acclaimed that the outflow may decrease at night and reduce with advancing age. Quaranta et al., (2013) also added that prostaglandin derivatives causes relaxation of the ciliary muscles and hence aid in the hypotensive effect by enhancing the drainage of aqueous humor.

1.3 FIBROUS COAT

1.3 (A) SCLERA

The outer, posterior $5/6^{th}$ shell of the globe is protective in nature and hence fibrous, called the sclera.

1.3 (Ai) Macroscopic structure

It is composed of densely, irregularly woven collagen fibers conveying to it opacity, hence called as white of the eye. According to Ross and Pawlina (2018), the sclera where insertions of the extraocular muscles occur is thinnest, i.e., 0.3 to 0.4 mm, 0.7 mm at the corneoscleral junction or limbus and posteriorly thickest, i.e., 1 mm. The point where the optic nerve exits through it is the weakest and is known as the lamina cribrosa (LC). Here at this point the sclera is adherent to the dura mater. Sinnatamby (2011) explained that sclera receives anterior to and just posterior to the equator the insertions of extraocular muscles and vena vorticosae respectively. Sclera is penetrated by the ciliary neurovascular bundle around the optic nerve and the anterior ciliary veins penetrate sclera near the corneoscleral junction. The junctional point of sclera and cornea is known as the limbus. It also is connected by loose connective tissue to the overlying bulbar fascia and bulbar conjunctiva. Remaining part of sclera is almost avascular.

1.3 (Aii) Microscopic structure

Ross and Pawlina (2018) alienated the sclera into three vaguely defined layers, outermost episcleral; having between it and the middle scleral layer the episcleral space which enables the eyes to move, the middle substantia propria, sclera proper or Tenon's capsule and the innermost suprachoroid lamina, also known as lamina fusca. All the layers of the

sclera are composed of collagenous framework of irregular fiber dimensions and interspersed elastin fibers without any alignment with fibroblasts, macrophages and melanocytes.

Corneoscleral junction is called limbus and according to Miri (2012), can be regarded as the anterior corneal limbus and posteriorly scleral limbus. It is a transition zone, where the corneal five to six layer epithelium changes to the 10-12 layered conjunctival epithelium. The iridocorneal angle also lies at the same space, equipped with structures related to aqueous outflow.

1.3 (B) CORNEA

1.3 (Bi) Macroscopic structure

Cornea is the anterior one sixth transparent counterpart of the outer ocular fibrous layer (Moore et al 2013), bulging in front of eyes due to extra curvature than the sclera. It is completely avascular, but is richly supplied by long and short ciliary nerves (Sinnatamby 2011). Cornea is different from sclera in the respect that the alignment of the collagen fibers is regular, imparting it transparency. It is regular with the sclera at limbus, where the conjunctival epithelium also gets continued with the cornea.

1.3 (Bii) Microscopic structure

Cornea is a lamellar structure, as elaborated by Ross and Pawlina (2018), having in total five layers, out of which three are cellular and two noncellular. Cornea is topped with corneal epithelium of stratified squamous non-keratinized variety, maintaining a nexus with the conjunctiva. This layer can get involved in a variety of inflammatory, physical or neoplastic disorders, and its partial or full thickness removal with the underlying layers of the cornea is termed as keratoplasty (Krumeich, Brand, Chankiewitz, Chankiewitz, & Guthoff . 2014). The five to six layered corneal epithelium rests over the acellular Bowman's membrane, which also confers it strength against the spread of infections, but this layer does not have the potential to regenerate, hence it is a culprit in corneal opacities as stated by Ross. Underlying the Bowman's membrane is a thick layer of corneal stroma, also known as the substantia propria that sits over another acellular membrane, the Descemet's membrane or posterior limiting membrane. This stroma has

precise assembly of the connective tissue elements within the ground substance, and it does have the capability for regeneration (Menke, Spitsbergen, Wolterbeek, & Woutersen 2011), under which lies the cellular endothelial layer of the cornea, composed of single layer of squamous cells. The endothelial layer regulates the water content of the cornea through its hydrating pump system, as stated by Menke and any disturbance would lead to corneal edema. According to Ross and Pawlina (2018), this layer has a limited ability to regenerate and in cases of opacities, a full thickness keratoplasty is the only solution.

1.4 LAMINA CRIBROSA

The point of the sclera posteriorly where the optic nerve fibers would exit through it is the weakest. Due to the perforations by the optic nerve it attains a sieve-like appearance, called as lamina cribrosa (Sinnatamby 2011). Lamina cribrosa has long been of interest to the researchers and studies have proven its worth in the pathogenesis of glaucoma. Park & Park (2013) regarded lamina cribrosa as the main site of injury to retinal ganglion cells at optic nerve head, as the lamina cribrosa is recipient to the pressure effects of intraocular pressure as well as the cerebrospinal fluid. Between the collagenous framework lies the porous structure, which is highly susceptible to changes in intraocular pressure. Superior and inferior poles of lamina are the weakest in this frail part of sclera, hence the formation of lamina dots can be clinically seen more at these respective poles (Turgut 2017).

1.4 (A) Macroscopic structure

According to Standring (2015), the inner part of the sclera anteriorly is attached to the ciliary body by lamina superficialis, while the posterior part on the inner side attains a mesh-like structure for the passage of optic nerve axons through it. This porous, sieve-like structure is known as the lamina cribrosa. The central retinal vessels have a large centrally place aperture through the lamina cribrosa, whereas the optic nerve axons have small perforations. Lamina cribrosa is the weakest part of the sclera and its displacements occur as a result of raised intraocular pressure (IOP).

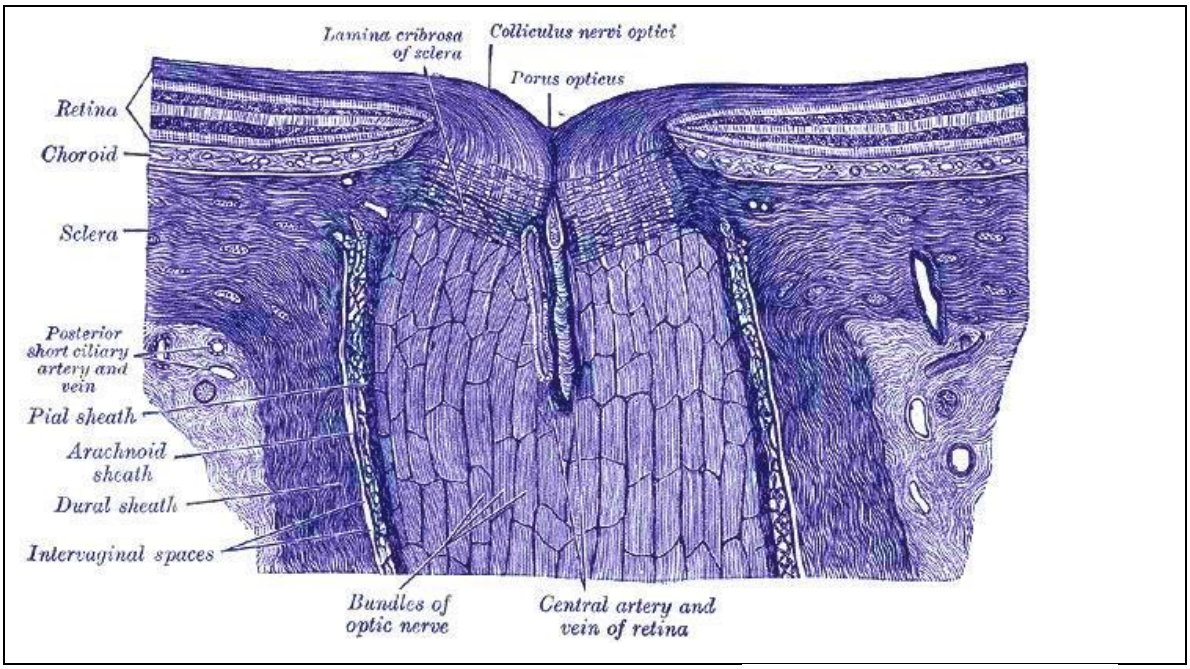


Figure 4: Macroscopic structure of lamina cribrosa (Bartlett, John. 1919. Familiar Quotations, 10th ed.)

1.4 (B) Microscopic structure

The lamina cribrosa is composed of collagen fibers of various diameters (Junqueira 2013). Collagen fibers are arranged in haphazard fashion in the rest of the sclera, but in lamina cribrosa they are aligned circumferentially (Standring 2015). Assessment and imagining of the 3D microscopic features of lamina cribrosa in-vivo had been found to be challenging due to the lack of an automated analysis tool (Wang, B et al 2014). The normal pore area measured in one research was (~1460 and 920 μm^2), which was larger than explored in conventional histological studies.

1.5 DEVELOPMENTAL ANATOMY OF EYE

Both the divisions of the ectoderm that is, the surface ectoderm and neuroectoderm contribute in the embryology of the eye along with the mesoderm and neural crest cells. Eye development starts at day 22 by appearance of optic grooves at the cranial end of the neural folds (Moore, Persaud & Torchia 2011). Failure of proper development of optic vesicles gives rise to a condition called as anophthalmia or microphthalmia (Verma and FitzPatrick 2007). Optic grooves evaginate as the neural folds fuse to form forebrain and

form a hollow diverticula emanating from diencephalon, the optic vesicle. With the growth of the optic vesicles, their distal ends constrict forming optic stalks. The optic vesicle soon contacts the surface ectoderm and induces it to form the lens placodes. The lens primordia start to invaginate through the lens pit, the edges of the lens pits approaching each other to form lens vesicles and they gradually lose their nexus with the surface ectoderm (figure 5).

The optic cups invaginate and form the double-walled optic cups, consisting of two layers that maintain their relation with the forebrain through the optic stalks. The optic cup develops into the retina while the optic nerves are the future derivatives of the optic stalk. Fissure, known as choroidal/ retinal fissure, appears on the ventral surface of optic disc, extending posteriorly on the inferior surface of optic stalk. The center of optic cup fissures appear, called optic (retinal) fissure, the point where it is deepest becomes the optic disc. The retina is continuous with the optic stalk at the retinal fissure, and the retinal ganglion cells axon pass directly into the optic nerve through this junction. Retinal fissures contain vascular mesenchyme from which hyaloid vessels develop (Sadler 2011). Hyaloid artery is a branch of ophthalmic artery which nourishes the mesenchyme of the cavity of optic cup, lens vesicle and inner layer of optic cup with the hyaloid vein bringing back down the venous blood. As the retinal fissure fuses, the hyaloid vessels are entrapped within the primordial optic nerve. Distal ends of the hyaloid vessels degenerate but proximal ones persist as central artery and vein of retina.

The outer layer of optic cup develops into the pigment layer of the retina, whereas the inner thicker layer forms the neural retina and gradually develops within it the light-sensitive receptors rods and cones (Standring 2015). Myelination of the optic nerve starts from the late fetal period and gets complete after the eyes are exposed to light for 10 weeks postnatally. Neonates are normally far sighted and visual acuity gets better to the normal adult levels by the first year of life (Figure 6).

Ciliary body develops from the choroid. The extensions of ciliary body emerging medially enclose the developing lens as ciliary processes, also secrete the aqueous humor. The pigmented portion of ciliary body forms from nonvisual retina. Ciliary muscles are

responsible for the focusing of the lens. Connective tissue in the ciliary body develops from mesenchyme (Moore, Persaud & Torchia 2011).

Tamm (2004) stated that any failure in the normal development of the rim of optic cup, which develops into the iris, may give rise to the condition known as aniridia. The iris develops from rim of optic cup, the part that partly embraces the lens. The covering epithelium of iris is continuous with the double layers of retina and ciliary body. The neuroectoderm within the retina would develop into the dilator pupillae and sphincter pupillae muscles.

The mesenchyme between the developing lens and cornea develops into the anterior chamber of eye. Mesenchyme superficial to the anterior chamber forms the substantia propria of the cornea. Aniridria association with markedly thick cornea has been reported (Olitsky 2004)

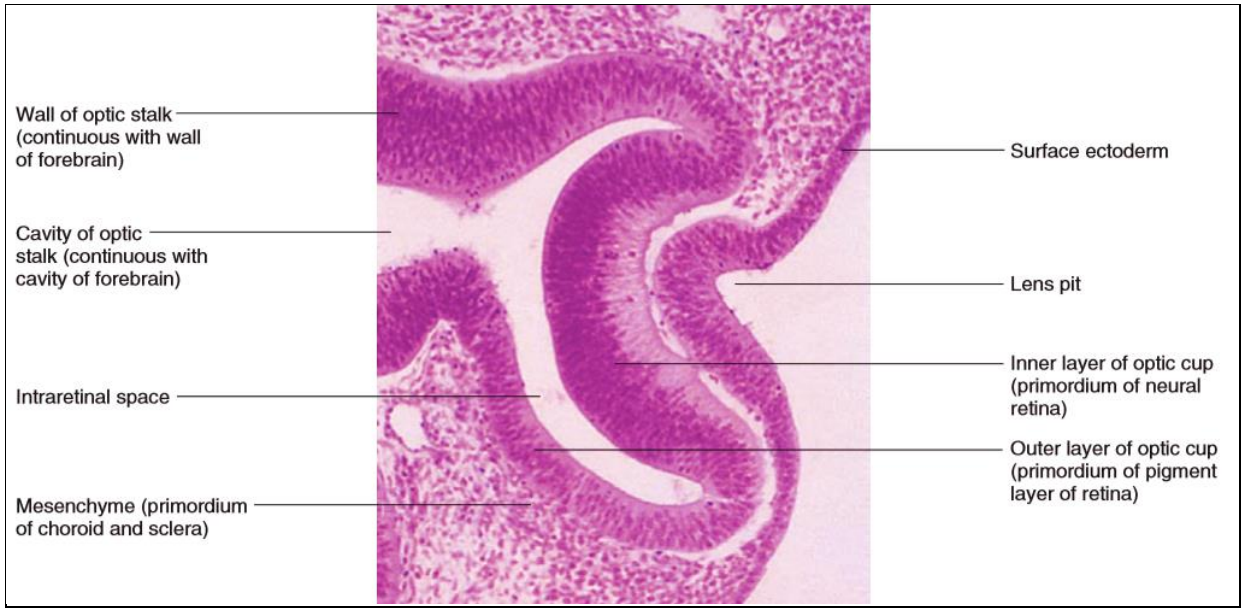


Figure 5: Photomicrograph of a sagittal section of the eye of an embryo (x200) at 32 days. The lens placode, the walls of the optic cup and the optic stalk (primordium of optic nerve) can be observed. (Moore KL, Persaud TVN, Shiota K: Color Atlas of Clinical Embryology, 2nd ed. Philadelphia, WB Saunders, 2000.)

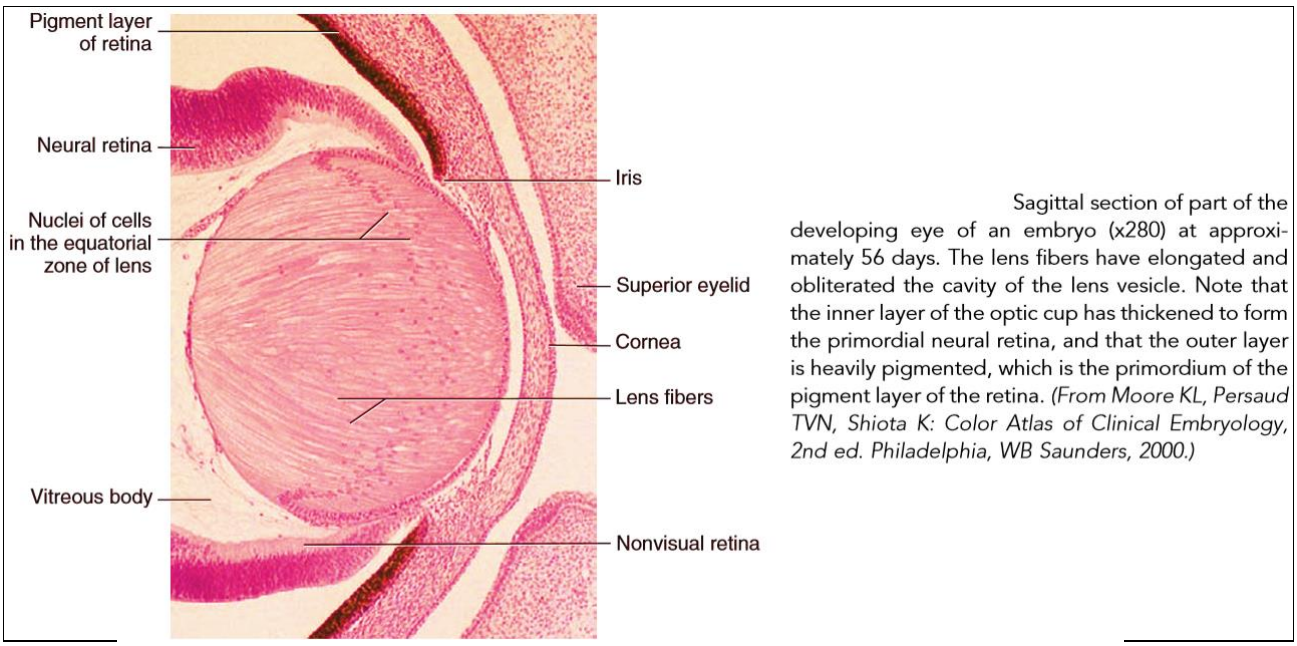


Figure 6: Courtesy From Moore KL, Persaud TVN, Shiota K: Color Atlas of Clinical Embryology, 2nd ed. Philadelphia, WB Saunders, 2000.

1.6 GLAUCOMA

Glaucoma is an ocular condition difficult to be defined, rather it can be regarded as a group of disorders. Glaucoma can be ranked on second position amongst the leading causes of blindness worldwide (Sarfraz, Mehboob and ul Haq 2017). This condition remains undetected in majority of people until the disease has progressed so far and advanced complications have already occurred. Bourne (2016) classified glaucoma along with macular degeneration as the top cause of irreversible blindness, and hence due importance needs to be given to this treatable ocular condition in order to decrease the global burden from this condition.

1.6 (A) Definition

Glaucoma can be defined as diverse group of ocular conditions grouped together, with common features, or advancing optic neuropathy and visual field defects which are usually related to the increased intraocular pressure IOP.

1.6 (B) Epidemiology

By the year 2020, the global prevalence of glaucoma is expected to touch an alarming figure of 80 million (Chen, Lu, Zhang and Lu 2012).

1.6 (C) CLASSIFICATION OF PRIMARY GLAUCOMA

1.6 (C i) PRIMARY OPEN-ANGLE GLAUCOMA

Primary open angle glaucoma is the most prevalent type of glaucoma. It is an ocular condition characterized by chronic advancing optic neuropathy, with elevated IOP in the presence of an open-angle (Chen et al., 2012).

Primary open angle glaucoma is defined as a type of long standing disease affecting often both eyes in aged population. POAG has IOP>21 mmHg, with developing glaucomatous optic nerve neuropathy in the presence of open anterior chamber angle on gonioscopy with ultimately establishment of visual field errors. According to a study done by Chen et al., (2012) that apart form high IOP, age, gender, race, optical aberrations, family history and genotype do play a role underlying primary open angle glaucoma disease causing

mechanism. There is increasing evidence that high myopia is linked with the causation of glaucoma (Marcus, de Vries, Montolio and Jansonius 2011).

The other types of glaucoma have been mentioned in the chapter of literature review.

1.7 GLAUCOMA-RELATED INVESTIGATIONS

Primary open-angle glaucoma (POAG) is a progressive optic neuropathy characterized by raised intraocular pressure (IOP) which creates a cascade of events. Raised IOP remains the only modifiable factor in the pathogenesis of the ailment and hence its estimation is of cornerstone importance.

1.7 (A) IMAGING IN GLAUCOMA

1.7 (A i) STEREO DISC PHOTOGRAPHY

Use of stereo disc photography as an early modality for imaging lamina cribrosa is of limited application (Tan, Koh, Girard & Cheng 2018). It can be said that a crude 2D detailing can be acquired using this technique. Stereo disc photography has limited application in early diagnosis since only a small part of LC is available for imaging because of the presence of the neruoretinal rim.

1.7 (A ii) CONFOCAL SCANNING LASER TOMOGRAPHY

The confocal scanning laser tomograph uses the diode laser beam across retina and optic nerve head at different depths. To obtain the gross features of lamina cribrosa, which can be converted from a 2D image to a 3D, confocal imaging had been used in the past. Estimation of area of lamina cribrosa, the count of laminar pores and measurement of pore sizes can be calculated using confocal scanning laser tomography (CSLO). Advent of a software program, Adaptive optics (AO) has enabled CSLO for acquisition of better images, but its use is still limited for laminar pore morphometry (Vilupuru 2007).

1.7 (A iii) SCANNING LASER POLARIMETRY

Scanning laser polarimetry is used to assess the retinal nerve fiber layer thickness. It provides the colored images of retina and the right and left sides of the retina can be compared at a single frame of time. It gives an hour glass shaped image of retina as the thickness of retina is more at superior and inferior aspects. The color red progressing to yellow signifies a thick retina, whereas blue turning to green tells about retinal thinness (Bowling 2015). It used to be a useful way of quantifying the thickness of retina in cases of glaucoma (Schulze 2015).

1.7 (A iv) OCULAR COHERENCE TOMOGRAPHY (OCT) WITH TYPES

Optical coherence tomography (OCT) is a modern invention, is a non-invasive and non-contact technique which enables detailed microanalysis of eyes at a deeper tissue level. High resolution images of sclera, uveal tract, vitreous, retina, optic nerve head can be obtained using this modality. According to Bowling 2015 the anterior segment of the eye can also be visualized by OCT. Taking a look into the newer and revised versions of OCTs' which have been invented now

1.7 (A v) TIME-DOMAIN OCULAR COHERENCE TOMOGRAPHY (TD-OCT)

Time-domain OCT is the most basic OCT modality. This machine had a lesser sensitivity for tissue penetrance and depth and also encountered the scattering of light waves by the blood vessels and any pigments (Sigal, Wang, Strouthidis, Akagi & Girard 2014). The axial resolution of TD-OCT was also low, 10 microns with only 400 A-scans.

1.7 (A vi) SPECTRAL-DOMAIN OCULAR COHERENCE TOMOGRAPHY (SD-OCT)

The advent of spectral-domain ocular coherence tomography has largely substituted for the use of TD-OCT. SD-OCT has a sophisticated 80,000 A-scans per second with axial resolutions of upto 2 microns. SD-OCT has a spectrometer that enables the machine for such high precision (Wojtkowski et al., 2005).

SD-OCT alone at greater depths is unable to visualize the structures buried within the bottoms of optic nerve head due to attenuated signal strengths. Improvements in

hardware of OCT; like enhanced depth imaging (EDI) and softwares like adaptive compensation (AC) have made the OCT a better choice for imaging deeper optic nerve head structures (Girard et al 2015). EDI-OCT specifically has been adopted to visualize the deeper structures, including choroid and lamina cribrosa. Girard, Strouthidis, Ethier & Mari (2011) elaborated that EDI-OCT can be used alone or with AC. AC minimizes the noise over-amplification, enhances the tissue contrast and also hurdles away the blood vessel shadows and pigment light ray scattering.

1.7 (B) PERIMETRY

Visual field is similar to a 3 dimensional entity, with increasing sensitivity for imaging, 50º superiorly, 60º nasally, 70º inferiorly and 90º temporally. The fovea represents the sharpest point of the field (Bowling 2015). The perimeter works on the principal of logarithmic scale, for each log the sensitivity increases by a fraction of 10. By application of logarithmic scale the lower end of the sensitivity can be assessed with greater precision. The sensitivity of visual field is measured in the units of decibels (dB), so as the strength of dB goes up, it signifies more sensitivity of retina requiring lessening of the intensity of luminance shown during the visual field testing. The blind spot has the sensitivity of 0dB.

There are various types of perimetry; kinetic, static, suprathreshold and threshold. Usually the threshold perimetry is employed for monitoring the glaucoma optic neuropathy defects.

1.8 ROLE OF LAMINA CRIBROSA IN DIAGNOSIS OF PRIMARY OPEN-ANGLE GLAUCOMA

Kim et al., (2016) has emphasized the role of lamina cribrosa as an integral contributor in the pathogenesis of glaucomatous optic neuropathy. Lamina cribrosa is a deeply placed structure in the core of optic disc and its in-vivo visualization has become possible since the invention of EDI spectral domain ocular tomography (Srinivasan et al 2008). This device can be used to explore the morphological parameters of lamina cribrosa relevant with the primary open angle glaucoma, and its association with visual field defects (Figure 7).

1.9 LAMINA CRIBROSA PARAMETERS RELATED TO PRIMARY OPEN-ANGLE GLAUCOMA

The lamina cribrosa parameters related to the primary open angle glaucoma are

1.9 (A) LAMINA CRIBROSA DEPTH (ALCD)

Optic cupping is a phenomenon related with the severity of glaucoma. Yang et al., (2007) had stated that optic cupping in glaucomatous optic neuropathy occurs due to prelaminar and laminar posterior displacement, and hence it can be inferred that as the severity level of glaucoma goes up, a greater depth of lamina cribrosa can be expected. Kim et al., (2016) had also explained the significance of lamina cribrosa depth in context of glaucoma severity and chronic intraocular pressure elevations.

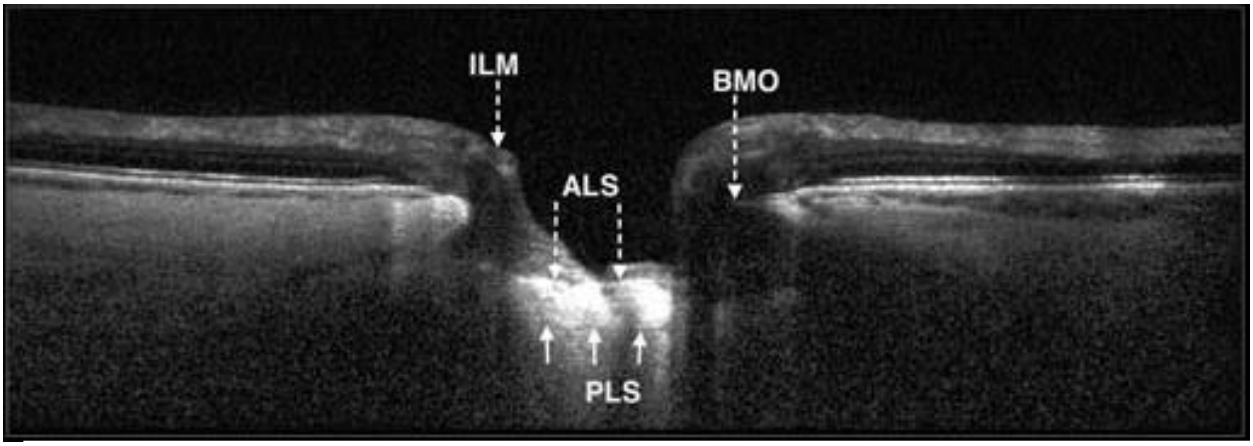


Figure 7: Enhanced depth spectral domain ocular coherence tomography (EDI SD-OCT) image of the ONH demonstrating better visualization of the anterior surface and posterior surface (solid arrows) of the lamina cribrosa (Reference Laxmikanth, K., Girkin, C. A 2011).

ILM = Inner Limiting Membrane
BMO = Bruch's membrane opening.
ALS= Anterior lamina surface
PLS= Posterior lamina surface

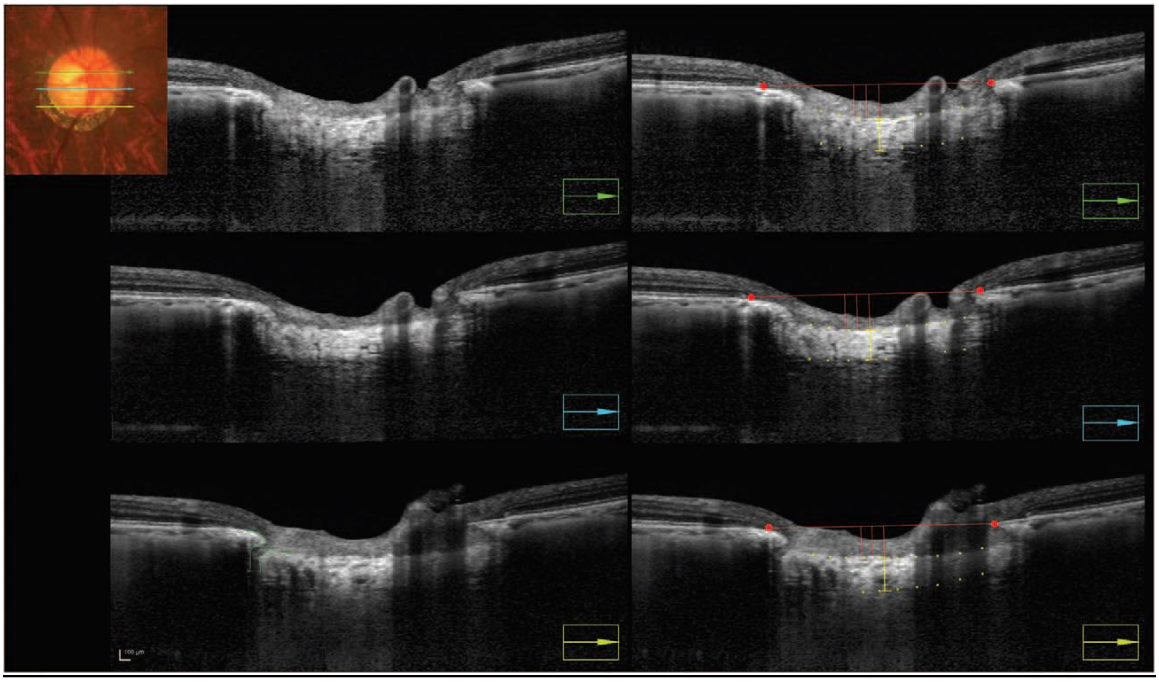


Figure 8. Enhanced depth imaging of the optic nerve head using Spectralis optical coherence tomography (Reference: Park, Kim and Park 2017)
A focal lamina cribrosa (LC) defect was considered as a violation of the curvilinear U- or W-shaped contour of the anterior LC surface (green outline).
Both LC depth (LCD) and LC thickness (LCT) were measured at three locations (superior midperipheral, green arrow; midhorizontal, blue arrow; inferior midperipheral, yellow arrow).
The LCD was determined by measuring the distance from the Bruch membrane (BM) opening plane to the level of the anterior LC surface. The average of the 3 values was used as the LCD (three red perpendicular lines) at that location.
The LCT was measured as the distance between the anterior and posterior borders of LC in the direction perpendicular to the anterior LC surface at the measurement point (yellow line between yellow glyphs marking the anterior and posterior border of the LC). The average of 3 values from 3 locations was used as the mean LCD and mean LCT

1.9 (B) LAMINA CRIBROSA THICKNESS (LCT)

Many researchers had proved a positive relationship between worsening of the glaucoma severity and the deteriorating lamina cribrosa thickness. Park, Jeon & Park (2012) had come up with logarithmic and Lee et al., (2012) had elaborated linear correlations between the thinning of lamina cribrosa and elevation of intraocular pressure. More thinness of lamina cribrosa can positively be linked with the degree of primary open angle glaucoma (Figure 8).

1.9 (C) VISUAL FIELD DEFECTS

Glaucoma optic neuropathy has a profound association with the retinal nerve fiber layer defects and hence the impairment in visual field. To assess the loss of function in glaucoma sufferers, a perimetry test has been devised, known as Glaucoma hemifield test. This test has different patterns, like 24-2, 30-2 (Bowling 2015) and the latest version 50-2. 24, 30 or 50 denotes how much the field is being tested on the temporal side of vision. The glaucoma hemifield test matche five corresponding areas on the superior and inferior fields of retina, due to the known fact of glaucomatous defects occurring vertical asymmetrically.

Mean deviation (MD) is a measure of summation of sensitivity of retinal field. It is calculated from averaging the total deviation values of a given field. The central deviation values having more significance.

Pattern standard deviation (PSD) designates a focal loss on the field of vision or a change in it, in the context of detecting any downhill depression in the field of vision. A greater value of PSD is thus more specific for showing glaucomatous optic neuropathy defect as compared to mean deviation (MD).

1.10 OPTIC NERVE HEAD FEATURES ASSOCIATED WITH GLAUCOMA

There are certain ocular features which are consistent with the development of glaucomatous optic neuropathy. Since these features also aid in the clinical detection of primary open angle glaucoma, they deserve description

1.10 (A) Optic disc size

The part of the optic nerve head which can be visualized ophthalmoscopically is known as the optic disc. The periphery of the optic disc are adjusted within the scleral canal, which governs its size as Naida (2016) stated that small scleral canals have smaller optic discs and vice versa. The size of the optic disc can best be ascertained using slit-lamp biomicroscope and a vertical diameter of optic disc remains essential to determine whether the optic disc is small, average or large in size. According to Reis, Toren & Nicolela (2012) the average vertical height of a non-diseased optic disc ranges from 1.8-2 mm, a small disc ranges to or less than 1.5 mm with a large disc greater than 2.2mm.

1.10 (B) Cup-to-disc ratio

The cup-to-disc ratio is dependent over the size of the optic disc which in turn relies over the size of the scleral canal. It goes without saying that larger discs have larger cup-to-disc ratios and smaller have small values (Turgut 2017), so area of cup-to-disc and optic disc are interrelated. Average normal values for the cup-to-disc ratio is 0.4, but due to anatomical variations it can range from 0.0 to 0.9. A cup-to-disc ratio of greater than 0.8 until proven otherwise is a sure sign of glaucomatous optic neuropathy.

1.10 (C) Neuroretinal rim defects

Is the amount of the tissue present around the edges of optic cup till the limits of optic disc. Normally this area is occupied by the blood vessels which are arranged circumferntially. Kampougeris, Spyropoulos, Mitropoulou, Zografou and Kosmides (2013) have highlighted in their study the importance of "ISNT" rule in ascertaining the normal thickness of the optic nerve, which should be thickest inferiorly than superiorly, following in thickness by nasal and temporal quadrants. It can be said that a neuroretinal rim that is not compatible with the ISNT rule and thinner can be regarded as a sign of glaucomatous optic neuropathy.

1.10 (D) Parapapillary atrophy

Parapapillary atrophy (PPA) refers to the thinning or degeneration of chorioretinal tissue and reflection of retinal pigment epithelium. As stated by Sivaswamy, Krishnadas, Chakravarty, Joshi & Tabish (2015), the combination of a shallow cup with parapapillary atrophy is more common in glaucoma. Parapapillary atrophy can be zone (α) which is peripheral or zone (β) which is always central. Zone (β) is also associated with glaucomatous optic neuropathy.

1.10 (E) Laminar dots

Nicolela and Vianna (2016) described the lamina cribrosa to be highly responsive to the fluctuating levels of intraocular pressure, with higher pressures making it to displace posteriorly and deform its pores. The variation in pore size creates a clinical sign of glaucoma known as **laminar dot sign** and due to anatomical weaker areas of lamina cribrosa superiorly and inferiorly, the dots have a predilection for these areas. Healey & Mitchell (2004) have depicted the shape of laminar dots of slit-like in glaucoma and a prequel to the subsequent development of visual field defects.

1.10 (F) Optic nerve head hemorrhages

Optic nerve head hemorrhages (ONHH) are known by so many other names like splinter, retinal nerve fiber, drans or peripapillary hemorrhages. They are said to be located within the disc or within one disc diameter of optic nerve head margin, but not in optic cup. Budenz et al., (2006) stated that optic nerve head hemorrhages occur more in glaucoma and one that is present at the optic disc is highly diagnostic of glaucomatous optic neuropathy.

1.11 HYPOTHESIS

1.11 (A) NULL HYPOTHESIS:

There is no correlation between anatomical dimentions of lamina cribrosa (LC); [anterior lamina cribrosa depth (ALD) and lamina cribrosa thickness (LCT)] with glaucomatous optic neuropathy (GON) in patients of primary open angle glaucoma (POAG)

1.11 (B) ALTERNATE HYPOTHESIS:

There is a correlation between anatomical dimentions of lamina cribrosa (LC) [anterior lamina cribrosa depth (ALD) and lamina cribrosa thickness (LCT)] with glaucomatous optic neuropathy (GON) in patients of primary open angle glaucoma (POAG)

1.12 OBJECTIVES OF STUDY:

1) To determine the lamina cribrosa (LC) morphology dimentions (LC thickness) and anterior LC depth (ALCD) in patients with primary open angle glaucoma (POAG) and normal healthy controls

2) To compare the lamina cribrosa (LC) morphology parameters (LC thickness) and anterior LC depth (ALCD) in patients with primary open angle glaucoma (POAG) and normal healthy controls

3) To correlate the morphological parameters of lamina cribrosa (LC) with retinal nerve fiber layer (RNFL) thickness and visual field (VF) changes in patients of primary open angle glaucoma (POAG)

1.13 STATEMENT OF THE PROBLEM

Alteration in the morphology of lamina cribrosa (LC) and its severity may have a correlation with glaucomatous optic neuropathy (GON) which can be detected by spectral

domain ocular coherence tomography (SD-OCT) in primary open angle glaucoma (POAG).

1.14 SIGNIFICANCE OF STUDY

Glaucomatous optic neuropathy begins from the optic nerve head (ONH), present at the scleral canal; from the lamina cribrosa. Imaging of the lamina cribrosa becomes indispensable in understanding the progression of the disease. Spectral domain optical coherence tomography (SD-OCT) offers in-vivo visualization of anterior lamina cribrosa and its various parameters with respect to glaucomatous optic neuropathy (GON), which are not appreciable with other techniques like optic disc photography, time-domain ocular coherence tomography (TD-OCT) or confocal scanner laser ocular tomography (CSLO). Early detection of lamina cribrosa damage dimentions will provide a lead in prevention from visual loss due to early detection of retinal nerve fiber layer (RNFL) thinning in glaucomatous optic neuropathy (GON) and monitoring the progression of glaucomatous changes in primary open angle glaucoma (POAG). There is a critical need for a study to provide with new endpoints for the disease prevention in Pakistan.

1.15 OPERATIONAL DEFINITIONS

1.15 (A) Primary Open-Angle Glaucoma- Patients with GON transformations, for example, distended cup to disc ratio (> 0.7), diffuse/ focal neural rim thinning, disc hemorrhage, or RNFL defects seen using OCT or characteristic visual field alterations on Humphry 50-2 VF analysis along with an open angle on gonioscopy

Reference: Strouthidis, N. G. (2012). *Three-dimensional optical coherence tomography imaging of the optic nerve head* (Doctoral dissertation, UCL (University College London).

1.15 (B) Anterior Lamina Cribrosa depth (ALCD) - The measurement between line linking both ends of Bruch's membrane (BO) and anterior border of the LC on enhanced depth SD-OCT

Reference: Kim, M., Bojikian, K. D., Slabaugh, M. A., Ding, L., Chen, P. P. (2016). Lamina depth and thickness correlate with glaucoma severity. *Indian journal of ophthalmology*, *64*(5), 358.

1.15 (C) Lamina Cribrosa thickness (LCT)- The area between the anterior and posterior borders of LC, visualized by highly reflective structure below the optic cup as seen on enhanced depth SD-OCT

Reference: Yun, S. C., Hahn, I. K., Sung, K. R., Yoon, J. Y., Jeong, D., Chung, H. S. (2015). Lamina cribrosa depth according to the level of axial length in normal and glaucomatous eyes. *Graefe's Archive for Clinical and Experimental Ophthalmology*, *253*(12), 2247-2253.

1.15 (D) Glaucomatous VF change is:

I. Outside normal limits on the Glaucoma Hemifield Test
II. Three abnormal points with $P < 5\%$ probability of being normal, 1 with $P < 1\%$ by pattern deviation;
III. Pattern standard deviation of <5% on automated Humphry 50-2 VF analysis

Reference: Kim, Y. W., Jeoung, J. W., Girard, M. J., Mari, J. M., Park, K. H., Kim, D. M. (2016). Clinical assessment of lamina cribrosa curvature in eyes with primary open-angle glaucoma. *PloS one*, *11*(3), e0150260.

CHAPTER 2

LITERATURE REVIEW

2.1 Axiom “eyes are window to the soul” can be rephrased in the world of medicine as “eyes serve as a window to unfold medical ailments”. We have discussed in the introduction of thesis about the importance of the eyes, the major causes of visual impairment and blindness and one of the top causes is glaucoma and it is focus of our research. Primary open-angle glaucoma has been elaborated in the preface, other varieties of glaucoma from whom the primary open-angle glaucoma can be differentiated and on which various researches have been conducted henceforth also deserve description.

2.2 NORMAL-PRESSURE GLAUCOMA

When all the readings of IOP come out to be equal to or lesser than 21mmHg, such category can be dealt under normal-pressure glaucoma as termed by Ren et al (2011). It is said to be variant of primary open angle glaucoma, with the feature of IOP equal to or less than 21 mm Hg, the typical glaucomatous optic neuropathy distortion of the disc, an open anterior chamber angle without the accompanying characteristics of any type of secondary glaucoma; progressing on to typical glaucomatous field damage (Bowling 2015). This presents a challenge as in such patients only modifying IOP does not control the condition of normal tension glaucoma and suggests that some other underlying condition is behind the pathogenesis. As researched by Mozaffarieh and Flammer (2013), blood flow reduction occurs in glaucoma but more so in normal tension glaucoma, the same study also concludes that blood flow reduction can also be observed in other peripheral body parts like nail beds, so a vascular pathology can be a dormant condition associated with normal tension glaucoma.

2.3 PRIMARY ANGLE-CLOSURE GLAUCOMA

Obstruction of trabecular meshwork by the peripheral extensions of iris, resulting in obscuring the drainage of aqueous humor is the anatomical cause of angle-closure variety of glaucoma. In an anatomically inclined globe, such condition would be termed as primary, while with other factors it is termed as secondary. According to Bowling 2015, at least three points need to have iridotrabecular contact (ITC) detected on gonioscopy,

with developing optic neuropathy for the diagnosis of primary angle closure glaucoma. Wang et al., (2011) have described primary angle-closure glaucoma in their study as the eyes with narrow angles, in which the posterior trabecular meshwork was not apparent on gonioscopy having an IOP equal to or greater than 21mmHg, associated with or without optic glaucomatous changes. Worldwide, over 15million people are said to be affected by primary angle closure type of glaucoma, and out of them a substantial 80% sufferers happen to be Asians (Vithana et al., 2012).

2.4 TYPES OF SECONDARY GLAUCOMA

2.4 (A i) SECONDARY OPEN-ANGLE can be subdivided on the basis of site of aqueous outflow obstruction

2.4 (A i) **Pre-trabecular**

According to Bowling (2015), if the secondary open angle glaucoma occurs due to impediment of aqueous flow by a membranous structure surfacing the trabeculum, it can be regarded as a pre-trabecular cause of secondary open angle glaucoma. A neovascular type of glaucoma can be regarded as one example. Success has been shown with the surgical use of trabecular micro-bypass stents, famous as iStents via microinvasive glaucoma surgery (MIGS) which advocate to increase the aqueous outflow, as documented by Le and Saheb (2014).

2.4 (A ii) **Trabecular**

Blockade occurring at the level of the trabeculum due to various causes, like pigment deposition, red blood cells or degenerated red blood cells, lens will offer resistance at the level of the trabeculum and result in raised IOP. Buchacra, Duch, Milla, and Stirbu (2011) assessed the efficacy of iStents in such secondary causes of glaucoma in a case series. As Bowling (2015) stated, trabecular variety can also occur due to alteration in the fibers of the trabecular meshwork, as in the cases of herpes zoster iritis or scarring after the trauma to the angle.

2.4 (A iii) **Post-trabecular**

The anterior segment and the trabeculum appear normal, but there is hindrance to the outflow of aqueous due to the increased pressure in episcleral veins. Rong & Li, (2018) stated in their case report that idiopathic dilated episcleral veins (IDEV) is an extremely rare condition and very difficult to diagnose according to the level at which the impediment to the aqueous outflow occurs within the anterior chamber. In cases of superior vena cava obstruction, or Carotid- cavernous fistula, the post-trabecular type of glaucoma may occur.

2.4 (B) SECONDARY ANGLE-CLOSURE GLAUCOMA

Occurs due to impairment of aqueous outflow due to a physical connection between peripheral iris and trabeculum, classified according to presence or absence of pupillary block. In angle closure pupillary block may or may not be present.

2009).

2.4 (B i) Secondary Angle-closure with pupillary block

Angle closure glaucoma is characterized by a precipitous acute attack, and certain attributes of people predispose towards this disorder with shorter axial lengths of eye, a bigger ocular lens, a shallow anterior angle and shorter drainage channel would predispose to distortion and sudden occlusion of angle (Lai and Gangwani 2012). Recurrent iridocyclitis and sublaxated lens are some examples of secondary angle closure with pupillary block type of glaucoma. Topical mydriatics and certain medications, like bronchodilators, general anesthetics and others may also exacerbate an acute attack of angle closure glaucoma with pupillary block (Volfson and Barnett, 2009).

2.4 (B ii) Secondary Angle-closure without pupillary block

Certain secondary cause of glaucoma, like advanced neovascular, malignant glaucoma or uveitis associated glaucoma (Siddique, Suelves, Baheti and Foster 2013) can be potential candidates that can cause secondary angle closure glaucoma without significant apposition between the iris and the angle.

2.4 (C) PSEUDOEXFOLIATION

Pseudoexfoliation is regarded as a syndrome rather than a single disorder (PXF). It is a common type of open angle glaucoma of chronic origin. It is an advanced age related phenomenon, more common as a syndrome in females but the pseudoexfoliation glaucoma (PXG) is more common in males. It is characterized by abnormal fibrillar extracellular matrix (ECM) composed of a protein core and surrounding glycosaminoglycans; deposition in the tissues of eyes in the trabecular meshwork, at the equator of the lens capsule, ciliary body and iris. As stated by Browne et al., (2011), pseudoexfoliation syndrome PXF ultimately culminates in glaucoma and cataract. Pseudoexfoliation glaucoma can be clinically diagnosed by a dilated pupil with sedimentation and deposition of fibrillar material in the anterior segment of the eye; as detected on slitlamp biomicroscopy. According to Browne et al., (2011), pseudoexfoliation accounts for more than fifty percent cases of open angle glaucoma in Saudia Arabia, Norway, Ireland and Greece.

2.4 (D)PIGMENTARY GLAUCOMA

Extreme pigment deposition and liberation from the iris pigment epithelium occurs within the anterior chamber of the eye, is the mechanism behind pigment dispersion syndrome (PDS) and pigmentary glaucoma (Akil et al., 2016). As per Bowling (2015), the condition may be inherited as autosomal dominant condition and mostly seen in white races. The excess pigment sets over the innermost cellular lining of corneal endothelium and at the trabecular meshwork, and thus causes elevation of IOP and subsequent optic nerve neuropathy. The concavity of iris with the posterior aspect of it rubbing against the lens zonular ligaments causes the liberation of iris pigment and the subsequent condition.

2.4 (E) NEOVASCULAR GLAUCOMA

Neovascular glaucoma is an unrelenting type the disorder, which is characterized by the neo-vascularization that is, development of new blood vessels (known as rubeosis iridis) in the anterior chamber of the eye, making hindrances for the drainage of the aqueous and causing neovascular variety. Angiogenesis subsequently changes into fibrous tissue and settling in within the anterior chamber (Simha, Braganza, Abraham, Samuel and Lindsley

2013). According to Bowling (2015), certain growth factors elaborated by the ischemic retinal tissue, especially vascular endothelial growth factor (VEGF) may predispose towards this condition. Other conditions as diabetes mellitus and retinal arterial vascular diseases may also predispose to this condition.

2.4 (F) INFLAMMATORY GLAUCOMA

A substantial 2 million people suffer from the inflammation of uvea, known as uveitis; out of those 2 million, 10% would ultimately be developing the symptomatology of optic neuropathy leading to blindness due to the emergence in them of uveitic glaucoma (Siddique et al., 2013). Uveitic glaucoma is said to be diagnosed when IOP gets elevated and causes typical optic neuropathy, which in turn produces the pathognomonic visual field defects. Baneke, Lim and Stanford (2016) stated that increase in IOP with uveitis may occur along with open anterior segment angle, or may collaborate with a closed anterior angle.

2.4 (F i) Angle-closure glaucoma with pupillary block in inflammatory glaucoma

The iridotrabecular contact (IRC) in the form of posterior synechiae, encompassing the whole circumference of 360^{o}, obstructing the drainage of the aqueous and so causing inflammatory angle-closure glaucoma with pupillary block (Bowling 2015).

2.4 (F ii) Angle-closure glaucoma without pupillary block in inflammatory glaucoma

In chronic anterior uveitis, settling in of the inflammatory debris in the angle and subsequent consolidation of it pulling over the iris on trabeculum, causes inflammatory angle-closure glaucoma without pupillary block (Bowling 2015).

2.4 (G) PHACOLYTIC

A variety of open angle glaucoma as a consequence of a hypermature cataract is known as phacolytic glaucoma. Peracha et al., (2017) described that high molecular weight proteins are liberated through intact lens capsule, macrophages imbibe the leaked proteins

and thus induce an inflammatory reaction and choke the trabecular meshwork. Yaakub, Abdullah, Siti and Ahmad (2014) state that the lens induced glaucoma (LIC) to be frequent in developing countries and owing to delay in cataract removal and it is not uncommon to find it in developed countries. Various anatomical factors can contribute towards elevation of IOP like lens dislocation, swelling of the lens and lens particle obstructing the trabecular meshwork. The lens proteins leaked are formed during embryological development and thus when leaked at the trabecular meshwork, they are regarded as foreign, and intense autoimmune granulomatous reaction may also occur (phacoanaphylactic glaucoma).

2.4 (H) TRAUMATIC

Red blood cells oozing out after injury to the eye can result in IOP elevation as they clog the trabecular meshwork, and this creates another entity of glaucoma, termed as traumatic glaucoma (Bowling 2015) that will need three months of glaucoma medication after sustaining the injury. The prevalence of traumatic glaucoma is rising to about 11-48% and hence deserves discussion (Oruçoglu, Blumenthal, Frucht-Pery and Solomon 2014). According to Bojikian, Stein, Slabaugh, and Chen (2015), trauma to the eyes can be a sequel to injury or also due to surgery. Turalba, Shah, Andreoli, Andreoli and Rhee (2014) stated that the predisposing factors of traumatic glaucoma as being older age, vitreous hemorrhage and some hemoglobinopathies like sickle-cell anemia. These risk factors not only predispose the suspects towards the development of traumatic glaucoma but also they are more prone to get the adverse complications related to the problem.

2.5 LAMINA CRIBROSA

Lamina cribrosa (LC) is the spongy, pore containing posterior component of sclera from where unmyelinated retinal ganglion cell axons (RGC) aggregate into a bundle and form optic nerve (ON). Optic nerve exits from the eyes from the scleral canal. According to the biomechanical theory the lamina cribrosa (LC) plays a fundamental role in the pathogenesis of glaucomatous optic neuropathy (GON) (Kim et al., 2016). The

anatomical aberrations of LC produced due to fluctuating pressures manifest in the form of posterior bowing and posterior displacements. These morphological aberration based researches had become possible only after the advent of enhanced depth imaging (EDI) spectral domain optical coherence tomography (SD-OCT), which enabled in-vivo imaging of LC damage in glaucomatous eyes and generated vigor in recent research related to ophthalmology. Even though optic nerve head (ONH) and optic disc are interchangeably used, actually optic disc is part of ONH examined during ophthalmoscopy. Turgut (2017) has proposed a three layered histological structure of the ONH. The layers include a superficial RNFL, pre-laminar, laminar (LC) and retrolaminar layers. Optic nerve head defects occur prior to any visual field changes and have a potential prophylactic role in diagnosis if explored timely before developing VF defects and development of glaucoma. Due to advent of enhanced depth imaging (EDI), in-vivo examination of the optic nerve head components has become possible. Even the deeper buried tissues of optic nerve head can also be monitored with precision.

Kim et al., (2018) validated that evaluation of LC structural morphological measurements may actually aid in envisaging disease outcome in patients of primary open angle glaucoma (POAG), as well as in glaucoma suspects. They conducted their examination over 102 eyes of 102 research subjects. They also observed traditional intraocular pressure (IOP) changes sometimes do not occur in some subjects, but they do suffer from glaucomatous optic neuropathy (GON). The research documented that treatment decision in such “suspects of glaucoma” has always remained an enigma since great majority of patients do not develop definite overt glaucoma signs. In such instances posterior bowing of LC is the earliest anatomical structural change that occurs prior to retinal nerve fiber layer (RNFL) defects.

Xu, Weinreb and Leung (2014) for a duration of 5 years examined 146 eyes of 90 patients with glaucoma and 70 normal eyes of 35 healthy subjects. They explained that depression of optic nerve head precedes retinal nerve fiber layer (RNFL) thinning in glaucomatous patients. Xu et al., (2014) thus had come up with an innovative idea of a window period for timely intervention upon detection of optic nerve head depression, since no retinal nerve fiber layer thinning occurs in patients of glaucoma during this

period. Lee, Kim, Lee, Girard and Mari (2017) in a case-control analysis had examined 77 eyes of primary open angle glaucoma patients and normal subjects respectively. They assessed LC displacements (LCD) and lamina cribrosa curvature index (LCCI) using SD-OCT and found a strong correlation between lamina cribrosa curvature index (LCCI) and primary open-angle glaucoma (POAG). There was no significant finding in normal subjects. They suggested lamina cribrosa curvature index (LCCI) as a beneficial guide in the management of glaucoma. LC has recently been a prime focus for investigators and its various dimensions are being studied extensively. A conflicting data has been reported by Kim, Lee, Lee and Lee (2014). They studied 71 Korean patients with low and high intraocular pressures and evaluated the thickness of lamina cribrosa. They could not get any significant difference in the thicknesses of lamina cribrosa amongst the two groups.

Contradictory to Kim et al., (2014) research, a case-control analysis over 139 glaucoma patients and 49 healthy controls was undertaken by Park, Jeon and Park (2012). They measued the thickness of lamina cribrosa. They found a thinner lamina cribrosa in normal-tension glaucoma (NTG) subjects than in primary open-angle glaucoma (POAG) patients, and a further thinner lamina cribrosa in NTG patients with disc hemorrhage than in the NTG patients without the hemorrhage. Ren et al., (2014) investigated the anterior lamina cribrosa surface depth (ALCSD) and retinal nerve fiber layer (RNFL) thickness against the variables of age and visual field. They found an age dependent relationship between ALCSD and RNFL thickness. On the other hand ALCSD was found to be strongly related to poor visual field in younger eyes and age groups. They also added that older eyes have shallower LC than younger eyes and is related to visual field and this age-related effect increases with advancing disease severity. Analogous age dependent relationship between ALCSD and RNFL thickness were recognized by Rho, Park, Lee and Park (2012).

Chung, Sung, Lee and Na (2016)had followed glaucoma patients or glaucoma suspects for about 2 years and investigated lamina cribrosa thickness, anterior lamina cribrosa distance and prelaminar tissue thickness. During the follow-up period, the POAG group showed thinner RNFL thickness and thinner prelaminar tissue. They concluded a significant association between progression of glaucoma and LC morphology. They

estabilished that LC thickness can well be regarded as a risk factor for diagnosing future glaucoma progression.

Consistent results that associated with the rate of progression of glaucoma and LC thickness have been reported by Park et al., (2013). They estabilished the diagnostic ability of laminar thickness in glaucomatous subjects. As was stated earlier, various scientific investigatory tools have been utilized for the early detection of the anatomical features of LC and thus to prevent glaucoma subjects from the detrimental hazards of visual loss. Substantial number of researches had been conducted to compare amongst the better investigatory tool for such purpose. One such study tested the correlation between the morphological features of LC and glaucoma severity in POAG using two imaging modalities, SD-OCT with EDI and Humphery visual field test (HVF) (Kim et al., 2016). The study concluded that POAG severity is significantly directly related with laminar depth (LD) and inversely related with laminar thickness.

A case-control analysis conducted by Furlanetto et al., (2013) where they compared 47 glaucomatous eyes and 57 normal subjects. The team found out that central and mid-peripheral LC was located more posteriorly in POAG patients than in normal subjects, as well as in eyes with visual field defects compared to opposite eyes with no visual field defects. These results support the concept of posterior LC displacement in glaucoma and provide a strong valid base for future in-vivo human studies. Sigal et al., (2014) further endorsed that new advents in technology have spectacularly rejuvenated the ability to visualize the LC. LC based examinations before the invention of EDI in SD-OCT, were dependent on histological measures and ex-vivo modeling. With dawn of newer imaging modalities better detection and overall management of glaucoma and other ocular diseases associated with ONH have now become possible by proper image guided risk assessments and treatment of patients. A significant reversal and reduction in posterior displacement of LC and increase in its thickness in prelaminar tissue were verified after glaucoma surgery using EDI with SD-OCT of the ONH. The magnitude of lamina cribrosa displacement reversal was related with younger age, larger baseline lamina cribrosa displacement, and greater IOP reduction (Lee, Kim and Weinreb 2012).

Efficacy of EDI with SD-OCT has been investigated by studies done by Girard et al., (2015) and Kimura et al., (2014). Both studies concluded the anterior LC was the most prominent imaged feature and EDI improved visibility of LC over plain SD-OCT. They also tried to analyze LC defects using a different mode of OCT known as three-dimensional (3D) swept-source optical coherence tomography (SS-OCT), and to establish factors related with this feature.

Much had been investigated about ONHH in association with clinical findings of POAG. Soares et al (2006) inspected the factors associated with the development of ONHH, and they found statistically positive associations of ONHH with diabetes mellitus, use of aspirin and IOP. It is a well-known fact that racial differences also account for the various types of clinical presentations. Bengtsson, Leske, Yang, Heijl, and EMGT group (2008) recorded in "Early Manifest Glaucoma Trial", a prospective study of 11 year duration that ONHH were found in more than 55.5% of their cases upon either ophthalmoscopy or fundus photography and were linked with the progression of the disease. De Moraes et al (2009) recorded 168 hemorrhages in 122 POAG subjects and suggested that visual field losses and subsequent defects appear in the future areas of ONHH. Ishida, Yamamoto, Sugiyama and Kitazawa (2000) in their prospective study with 70 subjects spanning for a duration of 5.6 years had proved similar results. De Moraes et al (2009) stated that probability of patients progressing to visual field defects was much stronger in the presence of ONHH than those without the ONHH.

Parapapillary atrophy (PPA) develops due to sparse nourishment to peripapillary choroidal circulation. Parapapillary atrophy (PPA) may signify the early signs of damage in glaucomatous optic neuropathy. It is observed in two patterns, alpha (α) or outer zone and (β) inner zone. An α- zone atrophy reflects the haphazard hypopigmentation or excessive pigmentation in the superficial layers of retinal pigment epithelium (Yamada et al 2016). The β-zone exhibits atrophy of the choriocapillaries and retinal pigment epithelium with obvious sclera. β-zone atrophy appears between the optic cup and the α-zone atrophy. Previous researches related the occurrence of central type beta (β) with GON. Such thought was entertained by Skaat et al (2016) in which they had run a prospective cohort on the 1950 eyes of 1172 subjects between the European and African

descent. Their main outcome of study revolved around the relationship of ONHH and the occurrence of β-zone PPA. African descent cases were found to have more significant predilection for β-zone PPA as compared to European descent cases, which were more likely to develop ONHH.

Angel, Serna and Valencia (2018) in their research found a substantial appearance of laminar dots in 67.6% of the 374 photographs of optic disc they recruited for their study

All of these above mentioned LC morphometric dimensions may prove valuable in detecting early changes and may prove an appraisal in the treatment and prognosis of glaucoma.

CHAPTER 3

METHODOLOGY

3.1 Research design

The research design for "Correlation between lamina cribrosa morphology and glaucoma severity in patients with primary open-angle glaucoma" is a case-control study. The research investigated lamina cribrosa depth (ALCD), lamina cribrosa thickness (LCT), visual field parameters VF-PSD and VF- MD and RNFLT. The functional significance had been associated with the findings of retinal nerve fiber layer (RNFL) thickness assessment and visual field analysis.

3.2 Ethical approval

The study was approved by ethical review committee (ERC) of Bahria University Medical and Dental College, Karachi after acceptance from Faculty Review Committee (FRC). ERC reference number ERC 60/ 2018.

3.3 Setting

Patients were inducted in study from the out-patient department of Al-Ain Eye Institute, Karachi after receiving their informed consent.

3.4 Inclusion criteria

The inclusion criteria for the cases and controls were

3.4 (A) CASES

3.4 (A i) Intraocular pressure (IOP): Patients with IOP of more than 22mmHg were termed as having primary open-angle glaucoma (POAG), as assessed by Goldmann Applanation tonometry.

3.4 (A ii) Assessment of open-angle (POAG): To ascertain that the angle was not blocked patients were examined through Slit-lamp biomicroscope and stereoscopic ophthalmoscope. Patients with mild cataract were included but mature and hypermature cataract subjects were excluded.

3.4 (A iii) Visual acuity: After this initial categorization of subjects as cases, they underwent refractive error assessment. Subjects needed to have best visual acuity of >20/40.

3.4 (A iv) Estimation of axial length of eyes (AXL): Optical Biometer Al scan I was used to measure the axial length of the eye. Eyes with axial lengths of up to 30 mm were included.

3.4 (A v) Optic disc findings: The subjects of POAG were subjected to stereoscopic ophthalmoscopy and Slit-lamp biomicroscopy. Optic disc size, cup-to-disc ratio and vertical cup-to-disc ratio were estimated.

3.4 (A vi) Optic disc size: The vertical diameter of the optic disc is 1.50mm (Ross, Pawlina 2018), whereas Turgut (2017) calculated the average vertical diameter as 1.88mm and the horizontal 1.77mm. Optic disc size was also calculated and compared with the above mentioned normal findings.

3.4 (A vii) Cup-to-disc ratio: Cup-to-disc ratio is expressed as the part of the disc occupied by the cup. The ratio is ascertained as both in vertical and horizontal meridians, but the vertical one is more clinically relevant.

3.4 (A viii) Neuroretinal rim (NRR) thinning*:* Neuroretinal rim is the tissue in the middle of the external edge of the cup and the optic disc border. The color of the NRR is usually pink or orange in the normal eyes. In this study neuroretinal rim was assessed both clinically using the slit-lamp biomicroscopy and ophthalmoscopy and also on SD-OCT (Danthurebandara et al., 2015).

3.4 (A ix) Parapapillary atrophy: We investigated peripapillary atrophy by using the slit-lamp biomicroscopy and ophthalmoscopy, as well as using the SD- OCT.

3.4 (Ax) Laminar dots: With receding neuroretinal rim, the linear fenestrations start to appear and these are known as laminar dots. Laminar dots were examined by using the slit-lamp biomicroscopy and ophthalmoscopy, as well as using the SD- OCT. Laminar dots express the advanced damage of glaucomatous optic neuropathy (Bowling 2015).

3.4 (A xi) Optic nerve head hemorrhages: s. Optic nerve head hemorrhages were identifiedby clinical observation through the slit-lamp biomicroscopy and ophthalmoscopy. Optic disc hemorrhages (ONHH) are linked with glaucoma as a risk factor for the progression of the disease. They usually appear in the inferior sector of the retina on the temporal side.

3.4 (A xii) VISUAL FIELD FINDINGS: The criteria that must be attained for a patient as suffering from glaucomatous optic neuropathy on Standard automated perimetry are

i. Results outside the normal limits on Glaucoma Hemifield test (a software program engineered for testing the glaucoma functional deficits in standard automated perimetry)
ii. Three abnormal points with P<5% probability of being normal, 1 point with P<1% by pattern deviation

PREREQUISITE VISUAL FIELD FINDINGS IN CASES

i. A pattern standard deviation (a value stated as a difference found out from the standard value pertaining to that age in general population) of <5% as confirmed on two consecutive tests.
ii. Visual field tests should have a false-positive rate (repondant informing about sighting of light flicker in its absence) of <25%
iii. Visual field tests should also have a false-negative test repondant not informing about sighting of light flicker in its presence) of <25%
iv. Fixation losses (inability to target the light stimulus) allowed to subjects are also <25% (Lopes et al., 2019)

3.4 (B) CONTROLS

3.4 (B i) **Intraocular pressure**: Controls with an IOP of <21 mm Hg, recorded by Goldmann applanation tonometry were considered in the study.

3.4 (B ii) **Optic disc**: Optic disc with vertical diameter equal to or lesser than 1.50mm and a vertical cup-to-disc ratio of <0.6 were considered normal in the study. Intact neuroretinal rim, with no optic nerve head hemorrhages and absence of peripapillary atrophy were considered normal for the control subjects.

3.4 (B iii) **Visual field**: A normal VF without glaucomatous VF defects.

3.5 Exclusion criteria

Ophthalmologic condition: Any ophthalmological condition other than open angle glaucoma, like angle closure variety of glaucoma, optic neuritis, mature/hypermature cataract, episcleritis, uveitis, and retinal detachment which had affected the optic disc causing subsequent visual field defects were excluded from the study.

Systemic conditions: Systemic conditions like autoimmune conditions, diabetic retinopathy, and hypertensive retinopathy that could had the similar picture of glaucomatous optic neuropathy were not included in the study.

Neurological conditions: Patients with neurological condition affecting VF were excluded from the study.

Surgeries: Refractive or intraocular surgeries, and inability to perform the examinations were excluded from the study.

Head trauma: Any trauma to the head causing functional deficit of visual field had also not been included in the study. (Lee, Kim, Lee, Girard, and Mari, 2017)

3.6 Duration of study

Individual study period: 04 months.

Total study period: 10 months.

3.7 Sample size estimation

Sample size for the study was estimated using the method of sample size for "comparing two means" on www.openepi.com. The mean and standard deviation of control group 85.8 ± 34.1 and for the primary open angle glaucoma cases as 85.8 ± 34.1. Glaucomatous group was taken from the study by Kim et al, 2016 was used as baseline study to calculate the sample size. Margin of error used for the sample size calculation was 5%. Confidence interval used for mean 95%. The required sample size in each group n1= 56 and n2= 56, (Total=112)

3.8 Sampling technique

Non Probability purposive sampling, as all the patients coming to the ophthalmological OPD were not chosen as the study participants.

3.9 Human subjects and consent

Human subjects, either control (selected on the basis of IOP < 21 mm Hg and absence of VF defects in VF-MD and VF-PSD) or having primary open angle glaucoma (cases) were selected. All the study subjects were explained the rationale of the study by the principal investigator of the research. They had the freedom not to participate in the study or to leave the study at any point of the research. A written informed consent proforma was produced in the mother tongue Urdu and English both.

3.10 Materials

3.10 (A) Ophthalmoscope- WelchAllyn, USA (Figure 9)

3.10 (B) Refractive error tests- subjective refraction was done with illumination Snellen's chart

3.10 (C) Slit-lamp Biomicroscope- Topcon SL-D 7, Topcon Corporation, Tokyo, Japan (figure 10)

3.10 (D) Axial length of Eye- The axial length of eye was calculated using AXL; Optical Biometer Al- Scan Class I device, Nidek, Gamagori, Japan (Figure 11)

3.10 (E) Goldmann Applanation Tonometry- At-900, Haag Striet, Switzerland for ascertaining the intraocular pressure (IOP) (Figure 12)

3.10 (F) Spectral domain ocular coherence tomography (SD-OCT) with enhanced depth imaging (EDI)- (REVO nx/SOCT Copernicus REVO OPTOPOL Technology, Wavelength 830nm, Axial resolution 2µm, scan speed 1,10,000 scans/sec, scan time

1.37seconds, OPTOPOL Technology Sp. Z o.o, ul. Zabia 42, 42-400 Zawiercie, Poland). Series of vertical B-scans obtained from the cases. The SD-OCT was set at 2.4mm diameter centered on optic disc, this area was scanned with approximately 128 B-scan images. Approximately 1024 SD-OCT images were averaged for each section. In the study were used three horizontal B-scans, one passing through the center, one mid-superior and one mid-inferior encompassing the ONH. Only good-quality scans with quality score ≥16 were used.

SD-OCT was used for the calculation of anterior lamina cribrosa depth (ALCD), lamina cribrosa thickness (LCT), and retinal nerve fiber layer thickness (RNFL) (Figure 13)

3.10 (G) Humphrey Field Analyzer- 50-2 glaucoma testing (Medmont M 700 Automated Perimeter, fast threshold, Vermont, Australia) for visual field analysis (Figure 14)

Figure 9: Ophthamloscope (Al-Ain Eye Institute)

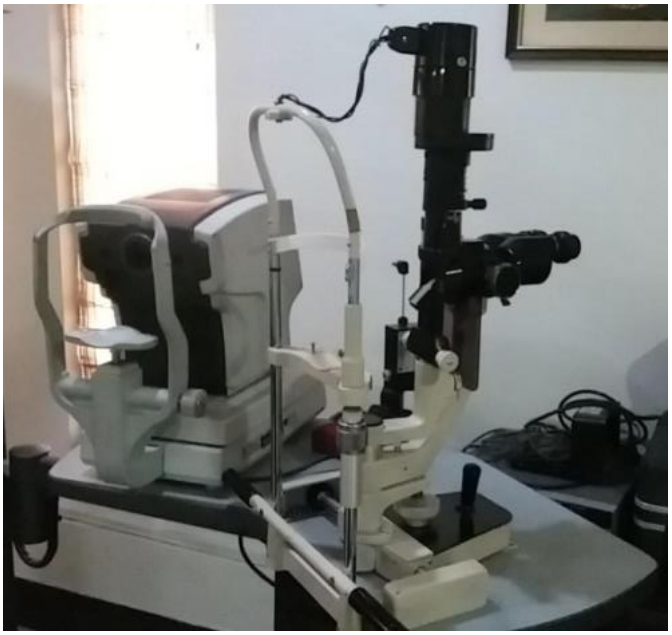


Figure 10: Slit-lamp Biomicroscope (Al-Ain Eye Institute)

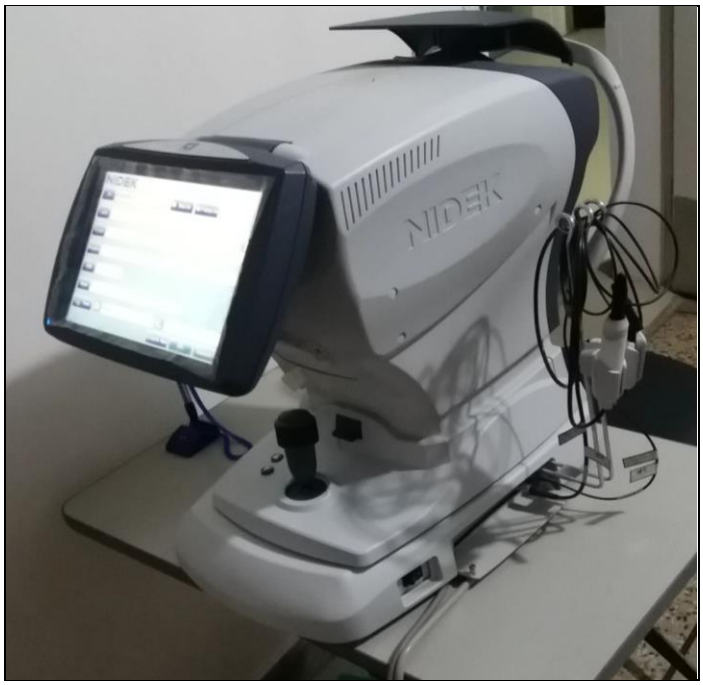


Figure 11: Instrument for measuring axial length of the eyes (Al-Ain Eye Institute)

Figure 12: Goldmann Applanation tonometer (Al-Ain Eye Institute)

Figure 13: Enhanced Depth Imaging Spectral Domain Ocular Tomograph (Al-Ain Eye Institute)

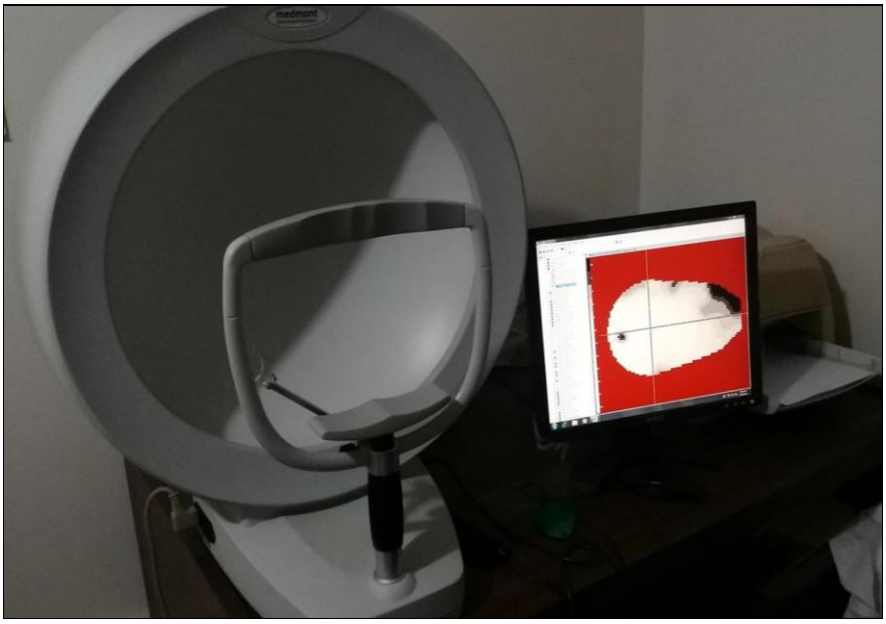


Figure 14: Humphery Field Analyzer (Al-Ain Eye Institute)

3.11 Study parameters

After gross inspection cases and controls underwent slit lamp biomicroscopy and tonometry by Goldmann Applanation tonometer. The anterior depth of lamina cribrosa was measured by EDI SD-OCT. VF testing was done on all subjects with POAG using Humphrey Field Analyzer.

3.11 (A) <u>Estimation of anterior lamina cribrosa depth (ALCD)</u>: Anterior lamina cribrosa depth (ALCD) was measured from the reference line constructed from the two end points of Bruch's membrane opening (BMO). The deepest vertical distance from the anterior surface of the lamina cribrosa (LC) to the reference line of Bruch's membrane opening was calculated as the Anterior lamina cribrosa depth (Fig 15). ALCD is calculated in µm.

3.11 (B) <u>Calculation of lamina cribrosa thickness</u>: Lamina cribrosa thickness (LCT) was measured as the distance between anterior and posterior lamina cribrosa (LC) surfaces. The thickness calculated had to cover the entire span of the lamina cribrosa. The thickness varies around the circumference. LCT is also calculated in µm.

The mean values of ALCD and LCT at three different horizontal meridians (central, mid-superior and mid-inferior) were taken and their average was recorded.

All the observations of the ophthalmoscopic history and visual field were masked from the observer XYZ.

3.12 Protocol

After taking an informed consent from the study participants, the subject evaluation proforma (attached as an annexure at the end) was filled either by the subject or by the principal investigator. A detailed eye examination including stereoscopic ophthalmology, slitlamp biomicroscopy, tonometry, axial length and SD-OCT was done meeting the pre-requisites of dark environment etc. The data collection was completed in nine months'

time period, that is from August 2018 to April 2019. Analysis of data and result compilation was performed in a month, followed by thesis compilation.

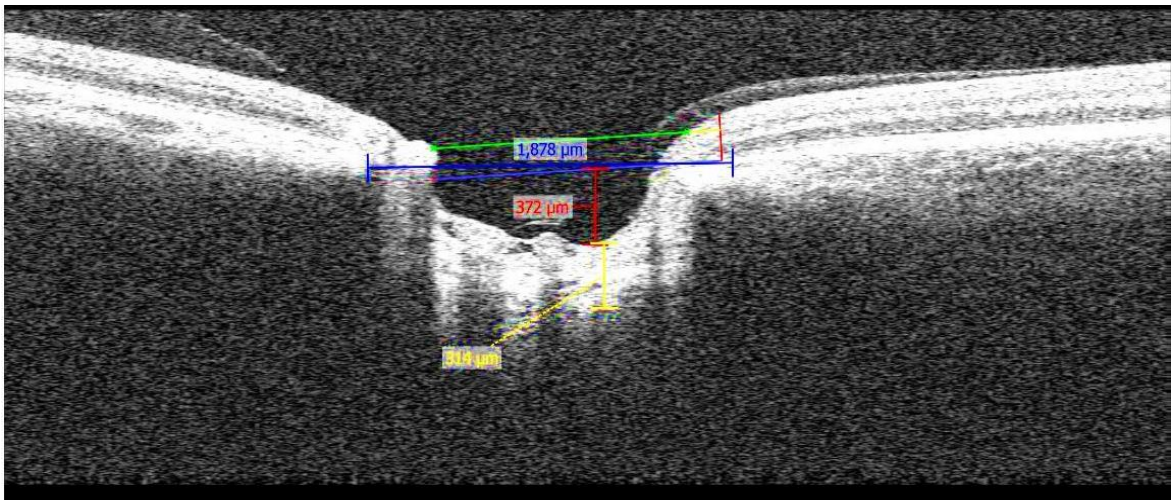
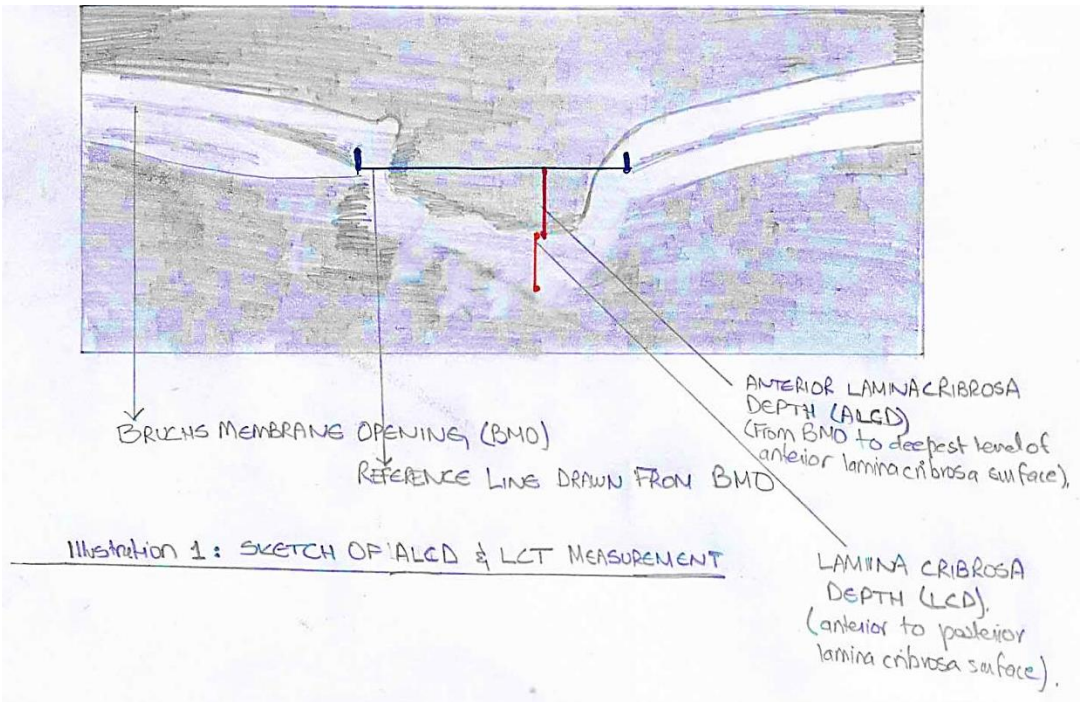
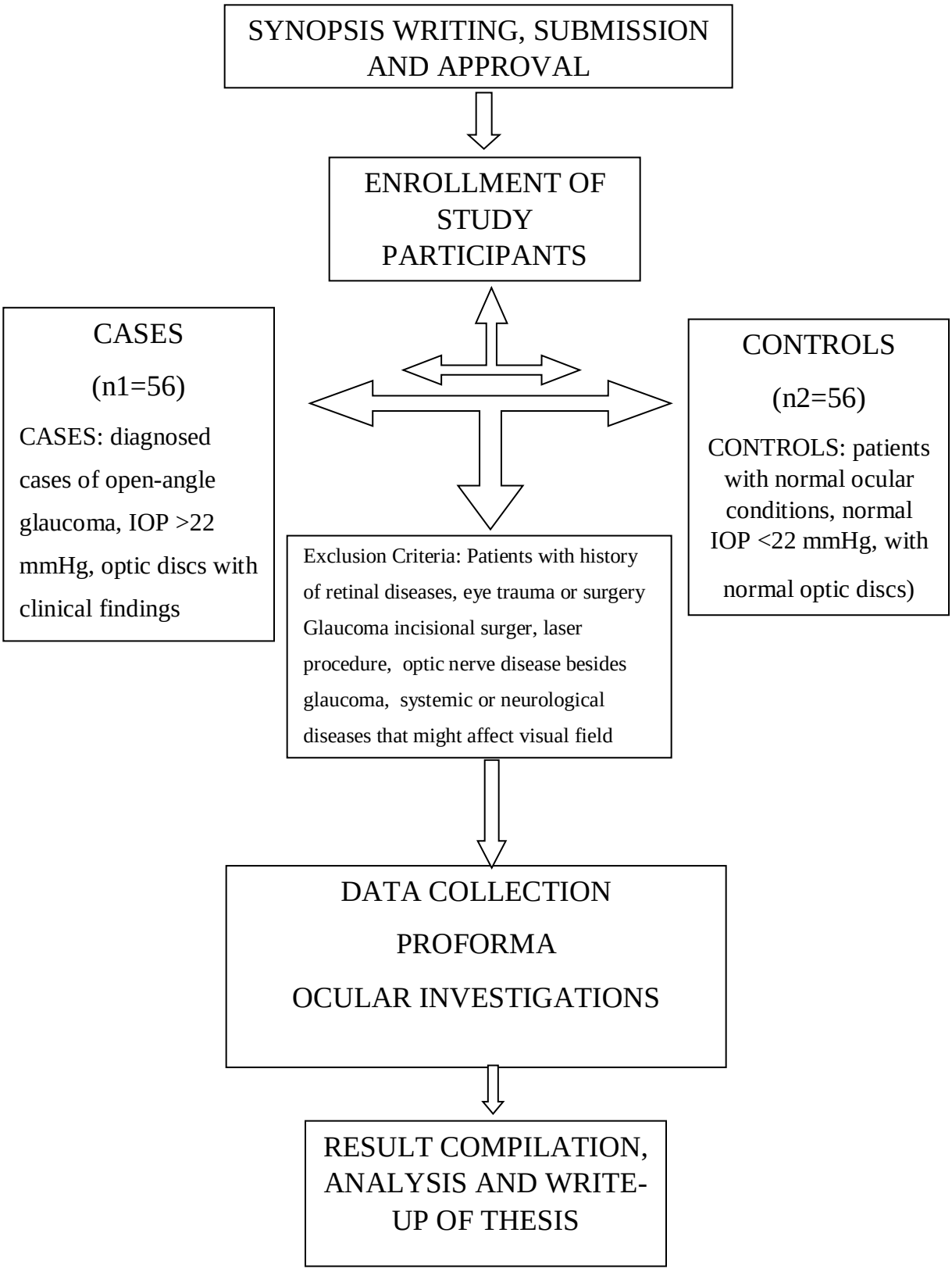


Figure 15: Example of EDI SD-OCT measurement of anterior lamina cribrosa depth and lamina cribrosa thickness



3.13 Algorithm of study



3.14 Statistical analysis

SPSS version 23.0 was used for data analysis. Continuous variables were shown in mean and standard deviation. The SPSS data was run on Kolmogorov-Smirnov test, the significance level was ≤ 0.05 and hence was found to be a non-parametric dataset. For categorical variables, such as frequency and percentages, baseline characteristics were compared between the POAG group and the control group using the Mann-Whitney U test. Categorical data was analyzed using the Fischer exact test. The relationships between the LC morphology (ALD and LT) and VF mean deviation (MD) and peripapillary RNFL thickness were evaluated by linear regression analyses and binary logistics. P-value < 0.05 was considered to be statistically significant.

CHAPTER 4

RESULTS

4.1 (A) BASELINE OCULAR DEMOGRAPHIC CHARACTERISTICS:

The present research statistics span around 57 eyes having primary open-angle glaucoma (POAG) cases and 46 eyes of healthy, age matched controls. 9 respondents were excluded due to poor image quality, obscuring visualization of anterior lamina cribrosa surface (ALCS), or inability to follow the standard automated perimetry test (SAP) for visual field analysis or inability to demarcate lamina cribrosa morphological features over the enhanced depth imaging spectral domain ocular coherence tomography (EDI SD-OCT).

Age and gender did not show any statistically significant association with POAG (table 1A). 56.1% male subjects and 43.9% female subjects and 63.0% Vs 37% of the controls were positive for the POAG. Maximum number of cases were found in the age group of 61-70 years (26.3% cases Vs 23.9% controls), followed by the age group 51-60 years (24.6% cases Vs 45.7% controls). Statistically no difference was found in characteristics of ONH, disc area and rim area among the cases and controls.

Table 1A shows the common characteristics, such as, axial length (AXL), intraocular pressure (IOP) and vertical cup-to-disc ratio (VCDR) statistically significant. Table 1A shows that the common characteristics have statistically significant dfference in two groups. Our study had shown statistically significant results for axial length of the eye, when it was compared in 57 POAG cases with 46 healthy controls. The value of AXL in cases in our study was (24.23 ± 1.99mm), as opposed to (23.27 ± 1.99mm) in controls. The IOP was significantly higher in cases as compared to controls (P-value 0.000); with range in cases analyzed (20.05 ± 2.47 mmHg) as compared to (15.59 ± 3.46 mmHg) in controls. The vertical cup-to-disc ratio also exhibited highly significant increase in cases (0.86 ± 0.24) as compared to controls (0.54 ± 0.19) (P-value 0.000).

4.1 (B) BASELINE STRUCTURE AND FUNCTIONAL DEMOGRAPHIC CHARACTERISTICS:

The general structural parameters were compared between the POAG cases and controls (table 1B). Anterior laminar depth showed an insignificant increase in cases as compared to control (cases 334.85 ± 154.96 µm Vs controls 300.87 ± 145.38 µm) (Table-1B).

Statistically significant difference was seen for the characteristics of visual field mean deviation (VF-MD), visual field pattern standard deviation (VF-PSD), retinal nerve fiber layer thickness (RNFLT) and lamina cribrosa thickness (LCT) (table 1B). Visual field mean deviation (VF-MD) in cases was (-2.92dB ± 2.52 dB) while in controls it was (-2.21 dB ± 2.52 dB). VF-PSD in cases was 7.54 dB ± 4.69 dB, and in controls it was 3.73 dB ± 2.12 dB. Statistically it was significantly related with the POAG cases (P-value 0.000).

Retinal nerve fiber layer thickness (RNFLT) in cases was 73.21 ± 13.63 µm, while in controls it was 78.85 ± 9.01µm. Statistically it was decreased significantly in cases. This finding can also be related with the occurrence of RNFLT in different study age groups (figure 17). Lamina cribrosa thickness (LCT) in cases was 218.07 ± 79.80 µm while in controls it was 271.77 ± 64.45. Statistically it was decreased significantly in cases.

4.2 COMPARISON OF ANTERIOR LAMINA CRIBROSA DEPTH (ACLD), LAMINA CRIBROSA THICKNESS (LCT), VISUAL FIELD MEAN DEVIATION (VF-MD), VISUAL FIELD PATTERN STANDARD DEVIATION (VF-PSD) AND RETINAL NERVE FIBER LAYER THICKNESS (RNFLT) IN PRIMARY OPEN-ANGLE GLAUCOMA (POAG) CASES AND CONTROLS

Comparison was run between anterior lamina cribrosa depth (ACLD), lamina cribrosa thickness (LCT) and retinal nerve fiber layer thickness (RNFLT), with visual field mean deviation (VF-MD) and visual field pattern standard deviation (VF-PSD) among the primary open-angle glaucoma (POAG) cases and healthy age matched controls (table 2).

The range of anterior lamina cribrosa depth (ALCD) was insignificantly enhanced in cases (334.85 ± 154.96 µm) as compared to the controls (300.87 ± 145.38 µm) (table 2). Lamina cribrosa thickness on the other hand showed statistically significant increased

thickness in controls (P-value 0.001). LCT in the cases was 218.07 ± 79.80 µm while in controls it was significantly less than was assessed in the control group (figure 21) which was 271.77 ± 64.45 µm. Statistically it was significantly lower.

The micro parameter of retinal nerve fiber layer thickness (RNFLT) also elicited statistically significant results (P-value 0.055). The ganglion cell layer showed a decline in thickness in cases 73.21 ± 13.63 µm than controls 78.85 ± 9.01 µm, (figure 17, table 2). As displayed in figure 17, the age group in which the RNFLT in cases was recorded the most was in ≤ 40 years, whereas the age strata having the least thickness was ≥ 81 years.

The anatomical defects associated with LC matched with functional variables findings of the study. Visual field mean deviation (VF-MD) in cases was (-2.92 dB ± 1.52 dB) while in controls was (-2.21 dB ± 1.57 dB) (P-value of 0.047). Statistically a significant difference was found between the two groups. Visual field pattern standard deviation (VF-PSD) in cases was (7.54 dB ± 4.69 dB) compared to the controls (3.73 dB ± 2.12 dB) with (P-value 0.000). A significant difference was found between the groups with the results in cases showing more damage.

4.3 EVALUATION OF SECTORIAL RETINAL NERVE FIBER LAYER THICKNESS (RNFLT) WITH ANTERIOR LAMINA CRIBROSA DEPTH (ACLD) AND LAMINA CRIBROSA THICKNESS (LCT) IN PRIMARY OPEN-ANGLE GLAUCOMA (POAG) CASES

The sectorial thickness of retinal nerve fiber layer in superior, inferior, temporal, nasal, superior-inferior, superior-inferior with nasal and global (superior, inferior, temporal and nasal) was assessed in conjunction with anterior lamina cribrosa depth (ACLD) and lamina cribrosa thickness (LCT) (table 3). Out of 57 primary open-angle glaucoma cases, majority of the subjects were seen sustaining superior (n=15) as well as superior-inferior (n=15) RNFL defects; whereas small number of cases (n=2 each) shown in superior-inferior with nasal and global defects. Isolated nasal and temporal RNFL defects were not recorded during the data collection during the study (table 3).

While examining the thickness of RNFL in various sectors, superior defects showed the maximum retinal nerve fiber layer thickness (75.50 ± 9.64 µm), while the most thin sector range was displayed by global RNFL defects (48.40 ± 0.84 µm). RNFLT in retinal sectors revealed a statistically significant association when compared to controls (P-value of 0.001).

Table 3 also shows the ALCD. Maximum depth is shown by the global RNFL sector (545.50 ± 3.53 µm) among 15 POAG cases. The minimum depth was observed with inferior RNFL defect sector (265.08 ± 64.51 µm) in the four POAG cases.

Lamina cribrosa thickness (LCT) analysis showed maximum thickness in the two POAG cases having superior-inferior and also in the nasal RNFL defects (table 3), both sectors displaying thickness (226.99 ± 136.23 µm). Minimum thickness of LCT was recorded in the four POAG cases in inferior retinal sector (204.57 ± 79.04 µm). Both the ACLD and LCT showed statistically insignificant changes in cases when compared with sectorial retinal defects in the controls.

4.4 ASSESSMENT OF RETINAL NERVE FIBER LAYER DEFECTS IN MILD AND MODERATE PRIMARY OPEN-ANGLE GLAUCOMA CASES

Association was seen in the previous table of sectorial retinal nerve fiber layer thickness (RNFLT) with anterior lamina cribrosa depth (ACLD) and lamina cribrosa thickness (LCT). Now it was interesting to explore the sectorial linkage between retinal nerve fiber layer defects (RNFLD), anterior lamina cribrosa depth (ALCD) and lamina cribrosa thickness (LCT) in mild and moderate stages of glaucoma. The categorization of glaucoma was also explained by McKean-Cowdin, Varma, Wu, Hays and Azen (2007), in which mild glaucoma was graded as VF-MD <-6 dB but > -2dB and moderate glaucoma to be > -6dB but < -12 dB.

Table 4 showed out of 49 subjects suffering from mild glaucoma, [n=19, 38.8%] 19 subjects did not develop frank RNFLT losses, so the progression of their disease needs to be monitored and steps could be taken for stopping the progression of disese. The 13 subjects having superior defects [n=13, 26.5%] were the next to be kept in strict monitoring of the disease to prevent them from visual impairment. As shown in table 4,

subjects sustaining superior and inferior RNFLD [n=5, 62.5%] were the ones with the mild disease. RNFLD had shown a statistically significant result (P-value 0.037) in the cases whereas ALCD and LCT showed significant changes in the comparison between mild and moderate cases of glaucoma.

4.5 VARIABLES ASSOCIATED WITH THE RATE OF RETINAL NERVE FIBER LAYER THINNING

After exploring the sectorial RNFLT with ALCD and LCT in table 3 and finding the relevant sectors of RNFLD targeted by mild and moderate glaucoma in table 4, it was very relevant to search for the variables which caused RNFL thinning.

Table 5 shows univariate logistic regression analysis was run between the factors that possibly caused RNFL thinning. There was an insignificant increase in the severity of glaucoma with advancing age (P-value 0.074, β -0.241). Pattern standard deviation (PSD) had shown a significant inverse relation with RNFLT (P-value 0.053, β – 0.269). Greater PSD values were linked with more RNFL damage, as observed in figure 23. Vertical cup-to-disc ratio (VCDR) was another factor correlated with RNFL thinning in our study (P-value 0.058, β – 0.255). So greater the VCDR, more of RNFL thinning can be expected (figure 22).

Gender, medical diseases, IOP, AXL, VF-MD, CDR, ALCD and LCT did not show any correlation with the RNFL thinning (Table 5). All the results were tabulated with 95% confidence interval for β.

4.6 ESTIMATION OF OPTIC DISC PARAMETERS USING SD-OCT BETWEEN EYES OF CASES WITH VISUAL FIELD DEFECTS AND HEALTHY EYES OF CONTROLS WITHOUT VISUAL FIELD DEFECTS

Optic nerve head attributes which were observed by slit-lamp biomicroscopy or ophthalmoscopy, like disc area, rim area, cup area, cup-to-disc ratio (CDR), vertical cup-to-disc ratio (VCDR) and parapapillary atrophy (PPA) along with other variables of intraocular pressure (IOP) and retinal nerve fiber layer thickness (RNFLT) were compared between the cases with VF defects, and the controls without the VF defects (table 6).

Statistically insignificant alterations were found with the parameters of the cases with VF defects, such as disc area [cases 2.46 ± 0.93mm^2 Vs controls 2.45 ± 0.68 mm^2], rim area [cases 1.00 ± 0.53 mm^2 Vs controls 1.10 ± 0.50 mm^2], cup area [cases 1.40 ± 1.09 mm^2 Vs controls 1.34±0.73 mm^2] and cup-to-disc ratio [CDR cases 0.59 ± 0.27 Vs 0.55 ± 0.32] when cases were compared with the controls having no VF losses.

Statistically significant diminished thickness of retinal nerve fiber layer was revealed by the cases with VF defects [RNFLT cases 73.21 ± 13.63µm Vs controls 78.85 ± 13.63 µm, P-value 0.018]. The finding was also related with RNFLT in different age groups as shown in figure 17. Similar strong correlation was revealed by the cases with VF defects in the occurrence of parapapillary atrophy [PPA cases 3.63 ± 0.77 Vs controls 3.15 ± 0.76, P-value of 0.002].

Highly significant results were illustrated by vertical cup-to-disc ratio and intraocular pressure. Vertical cup-to-disc ratio showed greater values in cases with VF defects when compared with the controls [VCDR cases 0.86 ± 0.24 Vs controls 0.54 ± 0.19, P-value of 0.000]. Analogous to VCDR, intraocular pressure (IOP) also exhibited highly statistically significant enhanced IOP levels in the cases [IOP cases 20.05 ± 2.47 Vs controls 15.59 ± 3.46, P-value 0.000].

4.7 COMPARISON OF LAMINA CRIBROSA MORPHOLOGICAL AND FUNCTIONAL CHARACTERISTICS IN CASES AND CONTROLS HAVING MYOPIA OR HYPEROPIA

Lamina cribrosa anatomical parameters of anterior lamina cribrosa depth (ALCD), lamina cribrosa thickness (LCT), retinal nerve fiber layer thickness (RNFLT) and the functional variables of visual field mean deviation (VF-MD) and visual field pattern standard deviation (VF-PSD) were assessed on the basis of refractive error type of myopia or hyperopia (only major refractive error types were included in the study).

The myopia cases (n=41) and controls (n=36) produced statistically insignificant increased values in visual field mean deviation [VF-MD cases -3.33 dB ± 1.98 dB Vs controls -2.91 dB ± 1.53 dB] and anterior lamina cribrosa depth [ALCD cases 338.72 ±

169.06 µm Vs controls 362.31 ± 124.79 µm], when the POAG cases and healthy age matched controls were compared in table 7.

Statistically significant decreased RNFLT was recorded in myopia cases in contrast to the controls [RNFLT cases 70.97 ± 12.41 µm Vs controls 82.03 ± 11.52 µm], with a P-value of 0.027. Pattern standard deviation also illustrated statistically significant increased values in cases in table 7 [VF-PSD cases 8.00 dB ± 4.85 dB Vs controls 4.29 dB ± 2.95 dB], with a significant P-value of 0.02 (figure 18). Lamina cribrosa thickness (LCT) also reflected significant diminished thickness for cases [LCT cases 178.66 ± 68.58 µm Vs controls 285.52 ± 67.07 µm], with a highly significant P-value of 0.002 (figure 21).

Hyperopia on the other hand showed insignificant diminished thickness in the cases for retinal nerve fiber layer thickness [RNFLT cases 74.09 ± 14.12 µm Vs controls 77.96 ± 8.15 µm], in conjunction with insignificant lesser values for visual field mean deviation [VF-MD cases -2.76 dB ± 1.71 dB Vs controls -2.02 dB ± 1.26 dB]. Anterior lamina cribrosa depth also revealed insignificant increased depth in hyperopia cases [ALCD cases 286.10 ± 134.33 µm Vs controls 327.22 ± 163.08 µm]. Significant diminished thickness of LC was produced with regards to hyperopia [LCT cases 233.45 ± 79.29 µm Vs controls 267.95 ± 64.14 µm] with a significant P-value of 0.054. Similar highly statistically significant increased values of PSD in the hyperopia cases as compared with the controls were calculated in table 7.

4.8 (A) COMPARISON OF OPTIC NERVE HEAD FUNDUS CLINICAL VARIABLES BETWEEN PRIMARY OPEN-ANGLE GLAUCOMA CASES AND HEALTHY CONTROLS

Summarization of typical clinical features of primary open-angle glaucoma cases (n= 57) and healthy age matched controls (n=46) were assessed in table 8A. Laminar dots were found in 75.4%. Table 8A presented a highly statistically significant P-value 0.000 for laminar dots, with absence of laminar dots in 65.2% of controls.

Optic nerve head hemorrhages (ONHH) were present in 78.9%, and were absent in only 21.1% of cases. Preponderance of ONHH in controls was 39.1%, whereas they were

absent in considerable 60.9% of controls. ONHH had also produced a highly significant result (P-value 0.000).

Parapapillary atrophy (PPA) revealed a highly significant analysis (P-value 0.000). In 60.9% of controls PPA were absent, while 77.2% of the cases had both α and β PPA (table 8A).

4.8 (B) COMPARISON BETWEEN STRUCTURAL PARAMETERS OF ANTERIOR LAMINA CRIBROSA DEPTH (ACLD), LAMINA CRIBROSA THICKNESS (LCT), AND RETINAL NERVE FIBER LAYER DEFECTS (RNFLD) IN PRIMARY OPEN-ANGLE GLAUCOMA CASES AND HEALTHY CONTROLS

Retinal nerve fiber layer defects (RNFLD) in cases were (66.6%), whereas was absent in 87% of the controls (table 8B). There was a highly significant association (P-value 0.000) of superior and superior-inferior RNFLD were observed the most (cumulative 26.3%). The findings of RNFLD can also be correlated with the retinal nerve fiber layer thickness (RNFLT) in different study age groups in figure 17.

Vertical cup-to-disc ratio (table 8B) shows a highly significant increase in cases (0.85 ± 0.24), while in controls it was (0.54 ± 0.19). Statistically a significant difference was found between the two groups (P-value 0.000). Similar to VCDR, LCT values were decreased in the cases (218.06 ± 79.79 µm) (figure 21, table 8B). In controls LCT was 271.77 ± 64.44 µm. Lamina cribrosa thickness (LCT) showed a statistically significant difference between the two groups (P-value 0.001).

Table 1A

Comparison of general demographic characteristics between cases and controls

N=103

Age (years)	SUBJECTS		P-value
	CASE (n=57)	CONTROL (n=46)	
<40 YEARS	4	3	0.163ɤ
	7.0%	6.5%	
41-50 YEARS	12	4	
	21.1%	8.7%	
51-60 YEARS	14	21	
	24.6%	45.7%	
61-70 YEARS	15	11	
	26.3%	23.9%	
71-80 YEARS	11	5	
	19.3%	10.9%	
>81 YEARS	1	2	
	1.8%	4.3%	
MALE	32	29	0.528 ɤ
	56.1%	63.0%	
FEMALE	25	17	
	43.9%	37.0%	
AXIAL LENGTH (mm)	24.23 ± 1.99	23.27 ± 1.99	0.020* §
INTRAOCULAR PRESSURE (mmHg)	20.05 ± 2.47	15.59 ± 3.46	0.000* §
DISC AREA (mm^2)	2.46 ± 0.93	2.45 ± 0.68	0.647 ɬ
RIM AREA (mm^2)	1.00 ± 0.53	1.10 ± 0.50	0.367 ɬ
VERTICAL CUP TO DISC RATIO	0.86 ± 0.24	0.54 ± 0.19	0.000* §

P-value ≤0.05 is significant and shown with asterisk *

ɤ- Fischer exact test

§- Mann Whitney-U test

ɬ- Independent sample T-testUnits used: mm- millimeter, mm^2 – millimeter square, mmHg- millimeter of Mercury

Table 1B

Comparison of structural and functional characteristics between cases and controls

N=103

Age (years)	SUBJECTS		P-value
	CASE (n=57)	CONTROL (n=46)	
MEAN DEVIATION (dB)	-2.92 ± 2.52	-2.21 ± 2.52	0.047* §
PATTERN STANDARD DEVIATION (dB)	7.54 ± 4.69	3.73 ± 2.12	0.000* §
RETINA NERVE FIBER LAYER THICKNESS (µm)	73.21 ± 13.63	78.85 ± 9.01	0.055* §
ANTERIOR LAMINAR DEPTH(µm)	300.87 ± 145.38	334.85 ± 154.96	0.220 §
LAMINA CRIBROSA THICKNESS(µm)	218.07 ± 79.80	271.77 ± 64.45	0.001* ŧ

P-value ≤0.05 is significant and shown with asterisk *

§- Mann Whitney-U test

ŧ- Independent sample T-test

Units used: dB- decibel**,** µm- micrometer

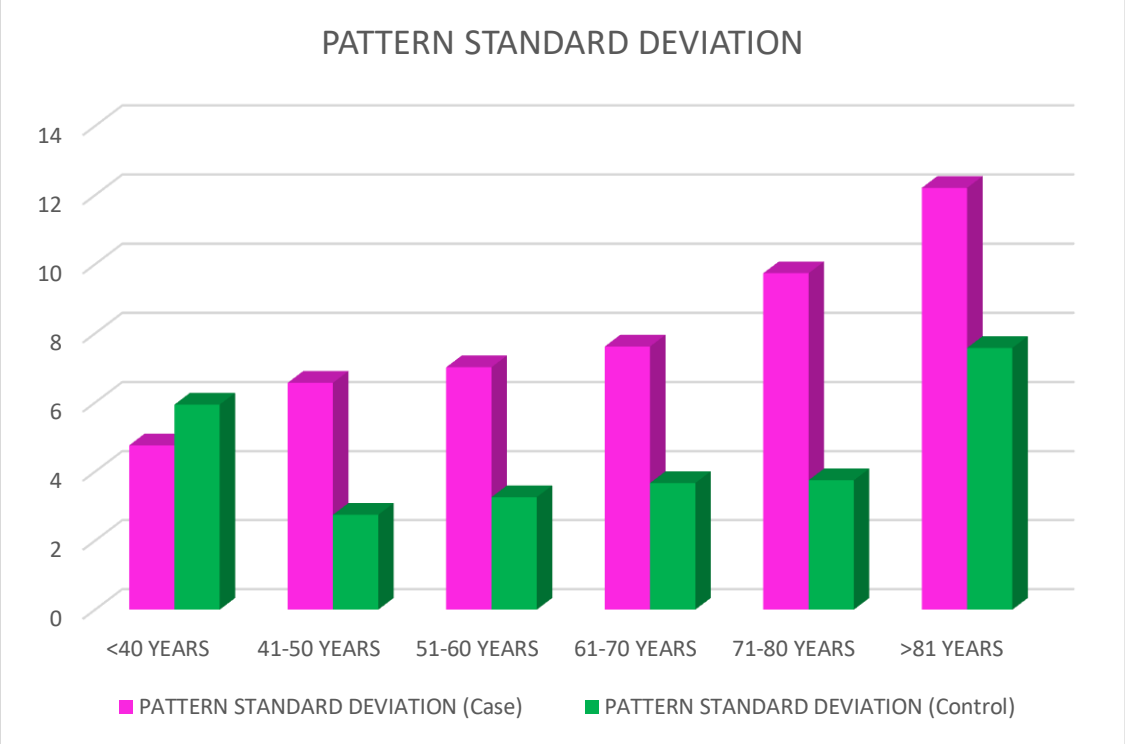


Figure 16: Bar chart showing pattern standard deviation (PSD) ranges in different study age groups of primary open angle glaucoma cases and controls

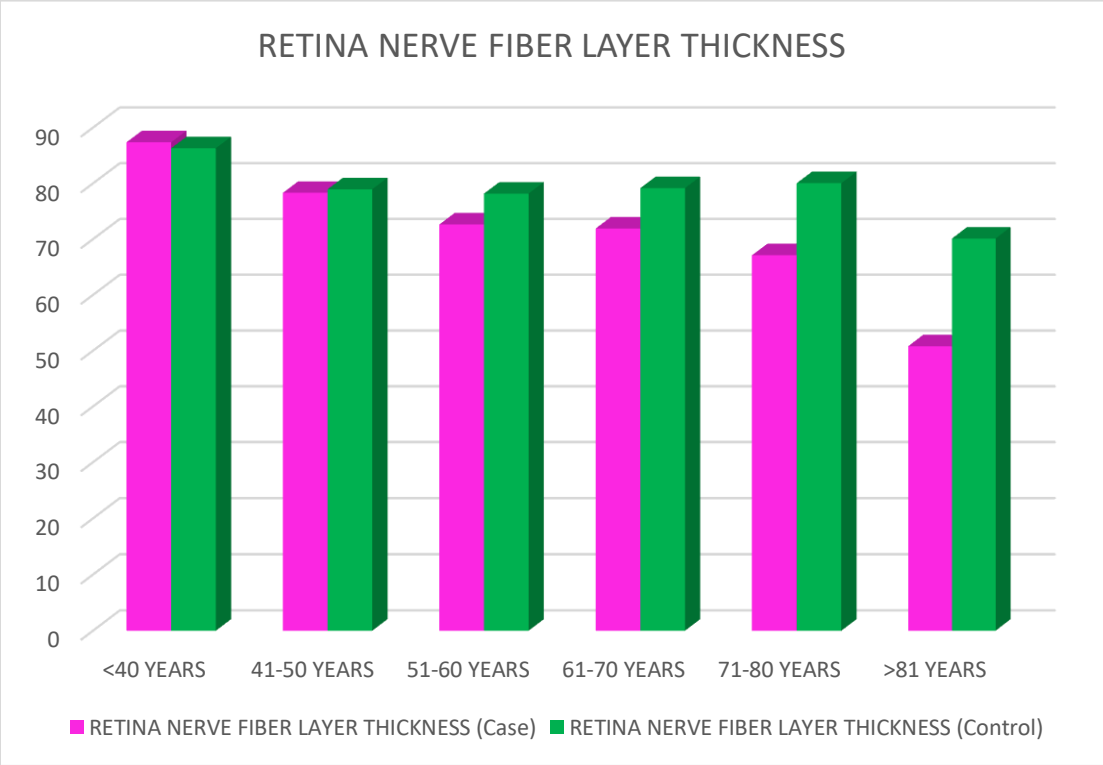


Figure 17: Bar chart showing retinal nerve fiber layer thickness (RNFLT) ranges in different study age groups of primary open angle glaucoma cases and controls

Table 2

Comparison of anterior lamina cribrosa depth (ALCD), lamina cribrosa thickness (LCT), visual field mean deviation (VF-MD), visual field pattern standard deviation (VF-PSD) and retinal nerve fiber layer thickness (RNFLT) in cases and controls

N=103

Parameters	**CASE (n=57)**	**CONTROL (n=46)**	**P-value**
ANTERIOR LAMINAR DEPTH (µm)	334.85 ± 154.96	300.87 ± 145.38	0.22 §
LAMINA CRIBROSA THICKNESS(µm)	218.07 ± 79.80	271.77 ± 64.45	0.001* ŧ
MEAN DEVIATION (dB)	-2.92 ± 1.52	-2.21 ± 1.57	0.047*§
PATTERN STANDARD DEVIATION (dB)	7.54 ± 4.69	3.73 ± 2.12	0.000* §
RETINA NERVE FIBER LAYER THICKNESS (µm)	73.21 ± 13.63	78.85 ± 9.01	0.055* §

P-value of ≤0.05 is significant and shown with asterisk *

§- Mann Whitney-U test

ŧ- Independent sample T-test

Units used: µm- micrometer, dB- decibel

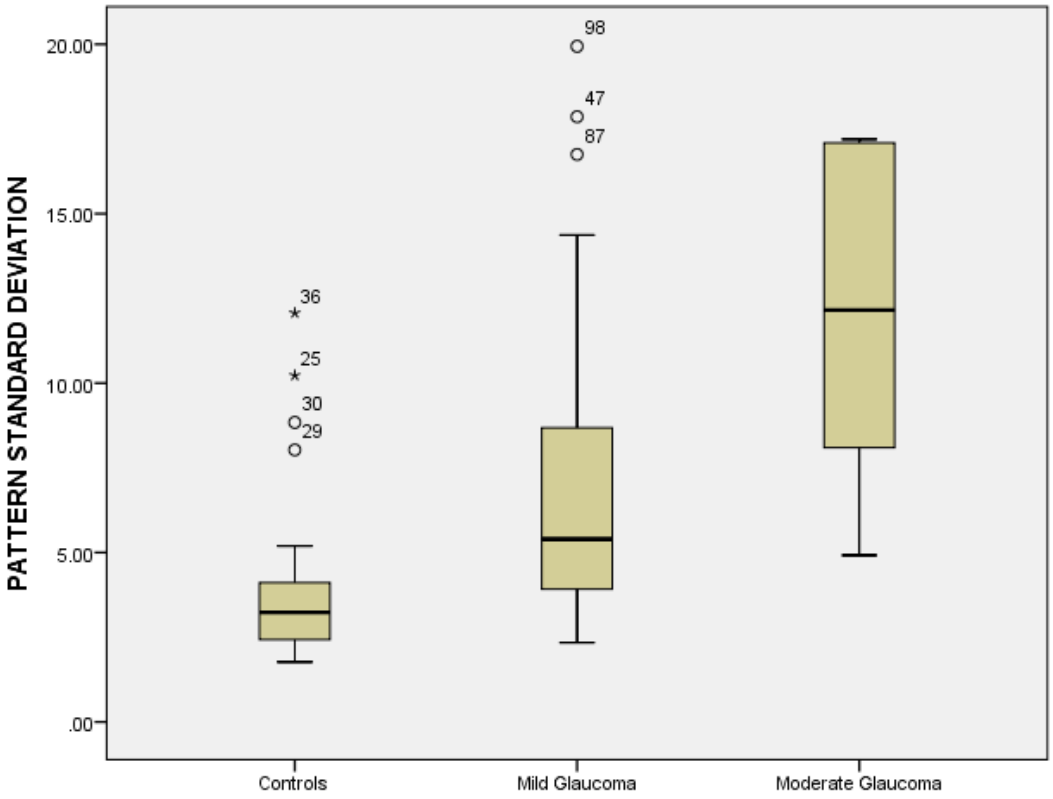


Figure 18: Box plot showing the ranges of pattern standard deviation (PSD) in controls, mild and moderate glaucoma subjects. The PSD had reflected a statistically significant result

Table 3

Evaluation of Sectorial Retinal Nerve Fiber Layer Thickness (RNFLT) With Anterior lamina cribrosa depth (ACLD) and lamina cribrosa thickness (LCT) in Primary Open-Angle Glaucoma (POAG) cases

N=57

Parameters	SUPERIOR (n=15)	INFERIOR (n=4)	NO RETINAL DEFECTS IN CASES (n=19)	SUPERIOR AND INFERIOR (n=15)	SUPERIOR, INFERIOR AND NASAL (n=2)	SUPERIOR, INFERIOR, TEMPORAL AND NASAL (n=2)	P-value
RNFLT (µm)	75.50 ± 9.64	67.45 ± 11.61	82.24 ± 9.24	67.00 ± 13.87	53.10 ± 8.62	48.40 ± 0.84	0.001 * ¶
ALCD (µm)	288.86 ± 83.91	265.08 ± 64.51	288.27 ± 138.86	284.1 ± 59.3	458.83 ± 431.57	545.50 ± 3.53	0.410 ¶
LCT (µm)	205.04 ± 66.98	204.57 ± 79.04	226.04 ± 136.23	223.25± 72.08	226.99 ± 136.23	214.33 ± 91.45	0.985 º

P-value of ≤0.05 is significant and shown with asterisk*

¶ - Kruskal –Wallis test

º - One way ANOVA

Units used: µm- micrometer

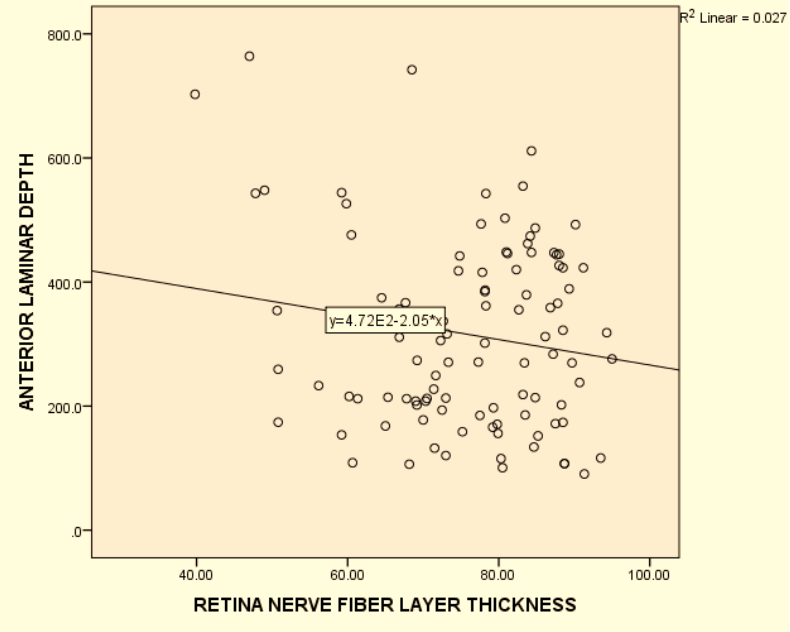


Figure 19: Scatter plot showing the inverse relation of anterior lamina cribrosa depth (ALCD) and retinal nerve fiber layer thickness (RNFLT)

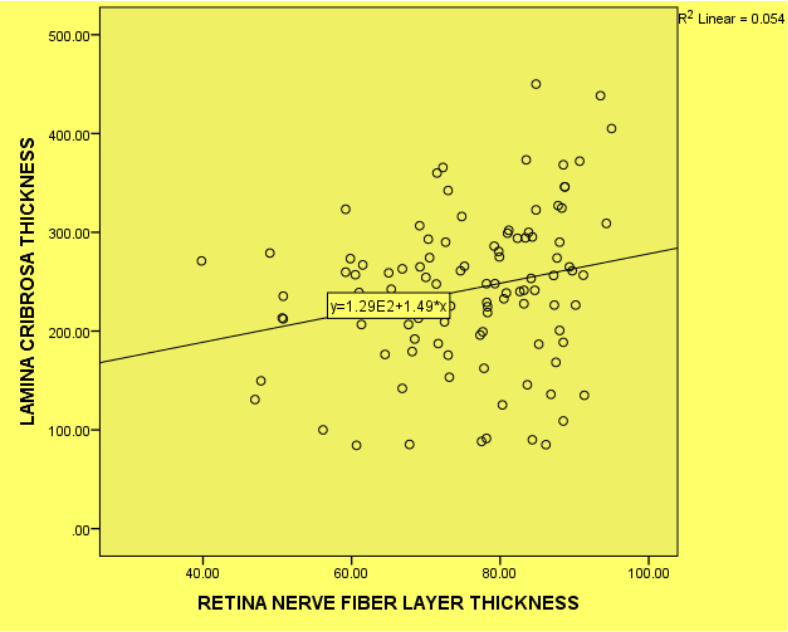


Figure 20: Scatter plot showing the relation of anterior lamina cribrosa thickness (LCT) and retinal nerve fiber layer thickness (RNFLT)

Table 4

Assessment of retinal nerve fiber layer defects with anterior lamina cribrosa depth (ALCD) and lamina cribrosa thickness (LCT) in mild and moderate glaucoma primary open-angle glaucoma (POAG)

N= 57

RETINAL NERVE FIBER LAYER DEFECTS	**Mild glaucoma (VF-MD ≤ -6) (n=49)**	**Moderate glaucoma (VF-MD > -6 to -12) (n=8)**	**P-value**
SUPERIOR	13	2	0.037* ɤ
	26.5%	25.0%	
INFERIOR	4	0	
	8.2%	0.0%	
NOT PRESENT	19	0	
	38.8%	0.0%	
SUPERIOR AND INFERIOR	10	5	
	20.4%	62.5%	
SUPERIOR, INFERIOR AND NASAL	2	0	
	4.1%	0.0%	
SUPERIOR, INFERIOR, TEMPORAL AND NASAL	1	1	
	2.0%	12.5%	
ANTERIOR LAMINAR DEPTH (µm)	300.13 ± 148.94	305.41 ± 130.15	0.778 §
LAMINA CRIBROSA THICKNESS (µm)	221.11 ± 80.14	199.40 ± 80.19	0.55 ŧ

P-value of ≤0.05 is significant and shown with asterisk*

ɤ- Fischer exact test

§- Mann Whitney-U test

ŧ- Independent sample T- test

Units used: µm- micrometer

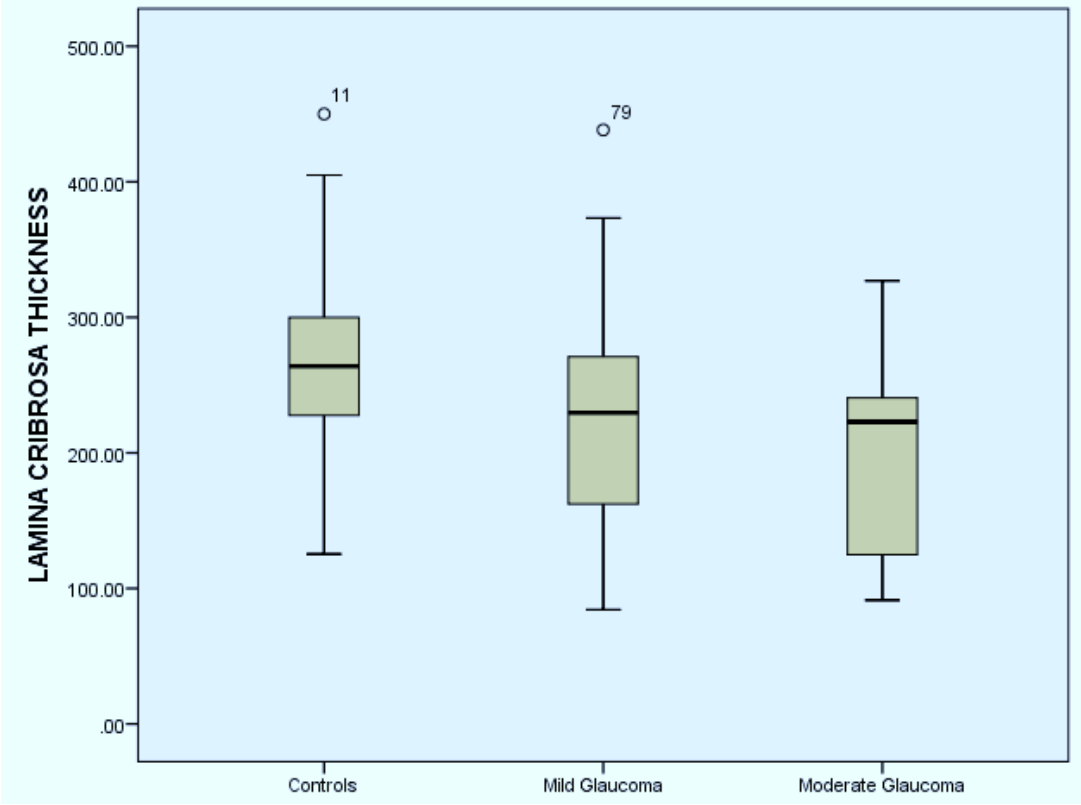


Figure 21: Box plot showing the ranges of lamina cribrosa thickness (LCT) in controls, mild and moderate glaucoma subjects. The LCT had reflected a statistically significant result

Table 5

Correlation using Univariate Regression Analysis between Variables Associated with the rate of Retinal Nerve Fiber Layer Thinning

N=103

	Univariate Regression Analysis		**95.0% Confidence Interval for Beta**	
Parameters vs RNFLT	**Beta**	**P-value**	**Lower Bound**	**Upper Bound**
AGE	-.241	0.074	-5.661	.274
GENDER	.003	0.982	-6.471	6.621
MEDICAL DISEASES	-.002	0.987	-1.305	1.283
INTRAOCULAR PRESSURE (mmHg)	-.078	0.626	-2.188	1.331
AXIAL LENGTH (mm)	-.174	0.265	-3.326	.938
MEAN DEVIATION (dB)	.108	0.425	-.878	2.046
PATTERN STANDARD DEVIATION (dB)	-.269	0.053*	-1.573	.009
CUP-TO-DISC RATIO	-.094	0.567	-23.959	13.302
VERTICAL CUP-TO-DISC RATIO	-.255	0.058*	-26.712	.466
ANTERIOR LAMINAR DEPTH (µm)	-.139	0.323	-.039	.013
LAMINA CRIBROSA THICKNESS (µm)	.159	0.322	-.028	.084

P-value of ≤0.05 is significant and shown with asterisk*

Significant beta value shown in boldface

Values are taken with 95% confidence interval

Units used: mmHg- millimeter of Mercury, mm- millimeter, dB- decibel, µm- micrometer

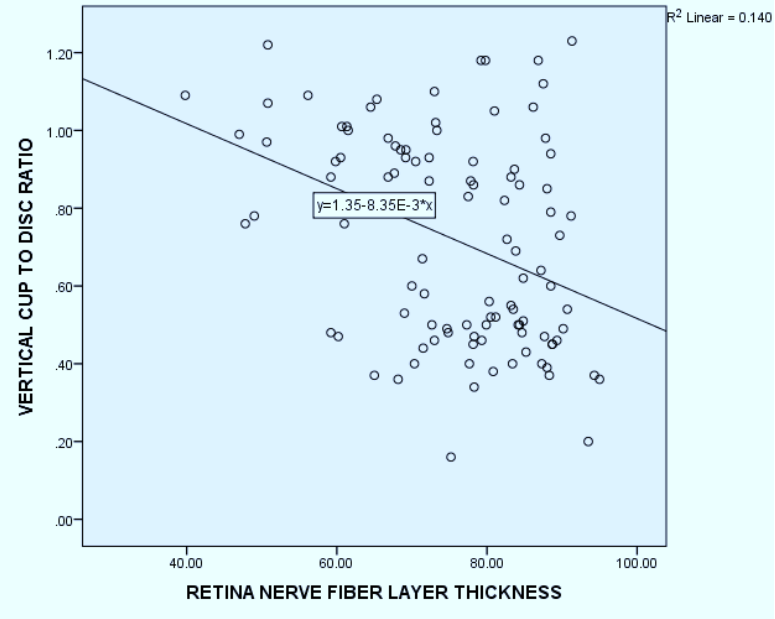


Figure 22: Scatter plot showing the correlation between retinal nerve fiber layer thickness (RNFLT) and vertical cup-to-disc ratio (VCDR)

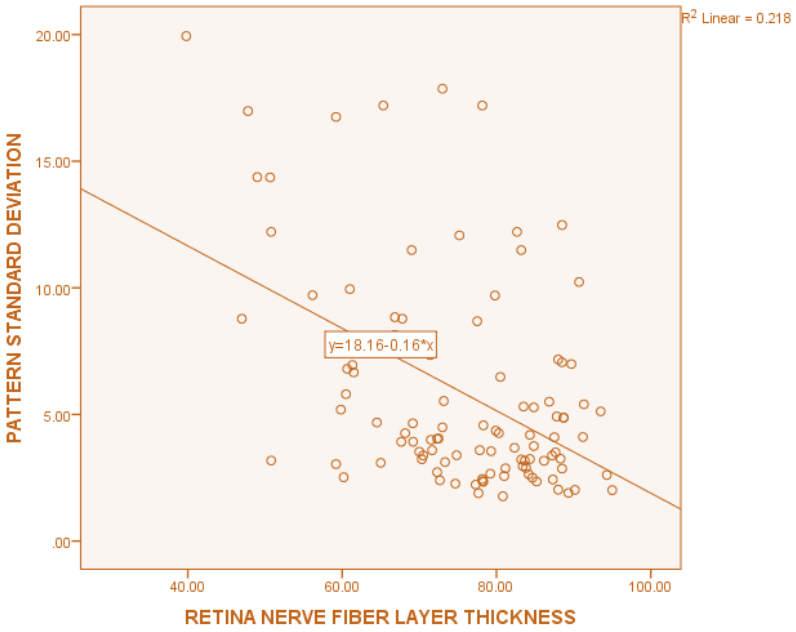


Figure 23: Scatter plot showing the correlation between retinal nerve fiber layer thickness (RNFLT) and pattern standard deviation (PSD)

Table 6

Estimation of Optic Disc Clinical Parameters in SD-OCT between Eyes of Cases with Visual Field Defects and Healthy Eyes of Controls without Visual Field Defects

N=103

Parameters	**CASE WITH VFD (n=57)**	**CONTROL WITHOUT VFD (n=46)**	**P-value**
DISC AREA (mm^2)	2.46 ± 0.93	2.45 ± 0.68	0.975 ŧ
RIM AREA (mm^2)	1.00 ± 0.53	1.10 ± 0.50	0.326 ŧ
CUP AREA (mm^2)	1.40 ± 1.09	1.34 ± 0.73	0.737 §
CUP-TO-DISC RATIO	0.59 ± 0.27	0.55 ± 0.32	0.518 §
VERTICAL CUP TO DISC RATIO	0.86 ± 0.24	0.54 ± 0.19	0.000* §
RETINA NERVE FIBER LAYER THICKNESS (µm)	73.21 ± 13.63	78.85 ± 13.63	0.018* §
INTRAOCULAR PRESSURE (mmHg)	20.05 ± 2.47	15.59 ± 3.46	0.000* §
PARAPAPILLARY ATROPHY	3.63 ± 0.77	3.15 ± 0.76	0.002* ɤ

P-value of ≤0.05 is significant and shown with asterisk*

ŧ-Independent sample T-test

§- Mann Whitney-U test

ɤ- Fisher exact test

Units used: mm^2- millimeter square, µm- micrometer, mmHg- millimeter of mercury

TABLE 7

Comparison of Lamina Cribrosa Morphological and Functional Characteristics in Cases and Controls having Myopia or Hyperopia

N=103

Parameters	Hyperopia CASE (n=16)	Hyperopia CONTROL (n=10)	P-value
RETINA NERVE FIBER LAYER THICKNESS (µm)	74.09 ± 14.12	77.96 ± 8.15	0.444 §
MEAN DEVIATION (dB)	-2.76 ± 1.71	-2.02 ± 1.26	0.16 §
PATTERN STANDARD DEVIATION (dB)	7.36 ± 4.68	3.58 ± 1.85	0.000* §
ANTERIOR LAMINAR DEPTH(µm)	286.10 ± 134.33	327.22 ± 163.08	0.312 §
LAMINA CRIBROSA THICKNESS (µm)	233.45 ± 79.29	267.95 ± 64.14	0.054* ŧ
Parameters	**Myopia CASE (n=41)**	**Myopia CONTROL (n=36)**	**P-value**
RETINA NERVE FIBER LAYER THICKNESS (µm)	70.97 ± 12.41	82.03 ± 11.52	0.027* §
MEAN DEVIATION (dB)	-3.33 ± 1.98	-2.91 ± 1.53	0.262 §
PATTERN STANDARD DEVIATION (dB)	8.00 ± 4.85	4.29 ± 2.95	0.02§
ANTERIOR LAMINAR DEPTH (µm)	338.72 ± 169.06	362.31 ± 124.79	0.623§
LAMINA CRIBROSA THICKNESS (µm)	178.66 ± 68.58	285.52 ± 67.07	0.002* ŧ

P-value of ≤0.05 is significant and shown with asterisk*

ŧ-Independent sample T-test

§- Mann Whitney-U test

Ψ- Chi-square test

Units used: dB- decibels, µm- micrometer

Table 8 A

Comparison of Fundus Variables Between Primary Open-Angle Glaucoma Cases And Healthy Controls

N= 103

	CLINICAL PARAMETERS	CASE (n=57)	CONTROL (n=46)	P-value
FUNDUS VARIABLES ASSOCIATED WITH PRIMARY OPEN-ANGLE GLAUCOMA	**DISC AREA**	2.45 ± 0.97	2.46 ± 0.62	0.973
	RIM AREA	0.97 ± 0.50	1.11 ± 0.66	0.491 ☨
	CUP AREA	1.41 ± 1.14	1.34 ± 0.69	0.848§
	VERTICAL CUP TO DISC RATIO	0.85 ± 0.24	0.88 ± 0.19	0.848§
	LAMINAR DOTS			
	PRESENT	43	16	0.000ɤ
		75.4%	34.8%	
	ABSENT	14	30	
		24.6%	65.2%	
	OPTIC NERVE HEAD HEMORRAHGES			
	PRESENT	45	18	0.000ɤ
		78.9%	39.1%	
	ABSENT	12	28	
		21.1%	60.9%	
	PARAPAPILLARY ATROPHY			
	ALPHA	2	3	0.000ɤ
		3.5%	6.5%	
	BETA	4	1	
		7.0%	2.2%	
	NOT PRESNT	7	28	
		12.3%	60.9%	
	ALPHA AND BETA	44	14	
		77.2%	30.4%	

P-value ≤0.05 is significant and shown with asterisk *

ɤ- Fischer exact test, §- Mann Whitney-U test

☨- Independent sample T-test

mm- millimeter, mmHg- millimeter of Mercury, dB- decibel**,** µm- micrometer, mm^2 – millimeter sqaure

Table 8B

Evaluation of structural variables of Anterior Lamina Cribrosa Depth (ACLD), Lamina Cribrosa Thickness (LCT), Retinal Nerve Fiber Layer Defects (RNFLD) in cases and controls

N= 103

	RETINAL NERVE FIBER LAYER DEFECTS	**Mild glaucoma (VF-MD ≤ -6) (n=49)**	**Moderate glaucoma (VF-MD > -6 to -12) (n=8)**	**P-value**
STRUCTURAL VARIABLES ASSOCIATED WITH PRIMARY OPEN-ANGLE GLAUCOMA	SUPERIOR	13	2	0.037*§
		26.5%	25.0%	
	INFERIOR	4	0	
		8.2%	0.0%	
	NOT PRESENT	19	0	
		38.8%	0.0%	
	SUPERIOR AND INFERIOR	10	5	
		20.4%	62.5%	
	SUPERIOR, INFERIOR AND NASAL	2	0	
		4.1%	0.0%	
	SUPERIOR, INFERIOR, TEMPORAL AND NASAL	1	1	
		2.0%	12.5%	
	ANTERIOR LAMINAR DEPTH (µm)	300.13 ± 148.94	305.41 ± 130.15	0.778§
	LAMINA CRIBROSA THICKNESS (µm)	221.11 ± 80.14	199.40 ± 80.19	0.55 ŧ

P-value of ≤0.05 is significant and shown with asterisk *

ŧ-Independent sample T-test

§- Mann Whitney-U test

Ψ- Chi-square test

CHAPTER 5

DISCUSSION

Patients of primary open-angle glaucoma (POAG) have shown an anatomically distorted, thinner lamina cribrosa with loss of microarchitecture of retinal nerve fiber layer (RNFL), visual field defects and myopia.

Higher axial lengths in patients of POAG had resulted in thinning of sclera and anatomical aberrations of LC. This study has also shown thinning of LC. Similar findings have also been reported by Yun et al (2015), Jonas and Xu (2014) and Jonas, Ohno-Matsui and Panda (2017). Likewise Shen et al (2016) revealed that axial length has a reciprocal relationship with the laminar thinning and reflected a statistically significant result.

This study records a significant association between the raised intraocular pressure (IOP) in POAG. Esfandiari, Efatizadeh, Hassanpour reported an association between distorted laminar morphology and rasied IOP. Similar findings have also been reported by Doozandeh and Loewen (2018), Lanzagorta-Aresti et al (2017) and Pérez Bartolomé et al (2018) between IOP and glaucoma.

This study finds a statistically significant association between VCDR and POAG. A vertical cup-to-disc ratio (VCDR) of $\geq$ 0.8 until proven otherwise is a clear pathognomonic sign of GON Loss of neuroretinal rim and retinal ganglion cells provides the structural basis for this finding. Kim et al (2012), Omodaka et al (2016) and Akagi et al (2018) have also reported significant association between the severity of laminar defects and a larger VCDR.

This study finds a significant positive association between laminar dots and the POAG This study records maximum number of laminar dots in superior RNFLD sector, followed by the superior-inferior sectors of the retina. This finding is in agreement with the findings done by earlier researchers (Turgut 2017). It can also be summated that there is a strong relationship between laminar dots with VCDR. Analogous to our findings, Zwillinger, Paques, Safran and Baudouin (2016) had shown a study upon ascertaining the pore morphology of LC in patients of POAG and controls. They found 95% of their subjects to have a porous structure of LC, but the shape of the pore was more elongated

in the POAG group as compared to the controls. Similar findings have also been recorded by Miki, Ikuno, Jo and Nishida (2013) and Healey and Mitchell (2004).

Optic nerve head hemorrhages (ONHH) are considered a significant clinical sign of glaucomatous optic neuropathy (GON) so their assessment merited value. They are linked with glaucoma as a risk factor for the progression of the disease. According to literature they usually appear in the inferior sector of the retina on the temporal side. This study recorded a statistically significant association between ONHH and POAG. This is in conjunction with the work done by earlier researchers on ONHH. Optic nerve head hemorrhages are also considered as a prequel in the development of neuroretinal rim deficits, and thinning of retinal nerve fiber layer that leads to the visual field loss (Sharpe et al 2016).

We recorded PPA in our 50 cases in their ONH. Majority (77%) of the 50 subjects had highly significant both β and α zone PPA. According to Teng et al 2010, the β-zone atrophy is common in glaucoma and can be related with glaucoma severity. Lee, Lee and Kim (2015) researched the causative factors for the retinal nerve fiber layer thinning. In the multivariate analysis, the (β) zone PPA was found to be well related with the thinning of RNFL. Choi, Lee, Kim and Kim (2014) in their prospective study showed PPA to have a strong association with lamina cribrosa anatomical aberration. Kim, Kyung, Azarbod, Lee and Caprioli (2014) also found similar results regarding PPA.

Myopia has well been interrelated with glaucoma. This study records a statistically significant association between myopia and POAG when compared cases and controls Similar findings have been reported by Karaca and Yilmaz (2018), Miki, Ikuno, Asai, Usui and Nishida (2015), Han, Lee, Kim and Kee (2016), Nagaoka et al (2015,. Hayashi et al (2012) and Sawada et al (2018). Laminar dots and visual field defects arise more in glaucomatous patients (Sawada, Araie, Ishikawa and Yoshitomi 2017).

One of the contributory elements having strong correlations with POAG and LC distortions is the loss of retinal nerve fiber layer thickness (RNFLT) (Hao, Xiao, Gao, Xu and Liu 2019. Similar findings have been reported by Krzyżanowska-Berkowska, Czajor, Helemejko and Iskander (2018) and Lee, Kim, Lee, Lee and Kim (2017).

This study finds an inverse relationship between age and RNFLT (figure-17). Similar association has also been reported by Wu et al (2017) and Leung et al (2012).

We have also plotted the RNFLT according to sectorial basis, with superior followed by superior-inferior retinal sectors displaying the maximum retinal nerve fiber layer defects (n=15 in both sectors respectively). The minimum thickness recorded is in the global sector (48.40 ± 0.84 μm). Kim et al (2018) had also reported similar findings.

This study records a statistically significant association of POAG cases with visual field mean deviation (MD) and visual field pattern standard deviation (PSD). This is consistent with the findings of Tun et al (2018) and Rao (2014).

This study also finds a significant association between LC structural abnormalities and functional visual field defects in POAG cases with myopia, without myopia when were compared with controls (tables 2, 6 and 7; figures 18 and 23). Hung, Lee, Lin, Lin and Chen (2018) and Han, Cho, Sohn and Kee (2016) have recorded similar findings

The main focus of this study revolves around the morphological parameters of LC, the anterior lamina cribrosa depth (ALCD) and lamina cribrosa thickness (LCT). Our study finds a statistically significant result for LCT. Fard, Moghimi, Sahraian and Ritch (2019) have also reported a statistically significant association for LCT in glaucomatous group. This finding can be matched with our findings of a thinner LCT among POAG cases and normal thickness of LC in controls. Similar findings have been recorded by Park, Shin and Park (2014), . Kwun, Han and Kee (2015), Lee, Kim, Weinreb, Suh and Kim (2013), Jonas and Holbach (2005), Ren et al (2010) and Li, Bian, Cheng and Zhou (2016).

This study does not find significant results for anterior lamina cribrosa depth (ALCD). Literature has mixed views about associating the significance of ALCD with POAG. Agoumi et al (2011) concluded that lamina cribrosa surface is not compliant to the acute IOP elevations, as the prelaminar tissue is remodeled and no posterior displacement of LC occurs. Contraray to this Reis et al (2012) concluded that IOP changes could cause the anterior displacements of LC. Similar findings have also been reported by Barrancos, Rebolleda, Oblanca, Cabarga and Muñoz-Negrete (2014) have reported a significant anterior displacement of LC with IOP reduction. Wu, Xu, Weinreb, Yu and Leung (2015)

have presented a remarkable finding that LC displacements not only occur posteriorly but they also occur anteriorly.

CHAPTER 6

CONCLUSION

We concluded from our research "Correlation between Lamina Cribrosa Morphology and Glaucoma Severity in Patients with Primary Open-Angle Glaucoma"
that a thinner lamina cribrosa, signified by lamina cribrosa thickness (LCT) in primary open-angle glaucoma (POAG) correlated significantly with the decrease in retinal nerve fiber layer thickness (RNFLT) and visual field (VF) mean deviation (VF-MD) and visual field pattern standard deviation (VF-PSD) defects. Lamina cribrosa parameters also significantly associated with a greater axial length of the eyes (AXL), raised intraocular pressure (IOP), superior and superior-inferior sectorial retinal nerve fiber layer defects (RNFLD) and a greater vertical cup-to-disc ratio (VCDR).

Lamina cribrosa anatomical parameters of anterior lamina cribrosa depth (ALCD) and lamina cribrosa thickness (LCT) can be estimated with precision using enhanced depth imaging spectral domain ocular coherence tomography (EDI SD-OCT). Timely evaluation and monitoring of lamina cribrosa parameters can prove prophylactic and prognostic against the deleterious effects of glaucomatous optic neuropathy (GON).

6.1 RECOMMENDATIONS

Further prospective studies are warrented in which the study participants should be followed up, so that earliest discernible optic nerve head and lamina cribrosa morphological parameters should become available for detection of primary open-angle glaucoma and glaucomatous optic neuropathy at most earliest stage.

A new lamina cribrosa parameter, lamina cribrosa curvature index (LCCI) was recently introduced. This parameter is said to be more related with the primary open-angle glaucoma clinical characteristics and hence studies should be targeted for this parameter

6.2 STRENGTHS OF STUDY

This research topic, "Correlation between Lamina Cribrosa Morphology and Glaucoma severity in patients with Primary Open-Angle Glaucoma" was conducted for the first time

ever in Pakistan. This sentinel study proved to be a milestone step in regards of a research conducted over lamina cribrosa morphological parameters done for the first time ever in Pakistan This research emphasises upon a rampant eye global and domestic disorder, Primary Open-Angle glaucoma. This study imparts special prophylactic measures against the deleterious glaucomatous effects on the eyes, known as the glaucomatous optic neuropathy (GON). Since the severity monitoring of ALCD and LCT related well with the progression of the disease, hence it can be said that this study will prove beneficial if the course of the GON has started. Utilization of the clinical, structural and morphological parameters which were chosen for the study, the advancement of POAG can be marked and the treatment option for the patient may be altered, so the knowledge can be used as prognostic reference to categorize the diseaseThe use of enhanced imaging spectral domain ocular coherence tomography (EDI SD-OCT) was limited for visualization of anterior and posterior segments of eye. This piece of study will prove beneficial to extend the usage of EDI SD-OCT to analyze lamina cribrosa morphological parameters in the Pakistani setups.

Our results may prove a step towards developing a better diagnostic and grading system for primary open-angle glaucoma

6.3 LIMITATIONS OF STUDY

This study has several limitations. Though the EDI SD-OCT was a sophisticated technique that visualized the posterior optic nerve structures, in some cases the posterior aspect of the lamina cribrosa was not defined and thus had to be excluded that also accounted for by the lesser number of age-matched healthy controls.

Another limitation was use of three meridians, central, mid-superior and mid-inferior for the estimation of lamina cribrosa depth and thickness, which supposedly represent the overall laminar characteristics. The study should had been conducted in a multicentric setup, but unavailability of SD-OCT at most medical centers made this impossible.

Majority of study subjects belonged to a single ethnicity, we should have compared the lamina parameters in different races and ethnicities. Participants enrolled for the study were not demarcated as newly diagnosed primary open-angle glaucoma for the first time

or were a chronic case of POAG, which might had produced false variations in the results.

The numbers of cases and controls were not equal. The study participants should have been followed to see progression of LC parameters and glaucoma severity.

CHAPTER 7

7.1 REFERENCES

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7.2 APPENDICES

(A) FRC APPROVAL LETTER

FACULTY RESEARCH COMMITTEE
BAHRIA UNIVERSITY MEDICAL & DENTAL COLLEGE

IRPERSON
Asadullah Khan
fessor of Surgery,
ncipal & DeanHealth
nces, Bahria University
dical and Dental College

CHAIRPERSON
Mehreen Lateef
ior Assistant Proff

RETARY
Sumaiya Shawana
ociate Professor

ORDINATOR
Ammar Javed

MBERS
f. Dr. Ambreen Usmani
f. Dr. Shakeel Ahmed
f. Dr. M. Alamgir
f. Dr. Nighat Rukhsana
f. Dr. Hassan Ali
f. Dr. Yasmeen Taj
f. Dr. Nasim Karim
f. Dr. Khalid Mustafa
f. Dr. S. Ijaz Hussain Zaidi
gCdre Dr. Shoaib Ahmed
g Cdre Nuzhat Mushahid
g Cdr M. Akhtar
g Cdr Asif Latif

TED MEMBERS
f. Dr. Wahab Bakhsh Kadri
ist Prof. Dr.Daud Mirza
ist Prof. Dr. Shama Asghar

CTIVE MEMBERS
g Cdr. Dr. Hamidullah Arif
ector Health Sciences

Faisal Aftab
ector ORIC, BU

Shezad Khalid
ector PGP

LETTER OF APPROVAL

Ref No: FRC-BUMDC -01/ 2018-011

Date: 1st October 2018

To,
Dr. Ayesha Saba
M.Phil. Student
Department Of Anatomy
BUMDC-Karachi

Subject: **APPROVAL OF SYNOPSIS**

The Faculty Research Committee has approved the synopsis of below mentioned student.

Student Name: **Dr. Ayesha Saba**

Title of Study: **Correlation between lamina cribrosa morphology and glaucoma severity in patients with primary open-angle glaucoma.**

The synopsis of the above mentioned student will be presented in the next FRC meeting for final approval on MS 11 form.

Further this letter is recommended and referred to ERC for approval on ethical grounds.

Regards

Assist Prof. Dr. Mehreen Lateef,
CO- CHAIRPERSON FRC-BUMDC

Cc:
DG
Principal
FRC Record
PG Secretariat

Faculty Research Committee, Bahria University Medical College
Sailor's Street, Adjacent PNS-SHIFA DHA
Webmail: rrc-bumdc@bahria.edu.pk

(B) ERC APPROVAL LETTER

BAHRIA UNIVERSITY MEDICAL AND DENTAL COLLEGE

Defence phase II, Sailor Street, adjacent to PNS Shifa, Karachi. Tel: 021-35319491-9

ETHICAL REVIEW COMMITTEE

LETTER OF APPROVAL

Date: 31.10.18

PATRON
Prof. Asad Ullah Khan
Principal & Dean
Health Sciences(BU)

CHAIRPERSON
Prof. Ambreen Usmani

SECRETARY
Prof Reza H Syed

MEMBERS
Prof M Alamgir
Prof Anis Jafarey
Ms Nighat Huda
Surg Cdre Amir Ejaz
Ms Shabina Arif
Mr M Amir Sultan
Surg Lt Cdr Farah
Surg Lt Cdr Sadia

Dr. Ayesha Saba
Senior Lecturer
Department of Anatomy
BUMDC-Karachi

Subject: Institutional Approval of research study

Title of Study: Correlation between lamina cribrosa morphology and glaucoma severity in patients with primary open-angle glaucoma.

Principal Investigator: Dr. Ayesha Saba, Senior Lecturer Department of Anatomy, Bahria University Medical and Dental College.

Reference No: ERC 60/2018

Dear Dr. Ayesha Saba

Thank you for submitting the above mentioned study proposal. ERC Bahria University has reviewed this project in the meeting held on 24th-Sep-2018 and gives approval. Kindly notify us when the research is complete.

Regards,

PROF DR AMBREEN USMANI
Chairperson
BUMDC

Cc:
DG-BUMDC
Principal BUMDC
Chairperson ERC

(C) CONSENT FORM URDU

تحریری رضامندی فارم برائے مریض

میں اس تحقیق ''بنیادی کھلی زاویہ گلوکوک کے ساتھ مریضوں میں لامنا سائبر وسا مورفولوجی اور گلوکوک کے درمیان رابطے'' جو کہ ڈاکٹر عائشہ صبا ناز کی تحقیق ہے، میں اپنی مکمل رضامندی اور مرضی سے شرکت کر رہی ہوں۔ اس منصوبے کا مقصد یہ ہے کہ آکولر پیرامیٹرز کا اندازہ سلٹ لیمپ، بائیومائیکروسکوپی Itonometry اور EDI SD-OCT کے ذریعے لگایا جائے کہ ان کے استعمال سے تحقیق کے شرکاء کو کوئی نقصان نہیں پہنچے گا۔ مجھے اس منصوبے میں حصہ لینے کی اہمیت کے بارے میں تفصیل سے وضاحت کی گئی ہے اور میں محقق کی طرف سے فراہم کردہ وضاحت کو سمجھ گئی ہوں۔

مجھے بتایا گیا ہے کہ میری بیماری کے متعلق حقائق اور میرے اعداد و شمار کو سختی سے صیغہ راز میں رکھا جائے گا اور صرف عوالناس ، اشاعت، مقالے اور طباعت کے فائدہ کے لئے استعمال کیا جائے گا۔ مجھے تفصیلاً بتایا گیا ہے کہ تشخیص کے لیے لیبارٹری تحقیقات کو استعمال میں لایا جائے گا اور اچ مقصد کے لیے میں مکمل طور پر رضامند ہوں کہ اس علمی تحقیق کے لیے آکولر پیرامیٹرز دوں۔ میں اس بات سے بھی اتفاق کرتی ہوں کہ اس سلسلے میں معلومات اور جتنا میرے علم میں ہے وہ تمام محقق کو فراہم کروں گی۔ مجھے یہ بھی وضاحت کر دی گئی ہے کہ اس علمی تحقیق میں حصہ لینے کے لئے کسی قسم کی مالی معاونت نہیں کی جائے گی۔ سوائے اس کے کہ اگر میں نان ایلیجیبل مریض ہوں تو خرچا محقق برداشت کرے گا اور مجھے یہ حق حاصل ہوگا کہ جب چاہوں اس علمی تحقیق سے الگ ہو جاؤں۔

مجھے مشورہ دیا گیا ہے کہ میں اپنی بیماری سے متعلق کسی بھی سوال/ ہنگامی صورتحال پر میں ڈاکٹر عائشہ صبا ناز کے موبائل نمبر 0345-2257226 پر رابطہ کروں یا پی این ایس شفاء ہسپتال کا دورہ کروں مجھ پر کی جانے والی تحقیقات کے نتیجے میں کسینا خوشگوار یا غیر معمولی اثر کی صورت میں یہ محقق کی ذمہ داری ہوگی کہ وہ مریض کا اپنے خرچے پر مئوثر علاج کروائے۔

مریض کا نام: _____ زوجہ: _____

دستخط/نشانِ انگوٹھا مریض: _____

محقق کا نام: _____

محقق کے دستخط: _____ تاریخ: _____

(C) CONSENT FORM ENGLISH

WRITTEN INFORMED CONSENT FORM FOR PATIENT

I am giving my consent to participate voluntarily and at my own will in this research" Correlation between Lamina Cribrosa Morphology and Glaucoma Severity In Patients with Primary Open-Angle Glaucoma" (by Dr Ayesha Saba Naz) project that aims to evaluate the ocular parameters assessed over non-invasive investigatory tools of slit-lamp biomicroscopy, tonometry and EDI SD-OCT, which will not be causing any harm to the research participants. I have been explained in detail the nature and significance of participating in the project and I understand the provided explanation.

I have been told that findings of my disease and my data will be kept strictly confidential and will be used only for the benefit of community, publications and paper presentation. I have been explained that the laboratory investigations will be conducted for diagnosis. For this purpose I fully agree to give my ocular parameters for the study. I also agree to give all relevant information needed, in full and to the best of my knowledge to the researcher. It is clarified to me that no incentives will be provided to me for participating in the study except the cost of investigations (in case of non-entitled patients) that will be borne by the researcher whereas I do have the right to withdraw from the study at any time.

I am advised to contact Dr. Ayesha Saba Naz on mobile number 0345-2257226 or visit PNS Shifa Hospital in case of any query/ emergency related to my disease. In case of any untoward effect resulting from the given investigation it will be responsibility of the researcher to effectively treat the patient at her own expense.

Name of Patient:_____ W/o_____

Investigation assigned to the patient:_____

Signature/ Thumb impression of patient: _____

Name of Researcher: _____

Signature of researcher:_____ Date: _____

(D) SUBJECT EVALUATION PROFORMA

SUBJECT EVALUATION FORM

SUBJECT: CASE ___ , CONTROL ___

DEMOGRAPHIC DATA

Hospital registration number/ID	
Name of subject	
Age <40 years 1 40-50 years 2 51-60 years 3 61- 70 years 4 71- 80 years 5 Above 81 years 6	
Gender (Male 1, Female 2)	
Marital status (Married 1, Unmarried 2, Any other 3)	
Ethnicity (Muslim 1, Christian 2, Hindu 3, Other 4)	
Occupation (Skilled office worker 1, nonskilled worker 2, housewife3, retired 4)	
Area of residence	
Contact number	

Medical History Record

Retinal disease (Yes 1, No 2)	
Eye/head trauma or surgery (excluding uncomplicated cataract surgery) Head trauma 1, Eye trauma 2, Eye surgery 3	
Any laser procedure over eyes Yes 1, No 2	
Any other optic nerve disease (other than glaucoma) Yes 1, No 2	
HTN 1, DM 2, CVS 3, Autoimmune 4/ diseases/Migraine 5/ Raynaud's 6	
Neurological diseases Yes 1, No 2	

Medication History Record

Drug	Name

Antiglaucoma Eye drops Yes 1, No 1	
Hypnotics, Antidepressants, use of β-blockers 1, Steroids 2, Antiplatelets 3, Others 4	
Any other substance use (Pan 1, Niswaar 2, Ghutka 3, Bettle nuts 4)	

Ophthalmological History Record

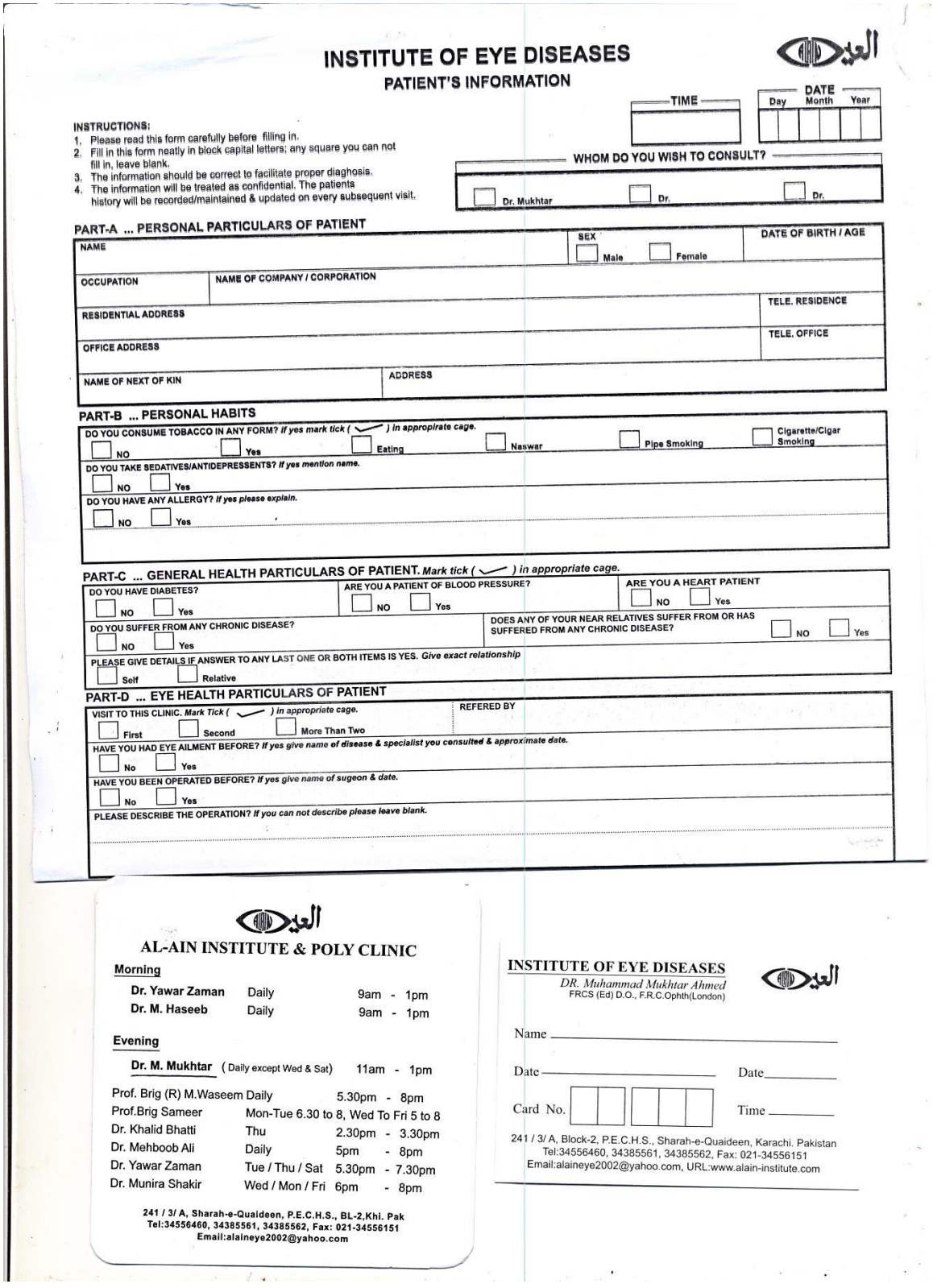
Any gross inspection findings Ptosis 1 Redness of eyes 2 Lacrimation 3 Any swellings 4 Movement disorders (Strabismus, Nystagmus) 5 Proptosis 6 Any opacity 7	
Eye power Emmetropia 1 Hyperopia 2 Myopia 3 Astigmatism 4	
Family history (Yes1, No 2)	

Examination

Visual acuity 6/18=1 6/24=2 6/36=3 6/48=4 6/60=5	(>20/40, spherical refraction within +-6 diopters, cylindrical correction within +-3.0 diopters	
Slit-lamp biomicroscopy	Exclude secondary glaucoma, like pigmentary or pseudoexfoliative	
Axial length	24.8±1.5mm	

Goldmann applanation tonometry (considering CCT is normal 520µm)		
Humphrey visual field analyzer VF 30-2 dB PSD 1 STF 2	Outside normal limits of GHT on two consecutive tests with presence of three consecutive test points	
Stereoscopic examination of optic disc and fundus NRR 1 Laminar dots 2 ONHH 3 PPA (α & β) 4 RNFL 5	i. NRR (must be orange/pink with normal "ISNT" rule ii. Laminar dots (slit-like) iii. ONHH inferotemporally (splinter type & if present at rim) iv. Peripapillary atrophy: α and β zones with β more specific v. RNFL: wedge-shaped defects	
SD-OCT imaging i. Prelaminar tissue 1 ii. Anterior lamina cribrosa depth 2 iii. Lamina cribrosa thickness 3 iv. Lamina cribrosa width 4 v. Lamina cribrosa curvature index 5	110.4±63.7 µm 539.4± 140.5µm 177.7 ± 53.0 µm	__in µm __in µm __in µm __in µm __in µm
Measurement of peripapillary retinal nerve fiber layer (dilated pupil) Ref (diagnostic capability of LC thickness by EDI and factors affecting thickness in patients with glaucoma2013)		

(E) HOSPITAL CARD



INSTITUTE OF EYE DISEASES

PATIENT'S INFORMATION

TIME

DATE Day Month Year

INSTRUCTIONS:
1. Please read this form carefully before filling in.
2. Fill in this form neatly in block capital letters; any square you can not fill in, leave blank.
3. The information should be correct to facilitate proper diaghosis.
4. The information will be treated as confidential. The patients history will be recorded/maintained & updated on every subsequent visit.

WHOM DO YOU WISH TO CONSULT?

☐ Dr. Mukhtar ☐ Dr. ☐ Dr.

PART-A ... PERSONAL PARTICULARS OF PATIENT

NAME	SEX ☐ Male ☐ Female	DATE OF BIRTH / AGE
OCCUPATION	NAME OF COMPANY / CORPORATION	
RESIDENTIAL ADDRESS		TELE. RESIDENCE
OFFICE ADDRESS		TELE. OFFICE
NAME OF NEXT OF KIN	ADDRESS	

PART-B ... PERSONAL HABITS

DO YOU CONSUME TOBACCO IN ANY FORM? *If yes mark tick (✓) in appropirate cage.*
☐ NO ☐ Yes ☐ Eating ☐ Naswar ☐ Pipe Smoking ☐ Cigarette/Cigar Smoking

DO YOU TAKE SEDATIVES/ANTIDEPRESSENTS? *If yes mention name.*
☐ NO ☐ Yes

DO YOU HAVE ANY ALLERGY? *If yes please explain.*
☐ NO ☐ Yes

PART-C ... GENERAL HEALTH PARTICULARS OF PATIENT. *Mark tick (✓) in appropriate cage.*

DO YOU HAVE DIABETES? ☐ NO ☐ Yes	ARE YOU A PATIENT OF BLOOD PRESSURE? ☐ NO ☐ Yes	ARE YOU A HEART PATIENT ☐ NO ☐ Yes
DO YOU SUFFER FROM ANY CHRONIC DISEASE? ☐ NO ☐ Yes	DOES ANY OF YOUR NEAR RELATIVES SUFFER FROM OR HAS SUFFERED FROM ANY CHRONIC DISEASE? ☐ NO ☐ Yes	

PLEASE GIVE DETAILS IF ANSWER TO ANY LAST ONE OR BOTH ITEMS IS YES. *Give exact relationship*
☐ Self ☐ Relative

PART-D ... EYE HEALTH PARTICULARS OF PATIENT

VISIT TO THIS CLINIC. *Mark Tick (✓) in appropriate cage.* REFERED BY
☐ First ☐ Second ☐ More Than Two

HAVE YOU HAD EYE AILMENT BEFORE? *If yes give name of disease & specialist you consulted & approximate date.*
☐ No ☐ Yes

HAVE YOU BEEN OPERATED BEFORE? *If yes give name of sugeon & date.*
☐ No ☐ Yes

PLEASE DESCRIBE THE OPERATION? *If you can not describe please leave blank.*

AL-AIN INSTITUTE & POLY CLINIC

Morning

Dr. Yawar Zaman	Daily	9am - 1pm
Dr. M. Haseeb	Daily	9am - 1pm

Evening

Dr. M. Mukhtar	(Daily except Wed & Sat)	11am - 1pm
Prof. Brig (R) M.Waseem	Daily	5.30pm - 8pm
Prof.Brig Sameer	Mon-Tue 6.30 to 8, Wed To Fri 5 to 8	
Dr. Khalid Bhatti	Thu	2.30pm - 3.30pm
Dr. Mehboob Ali	Daily	5pm - 8pm
Dr. Yawar Zaman	Tue / Thu / Sat	5.30pm - 7.30pm
Dr. Munira Shakir	Wed / Mon / Fri	6pm - 8pm

241 / 3/ A, Sharah-e-Quaideen, P.E.C.H.S., BL-2,Khi. Pak
Tel:34556460, 34385561, 34385562, Fax: 021-34556151
Email:alaineye2002@yahoo.com

INSTITUTE OF EYE DISEASES

DR. Muhammad Mukhtar Ahmed
FRCS (Ed) D.O., F.R.C.Ophth(London)

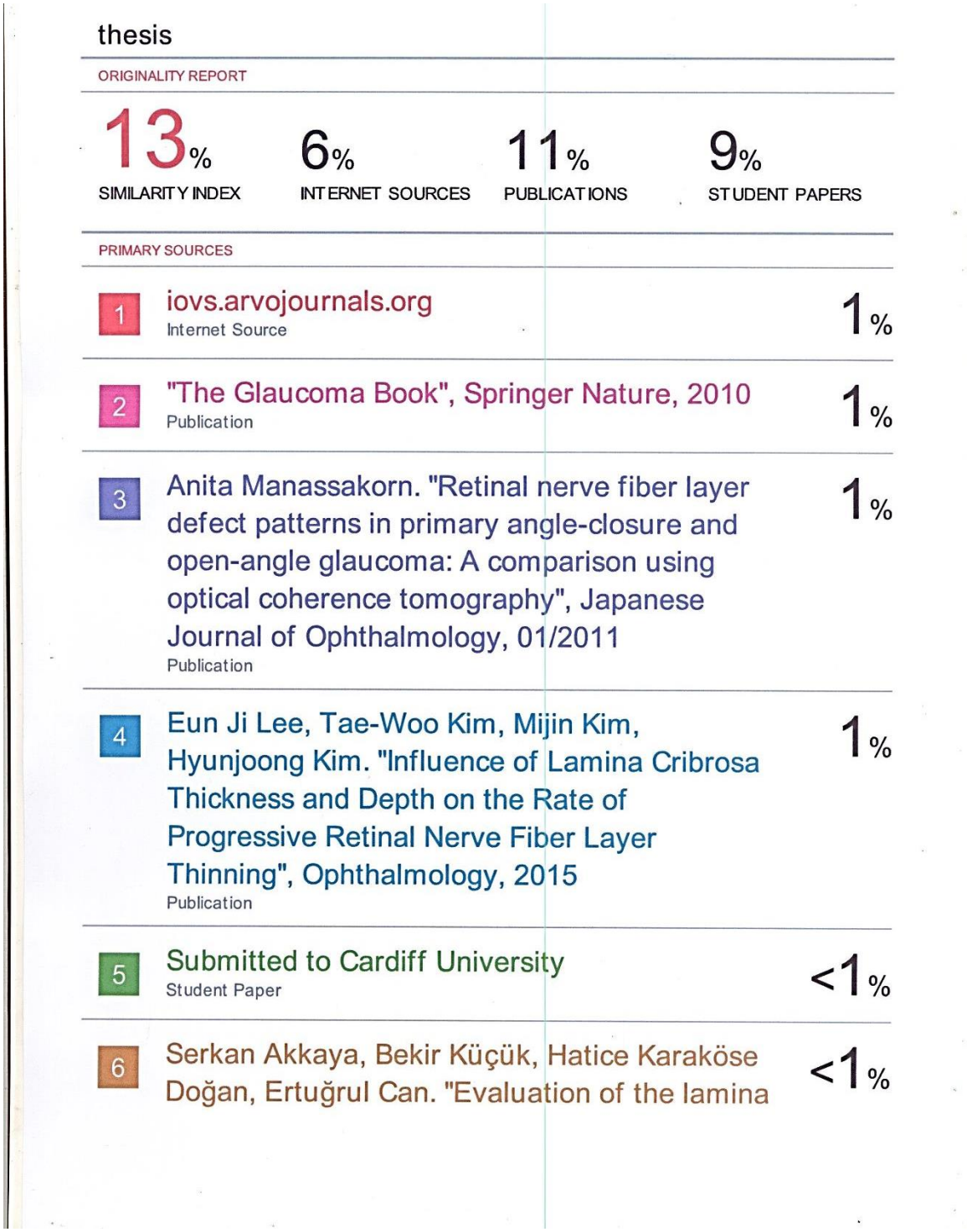
Name _____

Date _____ Date _____

Card No. ☐☐ ☐☐☐ Time _____

241 / 3/ A, Block-2, P.E.C.H.S., Sharah-e-Quaideen, Karachi. Pakistan
Tel:34556460, 34385561, 34385562, Fax: 021-34556151
Email:alaineye2002@yahoo.com, URL:www.alain-institute.com

(F) TURNITIN PLAGIARISM CHECK REPORT



thesis

ORIGINALITY REPORT

13%	6%	11%	9%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	iovs.arvojournals.org Internet Source	1%
2	"The Glaucoma Book", Springer Nature, 2010 Publication	1%
3	Anita Manassakorn. "Retinal nerve fiber layer defect patterns in primary angle-closure and open-angle glaucoma: A comparison using optical coherence tomography", Japanese Journal of Ophthalmology, 01/2011 Publication	1%
4	Eun Ji Lee, Tae-Woo Kim, Mijin Kim, Hyunjoong Kim. "Influence of Lamina Cribrosa Thickness and Depth on the Rate of Progressive Retinal Nerve Fiber Layer Thinning", Ophthalmology, 2015 Publication	1%
5	Submitted to Cardiff University Student Paper	<1%
6	Serkan Akkaya, Bekir Küçük, Hatice Karaköse Doğan, Ertuğrul Can. "Evaluation of the lamina	<1%