Review Article

Primary Open Angle Glaucoma: The Pathophysiolgy, Mechanisms, Future Diagnostic and Therapeutic Directions

ABSTRACT

Primary open angle glaucoma (POAG) is a multifactorial chronic optic neuropathy, characterized by progressive loss of retinal ganglion cells (RGC), leading to structural damage to the optic nerve head (ONH), retinal nerve fiber layer (RNFL), with visual field defects. It is occasioned by major risk factors of high intraocular pressure (IOP) and age. The pathogenesis of POAG is the imbalance between the production and drainage of the aqueous humour (AH). The resultant fluid back-up increases the IOP with consequent optic nerve damage, causing POAG. Modern diagnosis using scanning laser polarimetry (SLP), confocal scanning laser ophthalmoscopy (CSLO), optical coherence tomography (OCT) etc, plays a vital role in the assessment of the ONH, RNFL and the macular, in POAG. OCT operates on the principles of interferometery, utilizing light beams and their pattern of back-scattering, to build high resolution cross-sectional images of ocular tissues. It gives an objective evaluation of structural alterations in the ONH or macular area of the retina in vivo. POAG is managed medically using classes of drugs like α-adrenergic agonists, beta-adrenergic receptor antagonist, prostaglandin agonists, carbonic anhydrase inhibitors, ccholinergic agonists etc. Surgical intervention is indicated with laser or incisional surgeries, when medical option fails. Future pharmacotherapeutic directions in POAG management consider transgenic model, genetic model, stem cell technique, ~~neurodegeneration(neuroregeneration)~~ autoimmune response and T-cell autoimmune response attack.

Key Words: Intraocular pressure; Optical coherence tomography; Optic nerve head, Primary open angle glaucoma; Retinal nerve fiber layer; Trabecular meshwork; Future therapy.

1.0 INTRODUCTION

Glaucoma includes a complex of disease entities, characterized by a disturbance of the structural, functional, and atrophic changes of the optic nerve, with specific visual field defects over time [1]. It is basically classified into two major types: POAG and Primary angle closure glaucoma (PACG). POAG is a multifactorial, chronic optic neuropathy, characterized by progressive loss of RGC, leading to structural

damage to the ONH and RNFL, with subsequent visual field defects [2]. Though the cause is unknown, POAG is highly attributed to an imbalance in the production and drainage of the AH, which raises the IOP. It is chronic, insidious, typically adult in onset and slowly progressive. Other major characteristics of POAG include being frequently asymptomatic, generally bilateral, mostly asymmetrical, and absence of underlying cause [3]. POAG is associated with chronic disabilities, ranging from slight peripheral impairments, to complete blindness. Detection of glaucoma and its progression are based on identification of abnormalities in the ONH or the RNFL, either functional or structural. These defects can often be observed during fundus examination, or in red-free fundus photographs of the optic disc and surrounding retina [4]. New techniques have been developed for quantitative retinal imaging, and measurement of RNFL loss with good diagnostic accuracy. OCT images measures directly the thickness of the retinal nerve fiber layer using segmentation algorithms [4]. There are wide range of Anti-glaucoma medications, surgical techniques and future therapies

2.0. LITERATURE

2.1 Epidemiology
The World Health Organization reports that glaucoma is the second largest cause of permanent blindness worldwide. Various authors estimate that the disease causes 2.1 to 4.4 million such cases worldwide [5]. Glaucoma is undiagnosed in 50% of cases in the western world, with higher figures in specific ethnicities, as demonstrated by several epidemiological studies (Baltimore Eye Survey, Rotterdam Eye Study, Blue Mountains Eye Study, Visual Impairment Project, Proyecto VER, and Latino Eye Study) and in up to 90% of cases in developing countries (Aravind Eye Study). Only one half of the people who have glaucoma may be aware that they have the disease; and more than 2.25 million Americans aged 40 years and older have POAG [6]. POAG accounts for 90% of all the different forms of glaucoma. More than 3 million people are bilaterally blind from POAG worldwide, and more than 2 million people will develop the disease each year [7]. People of African descent are more likely to develop glaucoma early in life, and they tend to have a more aggressive form of the disease. Prevalence of POAG is 3-4 times higher in blacks than in Caucasians; in addition, blacks are up to 6 times more susceptible to optic nerve damage than Caucasians. A higher prevalence of larger cup-to-disc ratios exists in the normal black population as compared with white controls [6].

2.2 Pathogenesis
Though the cause is unknown, POAG is highly attributed to an increase in IOP which occurs slowly over time, due to an imbalance between the production and drainage of the aqueous humor. If too much aqueous is produced by the ciliary body, or the drainage channels of the trabecular meshwork (TM) are blocked, the IOP rises. The elevated pressure pushes harder against the nerve fibers of the optic nerve, reducing its blood supply, depriving it of oxygen and nutrients, with subsequent optic nerve damage and irreversible vision loss. AH is produced by the ciliary body in the posterior chamber and is secreted posterior to the iris. 80 % of the outflow goes through the TM which lies in the iridocorneal angle, and drains into the episcleral venous system; via Schlemm's canal (SC) into scleral plexuses and general venous blood circulation [8,9]. The remaining 20% passes through the uveoscleral pathway via the interstitial spaces between the iris root and ciliary muscle in a mechanism called uveoscleral outflow [10,11]. When this drain becomes clogged, attributable to its structural degeneration due to age, and aqueous cannot leave the eye as fast as it is produced, there is fluid back up. The eye being a closed compartment, the backed up fluid causes increased pressure build up within it, causing POAG. Multiple theories have been adduced as to the cause of the resistance and decrease facility of aqueous outflow to include: an obstruction of the TM by accumulated material, a reduction in trabecular pore density and size in the inner wall endothelium of the SC, a loss of trabecular endothelial cells, a loss of normal phagocytic activity and disturbance of neurologic feedback mechanisms. Histopathological assessment of the drainage angle in patients with POAG revealed narrowed intertrabecular spaces, thickened basement membranes, fused trabecular beams, reduction in trabecular endothelial cells, reduction in actin

filaments, narrowing of collector channels, foreign material accumulation and closure of SC [12]. Other processes thought to play a role in resistance to outflow include altered corticosteroid metabolism, dysfunctional adrenergic control, abnormal immunologic processes, and oxidative damage to the meshwork [7].   .

2.3 Pathophysiology

POAG is a multifactorial, chronic optic nerve neuropathy that is characterized by progressive loss of RGC, which leads to structural damage to the ONH and RNFL, with subsequent visual field defects [2]. The uniqueness of glaucoma among optic neuropathies is cupping rather than pallor of the optic nerve head. It is believed to be the loss of the RNFL tissue that leads to the increased cup to disc ratio [13]. Optic nerve is composed of axons of RGCs, which transmit visual information from the retina to the brain. The optic disc is the portion of the optic nerve visible in the posterior segment of the eye. The fibers from the nasal side of the retina travel directly to the optic disc, while the fibers from the temporal side follow a more complex pattern. Those from the macula travel straight to the optic disc via the papillomacular bundle, and those from the periphery form the superotemporal and inferotemporal arcs around the papilla-macular bundle. The axons on the temporal side do not cross the horizontal midline [14]. The ONH consists of axons from approximately 1.2 million ganglion cells that have their cell bodies in the retina. The blood supply to the ONH is derived from the ophthalmic artery, which supplies the anterior portion of the nerve through the central retinal artery, and the bulk of the prelaminar, laminar, and retrolaminar portions of the nerve via the short posterior ciliary arteries [8]. As axons within the nerve die, largely through apoptosis and the plates of the lamina cribrosa sclerae collapse due to IOP or ischemia, it reduces the blood supply to the optic nerve, depriving it of oxygen and nutrients [15]. Loss of optic nerve tissue produces a characteristic "cupping" of the optic nerve head. The nerve damage involves loss of RGCs in a characteristic pattern seen in glaucoma, with changes in the appearance of the ONH and RNFL. These are the most important aspect of glaucoma diagnosis as seen in ophthalmoscopy of the ONH (figure1) [16,17]. Diffuse enlargement is followed by elongation of the central cup of the optic disc to form a vertical oval excavation. Thinning or notching of the disc rim, or disc hemorrhages might also be seen. When a vertical cup-to-disc ratio (CD) ratio of 0.6 or greater is seen, glaucoma should be suspected [18]. There is usually appreciable loss of central vision, after the appearance of field defects, which may represent a relatively late stage of disease. Visual field defects may not be apparent until over 40% of the optic nerve fiber layer has been lost [19]. Although ocular hypertension has an important role in the pathogenesis of glaucoma which proceeds glaucomatous nerve damage, it is thought that raised IOP primarily affects the optic nerve via the mechanical changes at the lamina cribrosa. There are patients in whom its therapeutic control is not enough to stop the progression of the disease. Glaucomatous optic nerve changes are also seen in patients with normal or low intraocular pressure, like in normal pressure glaucoma. This means that there are other factors involved in the initiation and development of glaucoma [20,21].

A Normal optic nerve head and visual field

B Glaucomatous optic nerve head and associated inferior visual field loss

C Extensive neural tissue loss in severe glaucoma and associated severe visual field loss
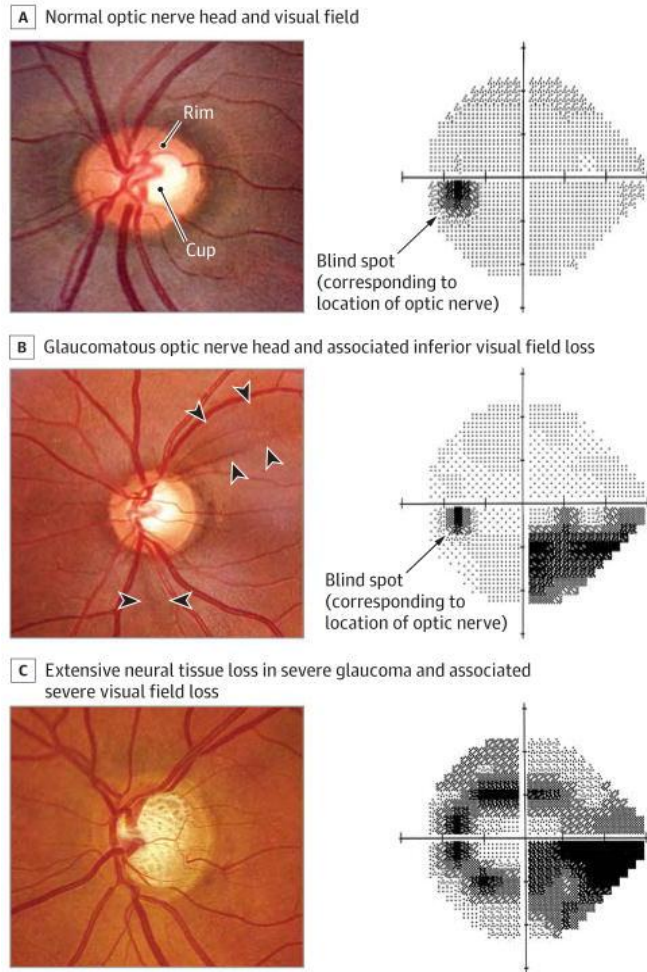
Figure 1 Showing Normal, Glaucomatous, and Severe Glaucomatous Optic Nerve Heads and Visual Field Test Results.
A. Normal optic nerve head and visual field. B, Glaucomatous optic nerve showing loss of superior neural retinal rim, corresponding to the inferior defect (black scotoma) on the visual field. C, More extensive neural tissue loss from glaucoma with severe neuroretinal rim loss, with severe loss of visual field both in the superior and inferior hemifield. Courtesy: Welram et - al [17]

2.3.1 Theories of Possible Mechanisms

Although the exact mechanism of POAG has not been completely elucidated, there are several theories regarding the events, like the vascular and mechanical compression theories. The vascular theory proposes vascular dysfunction, with the onset of ischemia which triggers cell death to the optic nerve, whether induced by elevated IOP or as a primary insult. The mechanical compression theory suggests a mechanical dysfunction via cribriform plate compression of the axons. It is as a result of elevated IOP causing a backward bowing of the lamina cribrosa, kinking the axons as they exit through the lamina pores. This may lead to focal ischemia, deprive the axons of neurotrophins, or interfere with axoplasmic flow, triggering cell death [22]. A mechanism proposes pressure on RGC followed by ischemia, hypoxia of the ONH, and consequent death due to glutamate-induced excitotoxicity, deprivation of energy and oxygen. There is increase in levels of inflammatory mediators and alteration of trophic factors flow. These events lead to blockage of anterograde and retrograde axonal transport with ensuing axotomy and eventual blindness [23]. Elevated IOP induces the expression of heat shock proteins, a family of proteins

4

that develop in response to stressful conditions. This leads to a response from immune cells, the memory T cells, which are programmed to respond to heat shock proteins. The memory T cells attack the neurons of the retina, leading to degeneration of the optic nerve and often permanent loss of vision. [24]. There is pathogenic mechanisms that underlie glaucomatous optic neuropathy, which include excitotoxic damage from excessive retinal glutamate, deprivation of neuronal growth factors, peroxynitrite toxicity from increased nitric oxide synthase activity, immune-mediated nerve damage and oxidative stress [22]. Genetic theories propose that genetic predisposition triggers cell death of axons. This releases substances like glutamate a neurotransmitter that causes excitotoxicity. Other substance such as the calcium, nitric oxide, and free radicals are also released into the environment and cause a secondary triggering of apoptosis in neighboring cells [22]. In the cell apoptosis theory, glaucomatous excavation appears because of the loss of RGC axons, which is accompanied by the loss of their cell body. It turned out that apoptosis (or programmed cell death) is a primary RGCs destruction mechanism in glaucoma, being involved in all stages of the disease. Apoptosis consists in the destruction of the cell nucleus, cell membrane rupture and phagocytosis of the disorganized cell by the neighboring cells [20]. In some situations, glaucomatous optic neuropathy occurs when IOP is within the normal range. It may be due to abnormally low cerebrospinal fluid pressure in the optic nerve subarachnoid space, resulting in a large pressure gradient across the lamina [25,26]. Impaired microcirculation, altered immunity, excitotoxicity, and oxidative stress may cause glaucoma. Primary neural pathological processes may cause secondary neurodegeneration of other retinal neurons and cells in the central visual pathway, by altering their environment, and increasing susceptibility to damage [27].

3.0 DIFFERENTIAL DIAGNOSIS

The deferential diagnosis considered for a tentative diagnosis of POAG were for: Ocular Hypertension, Normal Tension Glaucoma, PACG, Anterior Ischemic Optic Neuropathy, Physiological Cupping, Secondary Glaucoma and POAG

3.1 Ocular Hypertension
In Ocular Hypertension, there is an elevated IOP, above the statistically normal level of 12 – 21 mmHg, but with no definite signs of glaucomatous optic neuropathy, or any evidence of anatomic or functional damage to the eye and no asymmetrical increase of the size of the cup over a period of time. There is no central or visual field defect. They are considered glaucoma suspects [1].

3.2 Normal Tension Glaucoma
In normal tension Glaucoma, there is the presence of intraocular glaucomatous damage like the cupping of the optic disc, and visual field loss etc, but the intraocular pressure remains within normal range.

3.3 PACG
PACG is characterized by a sudden increase in intra ocular pressure. The attack is abrupt in onset, acute and occurs within a few minutes to hours. The IOP is marked, reaching four or five times the normal value (up to 80mmHg). The anterior chamber is anatomically shallow and the filtration angle is narrow. There is obstruction of aqueous outflow due to peripheral iris forcing against the trabeculum. It can develop only in one eye, with such symptoms as severe pain in and around the eye, pain radiating to the jaw, headache, fever, nausea and vomiting, ciliary injection, congestive hyperemia, blur vision, pseudoptosis, hazy cornea due to edema, dilated pupils without any reflex and sudden loss of vision [1]. There may be colored rings (Newton's rings), around a light dispersed by the edematous corneal epithelium [28].

3.4 Secondary Glaucoma:
Secondary glaucoma is due to raised IOP occurring as one manifestation of intraocular disease. It is also associated with topical/systemic corticosteroids, traumatic lens dislocation, cataract formation,

liquefaction of lens cortex, essential atrophy of the iris, massive hemorrhage into the anterior chamber, iris prolapse, flat anterior chamber following cataract surgery, central vein occlusion, presence of new abnormal vessels etc [3]. The treatment of the underlying cause, greatly resolves the condition.

3.5 Physiological Cupping:
In Physiological Cupping, the optic disc is large and physiologically normal. The CD ratio is usually large, of up to about 0.7. There is symmetry in the sizes of both disc and cup in both eyes. There is no pathology or excavation of the disc, There is no elevation in the intra ocular pressure of the eye, no central or peripheral visual loss. No symptoms or sign of glaucoma.

3.6 POAG
POAG is characterized by major risk factors of high IOP often greater than 21 mmHg, strong genetic tendency and age mostly adults and older patients. It is chronic, generally bilateral, slowly progressive and insidious in onset. POAG is mostly asymmetrical, with difference in cupping of more than 0.2, more severe in one eye than the other and with absence of underlying cause [3]. It is asymptomatic until visual impairment occurs. The irido-cornea (filtration) angle in POAG is usually open or wide, devoid of any narrowing tendency, with a normal anterior chamber depth. It is mainly characterized by glaucomatous optic neuropathy, with thinning of the temporal disc margin. In moderate to advanced POAG, there is cupping, resulting in the notching of the neuroretinal rim, with a vertical CD ratio of 0.6 or more [29], with the displacement of large neuroretinal vessels nasally. POAG manifests gradual but, significant peripheral field loss, compatible with nerve fiber damage, which may not be apparent until over 40% of the optic nerve fiber layer has been lost. The circumretinal vessel is bare and the optic disc appears milky white in color. There is normal pupil size in most cases and with normal reaction to light. In POAG, depreciation of vision is gradual, with irreversible visual loss. It Is associated with other such risk factors like myopia, race of African origin, age older than 40 years, corticosteroid use, trauma and elevated IOP, genetics etc [30].

4.0 RISK FACTORS

4.1 IOP:
Elevated IOP is the only clinical risk factor that has been able to be successfully manipulated to date [7]. Up to 10% of patients older than 40 have IOP above 21 mm Hg; those who have elevated pressures without optic nerve damage are termed ocular hypertensive or glaucoma suspects. Normal-tension glaucoma is defined as glaucomatous nerve damage and visual field loss with an IOP below 22 mm Hg. In fact, up to one in six patients with glaucoma have the normal-tension variety [31]. Several studies over the years have shown that as IOP rises above 21 mm Hg, the percentage of patients developing visual field loss increases rapidly, most notably at pressures higher than 26-30 mm Hg. A patient with an IOP of 28 mm Hg is about 15 times more likely to develop field loss than a patient with a pressure of 22 mm Hg [6].

4.2. Age:
The prevalence of glaucoma rises with age, approximately 1% in white patients younger than 40 and 2% to 5% among those older than 75, with respective values of 1% and 11% among patients of African descent [32]. In the United States, 3-6 million people, including 4-10% of the population older than 40 years, are currently without detectable signs of glaucomatous damage using present-day clinical testing, but they are at risk due to IOP of 21 mm Hg or higher. Roughly 0.5-1% per year of those individuals with elevated IOP will develop glaucoma over a period of 5-10 years [6].

4.3. Genetics and Familiarity:
In some studies, among those the Baltimore Survey, 50% of the suffering patients had a positive familiarity, suggesting the genetic defect as important for the pathology development [33]. Research has

shown that siblings of persons diagnosed with glaucoma have nearly a 10-fold increased risk of having glaucoma when compared to siblings of persons without glaucoma. This means that a 65 year old sibling of a European derived person has about a 10% chance of having glaucoma, while a 65 year old sibling of an African American has nearly a 20% chance of having glaucoma [34].

4.4. Race:
Prevalence of POAG is 3-4 times higher in blacks than in Caucasians; in addition, blacks are up to 6 times more susceptible to optic disc nerve damage than Caucasians. The Barbados Eye Study over 4 years showed a 5 times higher incidence of developing glaucoma in a group of black ocular hypertensives as compared with a predominantly white population [6].

4.5. Gender:
There is no clear consensus on gender predilection for POAG. In whites, the Baltimore Eye Survey and the Beaver Dam Eye Study showed no difference in prevalence by gender. In contrast, the Framingham Eye Study and the Rotterdam Study showed an increased prevalence among males, whereas the Blue Mountains Eye Study showed an increased prevalence among females [35].

4.6. Myopia:
The Beaver Dam Eye Study showed that after taking into account the effects of age, sex, and other risk factors, persons with myopia were 60% more likely to have glaucoma than those with emmetropia [36]. In Asian populations, the Singapore Malays Eye Study showed an association between moderate or high myopia (worse than –4 D) and POAG.

4.7. Steroid Users:
Some evidence links steroid use to glaucoma. A 1997 study reported in the Journal of American Medical Association, demonstrated a 40% increase in the incidence of ocular hypertension and open-angle glaucoma in adults who require approximately 14 to 35 puffs of steroid inhaler to control asthma. This very high dose is only required in cases of severe asthma [37,38].

4.8. Diabetes:
Individuals with DM have an approximately 1.4-fold increased risk of developing POAG in cohort studies, while they have an about 49% increased odds of developing POAG, in case-control studies, compared with individuals without DM [39]. Again, DM affects several organs of the body as well as the oculo-visual apparatus of the eye in several forms [38]. It is a leading cause of visual impairment and blindness with glaucoma [40,38].

4.9. Others:
Other risk factors with moderate-to-fair epidemiologic evidence include: Hypertension, type 2 diabetes, hypothyroidism, migraine, and sleep apnea. Others that could cause secondary glaucoma, include: Prolonged use of steroids (steroid-induced glaucoma), severe diabetic retinopathy and central retinal vein occlusion (neovascular glaucoma), ocular trauma (angle recession glaucoma), and uveitis (uveitic glaucoma) [41].

5.0 DIAGNOSIS

5.1. Preliminary diagnostic tools

The diagnosis of POAG is traditionally based on the findings of ONH damage, assessed subjectively through ophthalmoscopy, bimicroscopy, photography or visual field assessment by automated perimetry. Others are measurement of central corneal thickness and measurement of IOP through tonometry.

5.1.1. Visual field Assessment
Confrontation test is a quick, easy and earlier preliminary visual field assessment in glaucoma. It reveals substantial visual field defects. The Tangent screen plotting is the major preliminary determination of the extent of visual field loss. There is perimetry which is a better device for the assessment of the central and peripheral visual field, and could be static or kinetic. Automated perimetry, like the visual field analyzer, assesses the central and peripheral visual field defects along the visual pathway, and analyzes them.

5.1.2. Tonometry
Tonometry is a procedure for the determination of the IOP in a glaucoma suspect. There are contact, non contact and applanation tonometers. The contact and applanation tonometers require topical anaesthetics of the eye before their application. The non contact tonometer requires no anaesthetics, and depends on the principle of air puff applanation of the cornea by air. to the eye.

5.1.3. Ophthalmoscopy and Bimicroscopy
Ophthalmoscopy and Slit lamp bimicroscopy are very important tools in glaucoma diagnosis. They assess the optic nerve head for glaucomatous excavation, and the level of damage to the RNFL in glaucomatous optic neuropathy.

5.2. Modern diagnostic imaging tools

POAG manifests loss of retinal ganglion cell axons, routinely diagnosed by the presence of thinning of the neuroretinal rim of optic nerve, peripapillary RNFL, and inner layers of the macula. Since these structural changes may precede perimetric visual field changes, sensitive imaging tools like SLP, CSLO and OCT (write in full)provide an objective measure of the structural changes of RNFL thickness and ONH parameters [42].

5.2.1. SLP
SLP imaging dwells on the optical properties of the parallel bundled retinal nerve fibres. The size, intracellular arrangement, and the microtubule of the nerve fibres cause bifrigence of incident light, corresponding to the amount of birefringent tissue through which it passes. The projected polarized light is subject to reflected phase delay. This provides a means of estimation of the thickness of the RNFL tissue and region around the ONH. Measurements of the retinal birefringence can be mapped as estimated RNFL thickness based on a conversion from 0.67 nm of retardation equal to 1 μm of fiber [43].

5.2.2. CSLO
CSLO is a technique used primarily for topographic mapping of the retinal surface, particularly the ONH. This is estimated by measuring the distance between the reference plane and the surface along the contour line.

5.2.3. OCT
OCT operates on the principles of interferometry, in which a beam of light is directed into the retina, and the resulting back-scattered light travels an unknown distance to a detector, which is compared to a reference beam of known length, to calculate the echo time delay of light [44]. It is a non-invasive, non-contact, transpupillary imaging technique that provides micron-level resolution to depths of several millimeters without any ionizing radiation of cross sectional imaging of ocular tissues. The food and drug

administration's (FDA) approved three primary modalities of OCT are time domain (TD), spectral domain (SD) and swept source (SS). A brief comparison of the salient features of the three types of OCT, in terms of image acquisition, scanning speed, axial resolution, transverse resolution and range of imaging is demonstrated in Table 1 [45]. TD-OCT acquires 400 A-scans/s, so it can be used to collect no more than one to three circular OCT scans, with 256 A-scans/OCT at a time, otherwise movement artefacts make it too difficult to acquire accurate data. Its major challenge is limited speed, as data are collected pixel by pixel for each A- scan. SD-OCT allows faster scanning speed, approximately 25,000-55,000 A-scans/s. SD-OCT also provides reduced signal-to-noise ratio, 3D imaging capability and eye tracking. SD-OCT offers high and better axial resolution, approximately 5 μm, as well as the accuracy of glaucoma diagnosis progression analysis [46,47]. SS OCT identifies the deep retinal structure by its long-wave light source. Additionally, it deploys its advantage of wide scanning mode, with a scanning speed up to 100000 A-scans/s to obtain a large covering range, from the macula to the optic disc [48].

Table 1: Comparison of salient features of the three types of optical coherence tomography.
:

Type of OCT	Image acquisition	Scanning speed	Axial resolution	Transverse resolution	Range of imaging
Time domain	Superluminescent diode (810 nm) single photon detector, moving mirror	400 A-scans per second	10 μm	20 μm	Vitreoretinal interface to RPE
Spectral domain	Broadband superluminescent diode source (840 nm), array of detectors, fixed mirror	27,000-70,000 A-scans per second	5-7 μm	14-20 μm	Posterior cortical vitreous to sclera using EDI mode
Swept source	Swept-source tunable laser (1050 nm), single detector	100,000-400,000 A-scans per second	5 μm	20 μm	Posterior cortical vitreous to sclera (superior to SD OCT with EDI)

RPE: Retinal pigment epithelium, EDI: Enhanced-depth imaging, SD OCT: Spectral-domain OCT, OCT: Optical coherence tomography
Courtesy: Bhende M. et - al [45].

5.2.4. OCT Imaging in Glaucoma
In POAG, the loss of retinal ganglion cell axons is routinely diagnosed by the presence of thinning of the optic nerve neuroretinal rim, peripapillary RNFL and inner layers of the macula. These structural changes may precede perimetric visual field changes. OCT permits analysis of structural abnormalities in three anatomic locations in glaucoma: The ONH, circumpapillary (cp) RNFL, and macula with their individual layers [49].

(i) ONH
Advanced imaging and studies of the lamina cribrosa in vivo, point to this meshwork on the optic nerve head, as the principal site of glaucomatous damage to RGC axons [50]. 3D OCT may be useful in imaging the optic nerve and surrounding peripapillary area, post processing, and the creation of a virtual 3.4 mm circle. The 3D dataset provides precise placement around the centre of the optic nerve head by being resampled and segmented. This also allows more consistent placement over time, which produces more reproducible measurements, and may enable finer assessment of progressive RNFL thinning [51]. The ONH map is similar to the macular map, but is centered on the optic disc (Figure 2) [52]. It may be used to quantify ONH parameters like total diameter, the depth and diameter of the central cup, and the thickness of the neuroretinal rim [53].
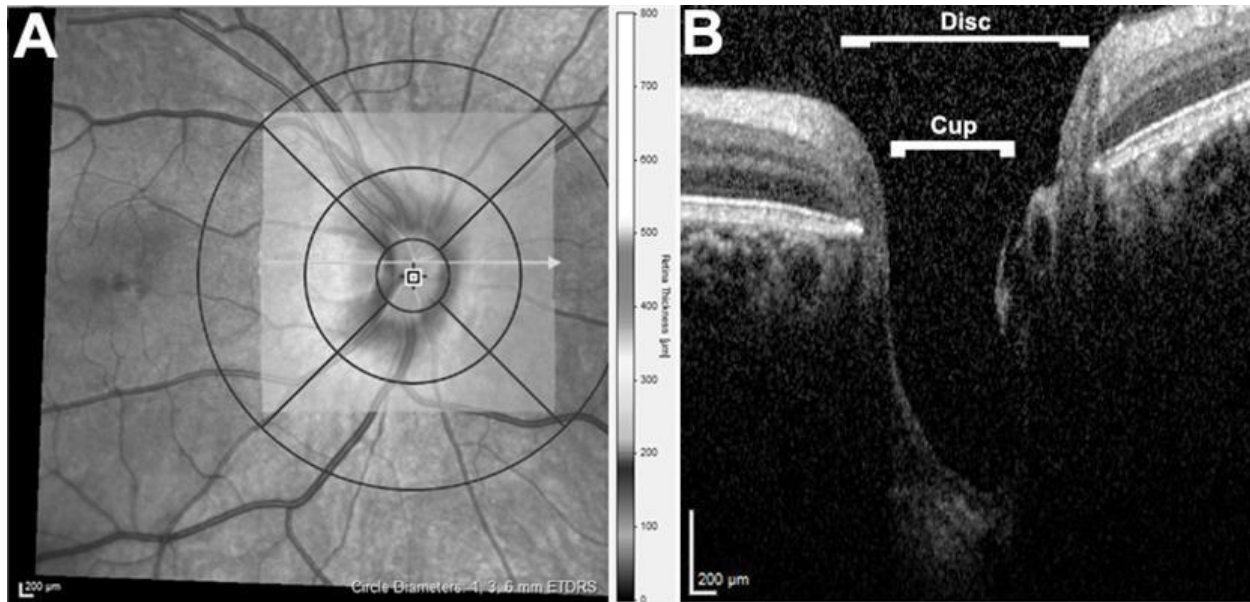
Figure 2.OCT of the optic nerve head (ONH).
(A) ONH map, with the thickness of neuroretinal tissue at each point depicted according to the scale bar to the right.
(B) Cross-sectional scan through the ONH. The border and contour of the ONH can be clearly assessed, as can the central cup. Courtesy: Gospe SM et-al [52].

(ii) (Cp) RNFL Imaging

The RNFL is the anterior-most layer of the retina, and one of the layers with the greatest reflectance (figure 3B), due to the structure of the fibres being perpendicular to the direction of the light beam. This allows for automatic segmentation and measurement by accurate computer algorithms [51]. Segmentation across the 3D data set can also provide a RNFL thickness map across the scanned area, measures thickness more directly with less confounding and fewer artefacts. RNFL analysis is performed by obtaining a circular scan at a diameter of 3.5 mm that is centered on the ONH (figure 3A). The axons of virtually all RGCs pass through this circular zone before converging at the ONH and will therefore be captured in this analysis. The scan is segmented, and the thickness of the peripapillary RNFL is measured along the circumference of the circle and reported by sector, along with the average RNFL thickness overall (figure 3B). RNFL thickness is quantified and plotted against the position along the peripapillary OCT scan (in degrees) (Figure 3C). These values are compared to a normative database to determine whether the overall peripapillary RNFL or particular sectors of it are thinner or thicker than those in a given percentage of the population (figure 3D). Focal RNFL thinning on OCT is known to correlate well with RNFL defects and neuroretinal rim thinning observed on ophthalmoscopy that are characteristic of glaucomatous damage [52,54].
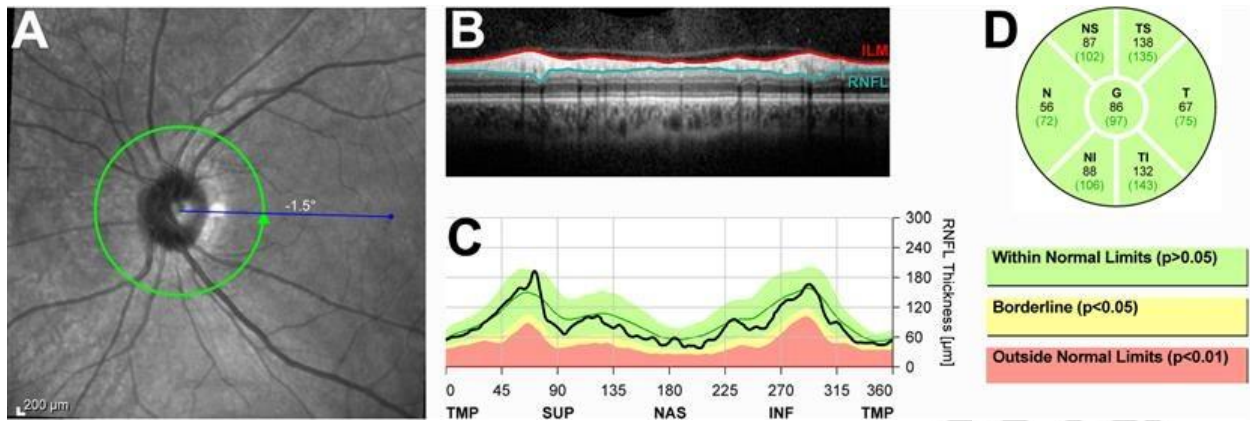
Figure 3: Normal OCT of the RNFL.

(A) RNFL thickness measured along the circumference of the 3.5 mm circle centered on the optic nerve head. **(B)** Circumferential OCT scan of the peripapillary retina along the circle depicted in (A). **(C)** Quantification of RNFL thickness plotted against the position along the peripapillary OCT scan (in degrees). **(D)** Quantification of peripapillary RNFL thickness by sector. Courtesy: Gospe SM et - al [52]

(iii) Macula Imaging
OCT measurements for macula analysis come either in the form of the combined ganglion cell and inner plexiform layers (GCIPL), or as the "ganglion cell complex" (GCC), which also includes the RNFL, since there is this difficulty distinguishing macula layers precisely. Currently, the combination of RNFL and ganglion cell analysis is generally considered the best approach to OCT-based glaucoma assessment [55]. The commonly used scan protocols for macular scanning in SD-OCT are: 3D scan, radial scan and raster scan [45]. The 3D macula cube scan is probably the most popular OCT scan protocol used. Covering the whole of the macula region, and typically consisting of over 30,000 A-scans, this scan gives high resolution view of all the retinal layers, while still being able to be captured in most commercially available equipment in just a couple of seconds, meaning patient comfort is maximised [56].

6.0 MANAGEMENT AND TREATMENT

The consequence of aggressive excavation of the optic disc, with RNFL and ONH damage, is irreversible blindness. Early detection and inter specialty referrals amongst physicians, optometrist and ophthalmologist in the management of POAG, are important. POAG is managed through counseling and education, anti glaucoma drugs or surgery.

6.1 Counselling and Education
Counseling and education convey explanations of realities and handling of the burden of specific ocular peculiarities associated with POAG to the patients. They create awareness and douse anxiety during the progression of the disease. Ccounselling touches on the visual expectations, needs, and referral to a low vision clinic, for assessment and acquisition of low vision aids and devices. It reassures patients on routine activities and meaningful living. Counseling guides consistency with prescription drugs, strict adherence to drug adjustments and the importance of regular follow-up visit [38]. However, education on the asymptomatic nature of POAG, its progression, the irreversible visual loss, the need for drug compliance is important [57].

6.2. Medical Intervention.

There are several treatment of glaucomatous optic neuropathy. Current management guidelines from the American Academy of Ophthalmology Preferred Practice Pattern, recommend lowering the IOP toward a target level, which is a value or range of values at which the clinician believes that the rate of disease progression will be slowed sufficiently to avoid functional impairment from the disease [58]. Anti-glaucoma agents depend on the aqueous humor dynamics, to reduce the intraocular pressure mainly by three mechanisms: Decrease aqueous production in the ciliary body, Increase aqueous humor outflow through the trabecular meshwork and via the uveoscleral pathway [59].

The classification of anti-glaucoma medications includes:

Alpa (α)-Adrenergic agonists: It decreases aqueous humor production and increases its elimination from the trabeculum, by reducing pressure in the episcleral veins, and increasing uveoscleral outflow [60].

Beta-adrenergic receptor antagonist: This reduces the production of aqueous humor by acting on the ciliary body, inhibiting beta 1 and beta 2 adrenergic receptors [61].

Prostaglandin Agonists: This pro-drug is activated by enzymatic hydrolysis in the cornea. The pharmacological response is mediated by prostanoid receptors. It increases the uveoscleral outflow of aqueous [62], by reducing the resistance to outflow through the uveoscleral pathway. It can also selectively mimic the effect of naturally occurring substance, prostamides.

Carbonic anhydrase inhibitors: This decreases the production of aqueous humor after corneal penetration, by inhibiting the enzyme carbonic anhydrase from the ciliary body, slowing local bicarbonate production and decreasing sodium and fluid transport. This in turn reduces the (IOP) [63].

Epinephrine: This class of drugs has a dual effect. It decreases the rate of aqueous humor production and increases the outflow of aqueous humor from the eye.

Combination of anti-glaucoma drugs: This is the combination of two anti-glaucoma agents with resultant effect on IOP.

6.3. Surgical Intervention.

When medical treatment does not achieve adequate IOP reduction, laser or incision surgeries are indicated. Laser trabeculoplasty lowers intraocular pressure by inducing biological changes in the trabecular meshwork, resulting in increased aqueous outflow while trabeculectomy is incisional surgical procedure [64].

7.0 IDENTIFICATION OF RESEARCH INSIGHT, EXISTING GAPS AND POSSIBLE FUTURE RESEARCH DIRECTIONS.

7.1. Current Advances in OCT imaging technology

SD-OCT raster scans places the circle in any location within the cube of data, because local wedge defect could occur outside of this location of the 3.4mm circle. One technique used for the 3D cube of data is summing adjacent pixel into superpixel, for comparison with normative superpixel data, highlighting regions of decrease RNFL thickness [65]. SS-OCT is a fourier domain OCT capable of scanning at a high speed, using tunable laser and single photodetector instead of CCD camera. It has shown the ability to produce promising image of deep structures of the posterior segment, such as the lamina cribrosa [66].

7.1.1. Future research directions in OCT imaging technology.

Further research to enhance the superpixel algorithms to maximize the sensitivity and specificity of 3D cube of data, to detect glaucomatous damage and monitor change, is on-going [67]. A research, focused on developing automatic segmentation algorithms in SD-OCT image analysis is ongoing. It will aid the visualization and quantification of the thickness of individual layers of microstructure of the retinal nerve fiber, retinal ganglion cell, plexiform, nuclear, and photoreceptor layers [68]. Current research is focused

on exploring OCT imaging at wavelengths of 1000 to 1100 nm to achieve deeper imaging capabilities, which allows penetration below retinal pigment epithelium [69].

7.2.0. Current Advances and innovations in Ppharmacotherapy(pharmacotherapy)

Neuroprotection of retinal ganglion cell is achieved by combining anti-hypertensive agents with drugs that directly protect the optic nerve from a variety of insults, through promoting cell survival and inhibition of neuronal signals that initiate apoptosis [20].

Nanomedicine advancements have been used to overcome obstacles of the blood-ocular barrier and low permeability of ophthalmic tissues leading to more effective and convenient treatment of ophthalmic diseases. Polycaprolactone (PCL) thin films are often used in intraocular drug delivery applications and it has been demonstrated that they are safe, structurally stable and well tolerated [70].

Rho kinase inhibitors (ROCK INHIBITORS) modulate cellular motility of the trabecular meshwork, schlemm's canal and ciliary muscle, thereby enhancing aqueous drainage. The ROCK inhibitors also modulate small interfering RNA, cytoskeleton agents, cannabinoids, adenosine/serotonin/dopamine receptor ligands, nitricoxide/carbon monoxide system modulators, and hydroxysteroid dehydrogenase inhibitors [71].

7.2.1. Future research directions in Pharmacotherapy

Elevated IOP can cause T cells to infiltrate the eye, and attack neurons. It leads to vision loss by setting into motion an autoimmune response that attacks the neurons in the eye, similar to immune responses triggered by bacterial infections. Current glaucoma therapies are designed solely to lower eye pressure; however, we've known that, even when patients with glaucoma are treated and their eye pressure returns to normal they can still go on to have vision loss. These findings open the door for targeting T cells in the eye as a treatment to halt the progression of vision loss in glaucoma [24].

Neuroenhancement is the concept of supporting injured RGCs and enhancing their function before they die. One promising potential therapy is an implant that provides sustained delivery of ciliary neurotrophic factor (CNTF), a growth factor known to promote the growth and survival of nerve cells. This concept is being considered for future glaucoma therapy I[72]. Further research on the development of possible drugs delivered slowly in biodegradable form through sub-conjunctival injection near the cornea, potentially providing pressure reduction for up to 3–6 month [73].

The genetic dimensions with the associated gene approaches play a good role in future research into glaucoma treatments. Identifying the molecules and genes activated in sick RGCs, ultimately provides an integrated understanding of RGCs death in glaucoma that will identify key targets for genetic therapy. These approaches include: (a) Candidate gene approach, where the researchers make a list of candidate genes that might cause glaucoma when normal functions were altered and then test a large group of unrelated glaucoma patients for defects in these candidate genes. (b) The linkage analysis approach to genetic causes, studies large families with several members having glaucoma, with their glaucoma-causing genes identified. The deoxyribonucleic acid (DNA) located within the linked regions of those segments of the DNA is always passed down through the family, along with glaucoma. (c) Modifier gene studies seek to identify genes that can be manipulated to increase RGC survival, which is critical due to their connections between the eye and the brain [73]. In the near future, if the sensitivity and specificity of genotyping increase and its cost decreases, it may become possible to screen individuals routinely for disease susceptibility, since growth arrest-specific proteins 7 (GAS7) and transmembrane and coiled – coil domains 1 (TMCO1) genes functionally interact with known glaucoma disease genes. They are highly expressed in the ciliary body and trabecular meshwork as well as in the lamina cribrosa, optic nerve and retina [74]. In transgenic, using mouse models to induce elevated IOP and possible development of glaucoma, the transforming growth factor-beta 2 (TGF-b2) and the connective tissue growth factor (CTGF) models can provide exciting new opportunities to study and understand the pathogenesis of

POAG. TGF-b2 levels are elevated in AH in greater than 50% of POAG patients [75]. On the other hand however, aged, overexpressing mutated optineurin mutation–carrying mice show distinct glaucomatous changes in the retina without an increase in IOP [76]. The optineurin transgenic mouse could therefore, be an important model to study normal-tension glaucoma and compare the associated molecular and cellular changes between normal and elevated mouse models of IOP. New drug targets, which can help regulate outflow pathway by restructuring already existing mechanisms in a way that is therapeutically useful can be identified [77].

A large number of studies involving multipotent meshenchymal stem cells (MSC) have demonstrated their ability to induce regeneration of damaged tissues and organs. The purpose of this project is to evaluate the ability of MSCs to induce regeneration of the trabecular meshwork and to assess their ability to lower IOP in open angle glaucoma. The impressive regenerative effects of MSC, along with their apparent lack of differentiation and their rapid clearance out of the anterior chamber implies a mechanism of action linked to secreted factors. This could represent a novel and promising approach in the management of open angle glaucoma [78].

7.2.3. New Paradigms in research
There is a paradigm shift in glaucoma treatment from applying therapy directly on RGC and ONH to targeting associated brain centers. Research has shown that glaucomatous nerve damage in the eye may spread to major visual centers of the brain. This is associated with well known process in other neurodegenerative diseases. When the damage spreads, nerve cells in the brain related to visual function begin to shrink and die. Treatments could be targeted at these brain centers. Recent research suggests that cells in the retina other than RGCs are equally affected or equally contribute to the rate of decline of the ganglion cells. This suggests looking at the occurrence of neurodegeneration in a new light, with research underway to identify connections in the brain, and how these connections may be strengthened [73].

Researchers no longer view glaucoma as an eye disease but rather a neurologic disorder that causes nerve cells to degenerate and die, much like in Parkinson's and Alzheimer's diseases. Focusing on the mechanisms that cause the degeneration of RGCs which connect the eye to the brain through the optic nerve, researchers are seeking ways to protect, enhance, and even regenerate ganglion cells. Many treatments that target retinal ganglion cells are now in clinical trials, including Injecting medications into the eye to deliver survival and growth factors to ganglion cells, administering medications known to be useful for stroke and Alzheimer's, such as cytidine-5-diphosphocholine and delivering electrical stimulation to RGCs via tiny electrodes implanted in contact lenses or other external devices [73].

Stem cell therapy trials are also currently in the planning stages. In-depth exploration of RGCs also has the potential to identify factors, such as genetics and why some people are more vulnerable to glaucoma. It has been recently shown that manipulating a gene in the supporting cell around the neurons involved in Parkinson's disease can dramatically slow down the progression of the disease. Not only is the same pathway prevalent in glaucoma, but it is activated very early in the progression of the disease. Researchers are exploring whether the same molecular pathway leads to degeneration in multiple neurodegenerative diseases [73].

8.0 DISCUSSION

The pathogenesis, of POAG was attributed to IOP build up due to an imbalance in the production and drainage of the aqueous humor by the ciliary body and the trabecular meshwork respectively. It affected the nerve fibers of the optic nerve, with apparently reduced blood supply, deprived oxygen and nutrients, with resultant optic nerve damage and vision loss. However there were varying opinions of researchers on the possible mechanisms of POAG like the pressure theory in ocular hypertension, vascular circulatory

dysfunction, and pathogenic theory etc. Glaucomatous damage is as a result of pressure on RGC, followed by ischemia, hypoxia of the ONH, with death due to glutamate-induced excitotoxicity [23]. There were other mechanisms like genetic theory, heat shock protein, pathogenic mechanisms and immune-mediated nerve damage [22]. Theories of IOP independent mechanisms of glaucomatous nerve damage included ischemia, loss of neurotrophic factors, neurotoxicity, and failure of cellular repair mechanisms [22] [19]. In patients with normal IOP but with glaucomatous optic neuropathy, the findings were due to an abnormally low cerebrospinal fluid pressure in the optic nerve subarachnoid space which resulted in a large pressure gradient across the lamina [25,26]. POAG manifests appreciable loss of central vision after the appearance of field defects, which represents a relatively late stage of disease. Visual field defects may not be apparent until over 40% of the optic nerve fiber layer had been lost [19. The diagnosis and follow-up of the disease has shifted from subjective techniques, to one measured quantitatively and objectively [4]. These techniques include: SLP which uses polarized light to measure the RNFL birefringence, which estimates tissue thickness. CSLO uses a technique primarily for topographic mapping of the retinal surface, particularly, the ONH. It also provided an estimation of RNFL thickness around the ONH. This was estimated by measuring the distance between the reference plane and the surface along the contour line. OCT is a non-invasive, imaging technique that uses low coherence light to create high-resolution tomographic images of the retina. The backscattered light measures the tissue thickness of the retinal layers and intraretinal structures. It uses Segmentation algorithms to measure the thickness of the retinal nerve fiber layer directly from the images [4]. Reliable diagnostic approach aids therapy of POAG. Researchers agreed that the therapeutic aim of anti POAG drug was the modification of IOP. Future research directions in pharmacotherapy involve exploring genetic model, neurodegeneration, meshenchymal stem cells etc.

9.0 CONCLUSION

The imbalance between the production and the drainage of aqueous humor is associated with the positive correlation of aqueous build-up, and increased IOP. This pressure on the RGC, results to ischemia and hypoxia of the ONH, with death due to glutamate-induced excitotoxicity. The events lead to blockage of anterograde and retrograde axonal transport with ensuing axotomy, retinal ganglion cell death and optic nerve fiber loss, with characteristic changes in their appearance. The loss of retinal ganglion cell axons is routinely diagnosed by the presence of thinning of the optic nerve neuroretinal rim, peripapillary retinal nerve fiber layer (RNFL), and/or inner layers of the macula, preceding perimetric visual field changes and eventual blindness. Quantitative and applicable objective evaluation of RNFL thickness and ONH parameters associated with structural changes using high-resolution sensitive imaging, could enhance detection of early glaucoma, and allowed timely intervention to prevent vision loss. There are future research directions on high precision modern diagnostic equipments and novel therapeutic research in the areas of neuroenhancement, neurodegeneration, stem cell technology, and genetic model, so that a permanent cure of glaucoma will be achieved.

REFERENCES

1. Vaughan, D. Asbury, T. General Ophthalmology.17th Edition. LANGE. 2010.

2. Quigley HA. Glaucoma. Lancet Lond Engl. 2011;377:1367–1377. https://doi.org/10.1016/S01406736(10)61423-7.

3. Bell JA. Glaucoma, Primary Open Angle, eMedicine, Nov 2008

4. Townsend KA, Wollstein G, Schuman JS. Imaging of the retinal nerve fibre layer for glaucoma. Br J Ophthalmol. 2009;93(2):139–143. doi:10.1136/bjo.2008.145540.

5. Resnikoff S, et al. Global data on visual impairment in the year 2002. Bull World Health Organ. 2004;82:844-851.

6. Biggerstaff KS. Primary Open-Angle Glaucoma (POAG). Practice Essentials. Drugs & Diseases > Ophthalmology. 2018.

7. Bell JA. Primary Open-Angle Glaucoma Medscape Reference. Drugs, Diseases and procedures. 2012.

8.Jocson VL, Sears ML. Experimental aqueous perfusion in enucleated human eyes. Results after obstruction of Schlemm's canal. Arch Ophthalmol. 1971;86(1):65–71.

9. Weinreb RN, Khaw PT. Primary open-angle glaucoma. Lancet. 2004;363:1711-20.

10. Adatia FA, Damji KF. Chronic open-angle glaucoma. Review for primary care physicians. Pub Med Central, CFP.MFC. Can Fam Physician. 2005;10;51(9):1229–1237. PMC1479464

11. Kwon YH, Fingert JH, Kuehn MH, Alward WLM. Primary open-angle glaucoma. N Engl J Med . 2009;12; 360:1113-24.

12. Schacknow P, Samples J. The Glaucoma Book: A Practical, Evidence-Based Approach to Patient Care. New York, NY: Springer; 2010:399-420.

13. Hollands H, Johnson D, Hollands S, et al. Do findings on routine examination identify patients at risk for primary open-angle glaucoma? The rational clinical examination systematic review.JAMA. 2013;309(19):2035-42.

14. Alward WLM. Glaucoma: the requisites in ophthalmology. Krachmer JH (Ed.). St. Louis: Mosby, 2000:128-40.

15. Heiting G. Haddrill M. Primary Open-Angle Glaucoma. All About Vision

16. Weinreb RN, Khaw PT. Primary open angle glaucoma. Lancet. 2004;363(9422):1711-1720

17. Weinreb RN, Aung T, Medeiros FA. The Pathophysiology and Treatment of Glaucoma: A Review.JAMA. 2014;311(18):1901–1911.

18. Bill A, Phillips CI. Uveoscleral drainage of aqueous humour in human eyes. Exp Eye Res. 1971;12(3):275–281.

19. Kanski J. Clinical Ophthalmology, A Systematic Approach, 5th ed. Butterworth Heinemann (2003).

20. Tătaru CP, Purcărea VL. Antiglaucoma pharmacotherapy. J Med Life. 2012;15;5(3):247–251. PMCID: PMC346499. PMID: 23049625.

21. Stamper R, Lieberman M, Drake M. Becker-Shaffer's Diagnosis and Therapy of the Glaucomas.8th Edition. New York, NY: Mosby; 2009:239-265.

22. Kristin SchmidBiggerstaff, IncilrakDersu. Primary Open-Angle Glaucoma (POAG). Medscape Oct 23, 2018

23. Evangelho K, Mogilevskaya M, Losada-Barragan M, Vargas-Sanchez JK. Int Ophthalmol. 2017 doi: 10.1007/s10792-017-0795-9. [Epub ahead of print]

24. Day S, Chen J, Chen H, Cho KS, Khanh-Vu TH. New Understanding of Glaucoma. Autoimmune response spurs vision loss. News and Research. Harvard Medical School. August 17, 2018.

25**.** Wang N, Xie X, Yang D, et al. Orbital cerebrospinal fluid space in glaucoma: the Beijing Intracranial and Intraocular Pressure (iCOP) study. Ophthalmology. 2012;119(10):2065e1–2073e1. [PubMed].

26. Ren R, Jonas JB, Tian G, et al. Cerebrospinal fluid pressure in glaucoma: a prospective study. Ophthalmology.2010;117(2):259–266. [PubMed]

27**.** Almasieh M, Wilson AM, Morquette B, Cueva Vargas JL, Di Polo A. The molecular basis of retinal ganglion cell death in glaucoma.ProgRetin Eye Res.2012;31(2):152–181. [PubMed]

28. Hollwich F. (1985) Ophthalmology: A short Textbook.2nd Revised Edition. New York. Thieme-Stratton Inc.

29. Glaucomatous changes of the optic nerve head viewed by ophthalmoscopy. Pub Med Central, Table 1. CFP.MFC. Can Fam Physician. 2005;10;51(9):1229–1237.

30. Kass MA, Gordon MO, Gao F, et al; Delaying treatment of ocular hypertension: the ocular hypertension treatment. Arch Ophthalmol. 2010;128(3):276-87.

31. Sommer A, Tielsch JM, Katz J, Quigley HA, Gottsch JD, Javit J, Singh K. Relationship between intraocular pressure and primary open-angle glaucoma among white and black Americans. The Baltimore Eye Survey. Arch Ophthalmol. 1991;109(8):1090–1095.[PubMed]

32. Tielsch JM, Sommer A, Katz J, Royall RM, Quigley HA, Javitt J. Racial variations in the prevalence of primary open-angle glaucoma. The Baltimore Eye Survey. JAMA.1991;266:369–374. [PubMed]

33. Tielsch JM., Sommer A., Katz J., Royall RM., Quigley HA. Javitt J. Racial variations in the prevalence of primary open-angle glaucoma. The Baltimore Eye Survey. JAMA.1991;266(3):369–374. doi: 10.1001/jama.1991.03470030069026.[PubMed] [CrossRef]

34. African Americans and Glaucoma. Glaucoma research foundation. www.glaucoma .org

35. Leibowitz HM, Krueger DE, Maunder LR. The Framingham Eye Study monograph: An ophthalmological and epidemiological study of cataract, glaucoma, diabetic retinopathy, macular degeneration, and visual acuity in a general population of 2631 adults, 1973–1975. Surv Ophthalmol. 1980;24(Suppl):335–610. [PubMed].

36. Wong TY, Klein BE, Klein R, Knudtson M, Lee KE. Refractive errors, intraocular pressure, and glaucoma in a white population. Ophthalmology. 2003;110(1):211–217. [PubMed]

37 Are you at risk for glaucoma? Glaucoma research foundation. www.glaucoma .org

38. Umezurike BC, Udeala O, Green UG, Okpechi-Agbo U, Ohaeri MU. The Pathogenesis of index myopia in hyperglycemia in type two diabetes : A Review. Ophthlmology Research: An international journal. 2018;9(2):1-17.

39. Minwen Z, Wei W, Wenbin H, Xiulan Z. Diabetes Mellitus as a Risk Factor for Open-Angle Glaucoma: A Systematic Review and Meta-Analysis. PLoS One. 2014; 9(8): e102972. Published online 2014 Aug 19. doi: 10.1371/journal.pone.0102972. PMCID: PMC4138056.

40. Centers for Disease Control and Prevention.National Diabetes Fact Sheet.United States; 2005.Available:http://www.cdc.gov/diabetes/pubs/general.htm (Assessed 14 November 2017)

41. Langman, M J S; R J Lancashire, K K Cheng, P M Stewart (2005). "Systemic hypertension and glaucoma: mechanisms in common and co-occurrence". British Journal of Ophthalmology 89 (8): 960–3. DOI:10.1136/bjo.2004.053397. PMC 1772770.PMID 16024843.

42. Kuang TM, Zhang C, Zangwill LM, et al. Estimating lead time gained by optical coherence tomography in detecting glaucoma before development of visual field defects. Ophthalmology. 2015;122(10):2002-2009.

43. Weinreb RN, Shakiba S, Zangwill L. Scanning laser polarimetry to measure the nerve fiber layer of normal and glaucomatous eyes. Am J Ophthalmol 1995;119:627 – 636.

44. Wojtkowski M, Srinivasan V, Fujimoto JG, et al. Three dimensional retinal imaging with high-speed ultra high-resolution optical coherence tomography . Ophthalmology. 2005;112:1734-46.

45. Bhende M, Shetty S, Parthasarathy MK, Ramya S. optical coherence tomography: A guide to interpretation of common macular diseases. Indian J Ophthal. 2018;66(1):20-23. PMCID: PMC5778576. PMID: 29283118

46. Drexler W, Fujimoto JG. State-of-the-art retinal optical coherence tomography. ProgRetin Eye Res. 2008;27:45–88. [PubMed: 18036865]

47. Leung CK, Cheung CY, Weinreb RN, et al. Evaluation of retinal nerve fiber layer progression in glaucoma: a study on optical coherence tomography guided progression analysis. Invest Ophthalmol Vis Sci. 2010;51:217-222.

48. Lee SY, Kwon HJ, Bae HW, Seo SJ, Lee YH, Hong S, et al. Frequency, type and cause of artefacts in swept-source and cirrus HD optical coherence tomography in cases of glaucoma and suspected glaucoma. Curr Eye Res 2016;41:957-64.

49. Ojima T, Tanabe T, Hangai M. Measurement of retinal nerve fiber layer thickness and macular volume for glaucoma detection using Optical Coherence Tomography. Jpn J Ophthalmol. 2007;51:197–203. [CrossRef]

50. Quigley HA, Addicks EM, Green WR, Maumenee AE. Optic nerve damage in human glaucoma, II: the site of injury and susceptibility to damage. Arch Ophthalmol. 1981;99:635-649.

51. Ishikawa H, Piette S, Liebmann JM, et al. Detecting the inner and outer borders of the retinal nerve fiber layer using optical coherence tomography. Graefes Arch Clin Exp Ophthalmol 2002;240:362–371. [PubMed: 12073059]

52. Gospe SM, Bhatti MT, El-Dairi MA. Optical Coherence Tomography in Pediatric Optic Neuropathies. American Academy of Ophthalmology Jan 18, 2017.

53. Marsh BC, Cantor LB, WuDunn D, et al. Optic nerve head (ONH) topographic analysis by stratus OCT in normal subjects: correlation to disc size, age and ethnicity. J Glaucoma. 2010;19(5):310-318.

54. Mrugacz M, Bakunowicz-Lazarczyk A. Optical coherence tomography measurement of the retinal nerve fiber layer in normal and juvenile glaucomatous eyes.Ophthalmologica . 2005;219(2):80-85.

55. Arvanitaki V, Tsilimbaris MK, Pallikaris A, et al. Macular retinal and nerve fiber layer thickness in early glaucoma: clinical correlations. Middle East Afr J Ophthalmol 2012;19:204–10.

56. Huang J, Liu X, Wu Z, *et al*. Macular thickness measurements in normal eyes with time-domain and Fourier-domain optical coherence tomography. *Retina*, 2009;29:980-987.

57. Glaucoma NICE Clinical Guideline (April 2009); Glaucoma: diagnosis and management of chronic open angle glaucoma and ocular hypertension

58. American Academy of Ophthalmology Preferred Practice Patterns Committee GP. Ophthalmology. Chicago, Illinois: American Academy of Ophtalmology; 2010. Preferred practice pattern: primary open-angle glaucoma.

59. Rohit S, Jai P, Priya M, Suresh KG. Pharmacotherapy of glaucoma. Indian Journal of Pharmacology 2002;34:71-85.

60. Novack GD. New glaucoma medications in the geriatric population: Efficacy and safety. J Am Geriatr Soc. 2002;50:956–962. [PubMed].

61. Zimmerman TJ. Topical ophthalmic beta blockers: A comparative review. J OculPharmacol. 1993;9:373–384. [PubMed].

62. Wistrand PJ. The incidence and time-course of latanoprost-induced iridial pigmentation as a function of eye color. SurvOphthalmol. 1997;41:S129–S138. [PubMed]

63. Silver LH. Clinical efficacy and safety of brinzolamide (Azopt): A new topical carbonic anhydrase inhibitor for primary open-angle glaucoma and ocular hypertension. Am J Ophthalmol. 1998;126:400–408. [PubMed].

64. Odberg T, Sandvik L. The medium and long-term efficacy of primary argon laser trabeculoplasty in avoiding topical medication in open angle glaucoma. ActaOphthalmol Scand. 1999;77(2):176–181.[PubMed]

65. Xu J, Ishikawa H, Wollstein G, Schuman JS. 3D optical coherence tomography super pixel with machine classifier analysis for glaucoma detection. ConfProc IEEE Eng Med BiolSoc 2011;2011:3395–8.

66. Srinivasan VJ, Adler DC, Chen Y, Gorczynska I, Huber R, Duker JS, Schuman JS, Fujimoto JG. Ultrahigh-speed optical coherence tomography for three-dimensional and en face imaging of the retina and optic nerve head. Invest Ophthalmol Vis Sci. 2008;49:5103–5110.

67. Folio SL, Wollstein G, Schuman JS. Optical Coherence tomography: Future trends for imaging in glaucoma. Optometry and vision science. 2012;89:5.

68. ishikawa H, Stein DM, Wollstein G, Beaton S, Fujimoto JG, Schuman JS. Macular segmentation with optical coherence tomography. Invest Ophthalmol Vis Sci 2005;46:2012-7.

69. Povazay B, Hermann B, Unterhuber A, Hofer B, Sattmann H, Zeiler F, Morgan JE, Falkner-Radler C, Glittenberg C, Blinder S, Drexler W. Three-dimensional optical coherence tomography at 1050 nm versus 800 nm in retinal pathologies: enhanced performance and choroidal penetration in cataract patients. J Biomed Opt 2007;12:041-211.

70. Huang SF, Chen JL, Yeh MK, Chiang CH. Physicochemical properties and in vivo assessment of timolol-loaded poly(D,Llactide-co-glycolide) films for long-term intraocular pressure lowering effects. J Ocul Pharmacol Ther. 2005;21(6):445-53.

71. Bucolo C, Salomone S, Drago F ,et al. Pharmacological management of ocular hypertension: Current approaches and future prospective. Curr Opin Pharmacol.2013;13(1):50–55.

72. Tony Realini. GLAUCOMA: How will glaucoma treatment change into the future? Eye World July 2015 coherence tomography for imaging the living retina. Opt Express 2005;13:4792–811.

73. Stuart Carduner. Patient's Guide to Living with Glaucoma. VisionAware 2019

74. Bettin P, Di Matteo F. Glaucoma: Present Challenges and Future Trends. Ophthalmic Res 2013;50:197208. https://doi.org/10.1159/000348736

75. Picht G, Welge-Luessen U, Grehn F, Lutjen-Drecoll E. Transforming growth factor beta 2 levels in the aqueous humor in different types of glaucoma and the relation to filtering bleb development. Graefes Arch Clin Exp Ophthalmol. 2001;239:199–207.

76. Chi ZL, Akahori M, Obazawa M, et al. Overexpression of optineurin E50K disrupts Rab8 interaction and leads to a progressive retinal degeneration in mice. Hum Mol Genet. 2010;19:2606–2615.

77. Citation: Roy Chowdhury U, Hann CR, Stamer WD, Fautsch MP. Aqueous humor outflow: dynamics and disease. Invest Ophthalmol Vis Sci. 2015;56:2993–3003. DOI:10.1167/iovs.15-16744

78. Renaud Manuguerra ; Denis-Claude Roy ; Mark Lesk. Cellular Therapy For Open Angle Glaucoma: Mechanism Of Tissue Regeneration By Mesenchymal Stem Cells. Investigative Ophthalmology & Visual Science March 2012;53:3635.