



HANDBOOK OF

Clinical Insights into Glaucoma Management



Editors

Shibal Bhartiya | Maneesh Singh

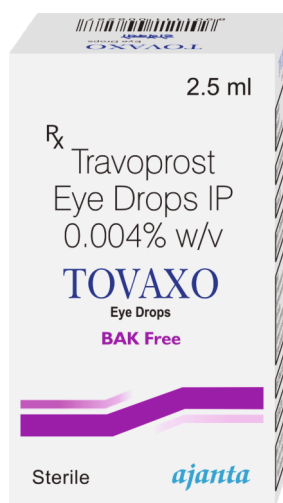
In POAG & Ocular Hypertension

Rx TOVAXO

Travoprost 0.004 % w/v Eye Drops

Most trusted 1st line therapy

Better improvement in OSDI scores
with Travoprost BAK Free



Clinical Insights into **Glaucoma Management**

Editors

Shibal Bhartiya

Additional Director,
Glaucoma Services,
Fortis Memorial Research Institute,
Gurugram, Haryana, India.

Maneesh Singh

Senior Consultant and Director,
Netralayam -The Superspeciality,
Eye Care Centre,
Kolkata, West Bengal, India

**Publishers Address:**

United Scientific Solutions
Office No.-8, 1st Floor, Block A4,
Pocket -6, Sector-35, Rohini, Delhi-110042
DELHI, INDIA
e-mail: info@ussolutions.in

The views and opinions expressed in this book are solely those of the original contributor(s)/author(s) and do not necessarily represent those of editor(s) of the book.

All rights reserved. No part of this publication may be reproduced, stored or transmitted in any form or by any means, electronic, mechanical, photocopying, recording or otherwise, without the prior permission in writing of the publishers.

All brand names and product names used in this book are trade names, service marks, trademarks or registered trademarks of their respective owners. The publisher is not associated with any product or vendor mentioned in this book.

Medical knowledge and practice change constantly. This book is designed to provide accurate, authoritative information about the subject matter in question. However, readers are advised to check the most current information available on procedures included and check information from the manufacturer of each product to be administered, to verify the recommended dose, formula, method and duration of administration, adverse effects and contraindications. It is the responsibility of the practitioner to take all appropriate safety precautions. Neither the publisher nor the author(s)/editor(s) assume any liability for any injury and/or damage to persons or property arising from or related to use of material in this book.

This book is sold on the understanding that the publisher is not engaged in providing professional medical services. If such advice or services are required, the services of a competent medical professional should be sought.

Every effort has been made where necessary to contact holders of copyright to obtain permission to reproduce copyright material. If any have been inadvertently overlooked, the publisher will be pleased to make the necessary arrangements at the first opportunity. Inquiries may be solicited at:
info@ussolutions.in Clinical Insights Into Glaucoma Management

First Edition: 2024

ISBN: 978-81-967083-0-6

Printed at: Shruti Print Solutions

Copyright © United Scientific Solutions

◆ Contributors

AJEET KUMAR DWIVEDI MS (OPHTHALMOLOGY), FCGP

Senior Glaucoma Consultant
Phaco LASIK and Oculoplastic Surgeon, Medical Director
Sharda Eye Dental Hospital, Patna, India



ALOKESH GANGULY MBBS.DO. DNB. MS. FICO

Consultant Glaucoma Services.
Priyamvada Birla Aravind Eye Hospital.
Kolkata. India

ARNAV PANIGRAHI

Department of Ophthalmology, RPC
All India Institute of Medical Sciences, New Delhi



ARUP CHAKRABARTI

Senior Consultant, Cataract and glaucoma services,
Chakrabarti Eye Care Centre, Trivandrum-695030
Kerala, India



MANJU R PILLAI

Medical Consultant, Glaucoma Services
Aravind Eye Care System
Madurai, India

PARUL ICHHPUJANI

Professor, Department of Ophthalmology
Government Medical College and Hospital Chandigarh, India



PRASANNA VENKATESH RAMESH

DNB, MNAMS, FAICO (Glaucoma), FICO (Glaucoma)

Glaucoma Consultant & Research Director Mahathma Eye
Hospital Private Limited, Trichy, Tamil Nadu, (India)



PURVI BHAGAT MBBS, D.O., M.S., FAIMER (CMCL)

Professor & Head of Glaucoma Clinic
M & J Western Regional Institute of Ophthalmology
Ahmedabad, Gujarat, India.



SACHIN DHARWADKAR D.O (Gold medal), D.N.B, F.R.C.S (Glasgow)

Consultant Glaucoma Surgeon, PD Hinduja Hospital and
Medical Research Centre, Mahim, Mumbai
Director, Samartha Specialty Clinics, Mumbai



SHWETA TRIPATHI DNB MNAMS FMRF

Senior Consultant Glaucoma Services
HOD Dept of Medical Education
Indira Gandhi Eye Hospital and Research Centre
Lucknow, Uttar Pradesh, India

SURAJIT SEN MBBS DO DNB FMRF FAICO MNAMS FACS (USA)

Consultant, Cataract Glaucoma and Refractive surgeon
Netralayam Superspeciality Eye Care Centre
Kolkata, India



TRUPTI SUDHIR PATIL

Senior glaucoma consultant,
Sankara Nethralaya,
Chennai, India

FOREWORD

The “Clinical Insights into Glaucoma Management” hopes to be an indispensable guide for glaucoma practitioners, eye doctors, and residents in training, as we negotiate the dynamic world of clinical practice. This collaborative compendium transcends the boundaries of conventional knowledge, offering a nuanced exploration of the intricacies surrounding glaucoma diagnosis, management, and innovative treatment modalities.

Written by esteemed experts in the field, each chapter is a testament to their collective commitment to advancing the understanding and practice of glaucoma management. From the fundamentals to the latest breakthroughs, this book serves as a compass, directing clinicians towards evidence-based approaches and best practices.

The amalgamation of clinical insights, research findings, and practical wisdom makes this handbook an invaluable resource.

It not only encapsulates the current state of glaucoma care but also anticipates future developments, empowering practitioners to stay at the forefront of their discipline.

In the spirit of collaboration and knowledge-sharing, this handbook is more than a reference – it is a companion for every glaucoma practitioner dedicated to enhancing the sight and quality of life for their patients.

May this volume be a source of inspiration, fostering a community of professionals committed to the relentless pursuit of excellence in glaucoma care.

Shibal Bhartiya

Maneesh Singh

Arijit Mitra

Dedication

To the practitioners, eye doctors, and residents in training who embrace the challenges of glaucoma management with passion and dedication, this dedication is a recognition of your unwavering commitment. May this Clinical Insights handbook serve as a companion in your pursuit of knowledge, a guide in your clinical endeavors, and a source of inspiration as you contribute to the betterment of eye care.

It not only encapsulates the current state of glaucoma care but also anticipates future developments, empowering practitioners to stay at the forefront of their discipline.

In the spirit of collaboration and knowledge-sharing, this handbook is more than a reference – it is a companion for every glaucoma practitioner dedicated to enhancing the sight and quality of life for their patients.

May this volume be a source of inspiration, fostering a community of professionals committed to the relentless pursuit of excellence in glaucoma care.

Shibal Bhartiya

Maneesh Singh

Arijit Mitra

CONTENTS

Chapter 1

Clinical Evaluation of a Glaucoma Patient 1

SHWETA TRIPATHI, M. SRINIVASAN

Chapter 2

Evaluation of the Optic Nerve Head 9

PARUL ICHHPUJANI, SURBHI KAPOOR

Chapter 3

Visual Field Analysis and Assessing Progression on Visual Fields 22

MANJU PILLAI, MAGHALAKSHMI UDHAYAKUMAR NAIDU

Chapter 4

Gonioscopy: The Basics 34

ARNAV PANIGRAHI, VINEY GUPTA, SHIKHA GUPTA

Chapter 5

Primary Open-Angle Glaucoma 41

PURVI BHAGAT, MARGI PANCHAL

Chapter 6

Ocular Hypertension 53

ALOKESH GANGULY

Chapter 7

Normal Tension Glaucoma 61

SACHIN DHARWADKAR

Chapter 8

Medical Management of Glaucoma

66

TRUPTI S PATIL

Chapter 9

Rho Kinase inhibitors in Glaucoma

76

SURAJIT SEN, ASIM GHOSH

Chapter 10

Management of coexisting Cataract and Glaucoma

83

ARUP CHAKRABARTI, NIRUPAMA KASTURI, SUBASHINI KALIAPERUMAL

Chapter 11

Drug Induced Glaucoma

92

AJEET KUMAR DWIVEDI

Chapter 12

The Role of Artificial Intelligence in Glaucoma: A Promising Pathway for Early Diagnosis and Management

105

PRASANNA VENKATESH RAMESH

CHAPTER

1

Clinical Evaluation of a Glaucoma Patient

Shweta Tripathi, M. Srinivasan

Summary (Key Points)

- Work up for Glaucoma patient needs a step by step approach.
- History taking is an art and reveals key cues to the diagnosis.
- Each component in diagnostic armamentarium needs appropriate skill acquisition for precise diagnosis.

Introduction

After cataract, glaucoma is the second most common cause of blindness worldwide. Glaucoma is becoming more common worldwide and is predicted to impact 111.8 million individuals by 2040.^[1] According to reports, Asia and Africa have the greatest rates of open-angle glaucoma and narrow-angle glaucoma, respectively. A thorough meta-analysis determined that 3.54% of people worldwide have glaucoma.^[2] About 47% of people with glaucoma and 87% of those with angle-closure glaucoma (ACG) are Asian.^[3] Southeast Asian nations have a higher prevalence of primary ACG (PACG) than the rest of the world. At least 12.9% of primary open-angle glaucoma (POAG) blindness and 12.7% of PACG blindness worldwide occur in India.^[4]

The only modifiable risk factors associated with glaucoma are elevated intraocular pressure (IOP).^[5] Lowering IOP reduces the risk of development or slows the progression of glaucoma. The other risk factors for glaucoma are age, gender, race, refractive errors, heredity, myopia, and systemic factors. It is imperative for reducing the prevalence, there should be an early diagnosis of glaucoma.

History Taking

The clinical presentation for POAG and primary angle-closure suspect is asymptomatic. A history of frequent changes of reading glasses may raise suspicion of diagnosis. The history needs to be structured for glaucoma suspects with a family history, myopes if having tilted disc raises high suspicion of glaucoma and hypermetropes are at higher risk for Nanophthalmos and primary angle-closure disease.^[6,7] Steroid use (in any form), trauma, sleep apnea, severe blood loss, thyroid eye disease, and migraine can be revealed after detailed history taking with the help of few leading questions.^[8]

History of bronchial asthma, compromised cardiac function, or any allergy to a sulpha group of drugs should be emphasized before writing the prescription. The use of any systemic medications (that may interact with anti-glaucoma medications [AGMs]) should be considered.

Significant ocular history such as uveitis [Figure 1] laser treatment, refractive surgery, and retinal pathology should be kept in mind while documenting the IOP recordings or making a note of gonioscopy evaluation of the peripheral anterior synechiae or when it comes to interpret the visual fields/optical coherence tomography.

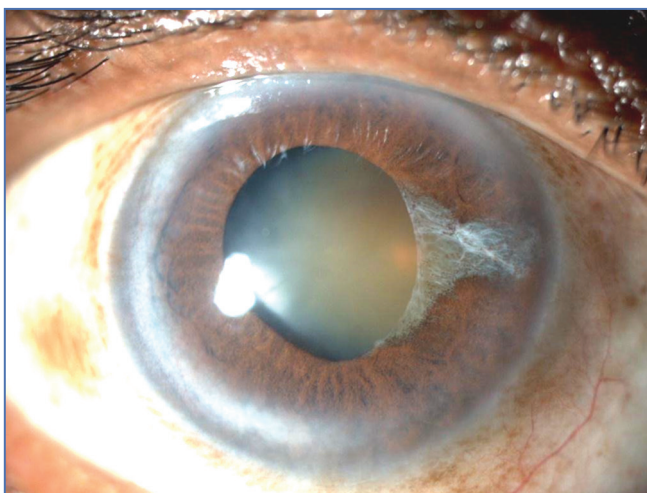


Figure 1: Post-inflamed eye



Figure 2: Allergy due to anti-glaucoma medication

Physical Examination

The following are the significant points.

Best-corrected visual acuity distance and near: Proper refractive correction is mandatory for correct visual field testing.

Eyelids, eyelashes, conjunctiva, and periocular tissues: Side effects of current topical drugs/ciliary conjunctival congestion which imply adverse intraocular pathology, including acute angle-closure attacks in small stain-positive areas on the cornea can also be a sign of toxicity to topical AGMs. [Figure 2] A featureless limbus with a hypoplastic iris is aniridia that is associated with raised IOP. Superior conjunctiva should be looked for any scar/Bleb with the nature of blood vessels in that area if any history of cataract or glaucoma surgery is given.

Pupil examination: Afferent pupillary defect – the pupillary edge should be examined for PXF material, and also, a high magnification evaluation of the pupil is indicated when suspicion of neovascular glaucoma is expected.

Iris: Transillumination defects. Anisocoria and polycoria should be evaluated. Atrophic areas on the iris can also be suggestive of past attacks of viral uveitis which can raise IOP.

Slit-lamp examination: Which is performed before and after dilatation: Signs of pseudoexfoliation, pigment dispersion, uveitis, or trauma should be assessed.

Cornea: Krukenberg Spindle is seen in pigment dispersion glaucoma (PDG) and corneal edema (may decrease the calculated IOP).

A horizontal break of the endothelium (Haab's striae), best seen on retroillumination, is seen in congenital glaucoma.

Any irregularities in the cornea: Scar/opacity may affect the IOP recording by routine methods, may warrant the use of Tonopen, etc.

Thickness assessment of the cornea, that is, pachymetry should be done with an optical biometer or ultrasound pachymeter. Thin corneas with low pachymetry are a risk factor for glaucoma progression

Lens: Glaucomflecken indicates previous acute attack of angle closure, Zentmayer Ring on the posterior capsule is seen in PDG.

A mature swollen lens blocking the pupil leads to phacomorphic glaucoma, eventually causing AC to be uniformly shallow. In phagocytic glaucoma, the lens will be hypermature with a cloudy AC sometimes associated with pseudohypopyon.

Tonometry

The gold standard for measuring IOP is still the Goldmann applanation tonometer (GAT).

In GAT, the cornea is hit by the applanating cylinder/prism in such a way that a certain portion of the cornea is flattened. According to the Imbert-Fick principle, the force needed to applanate depends on the IOP.

Measures must be carefully carried out to prevent inaccurate readings because they are susceptible to errors just like any other measurement. In addition, influencing the assessment is corneal thickness.

The two standard deviation values vary amongst populations, but for the Indian population, >22 mmHg is a suitable cutoff.

The tonopen and IC are Rebound Tonometer and air puff tonometers are also used in different situations but it is always advisable not to start treatment for glaucoma based on the readings of non-contact tonometer.

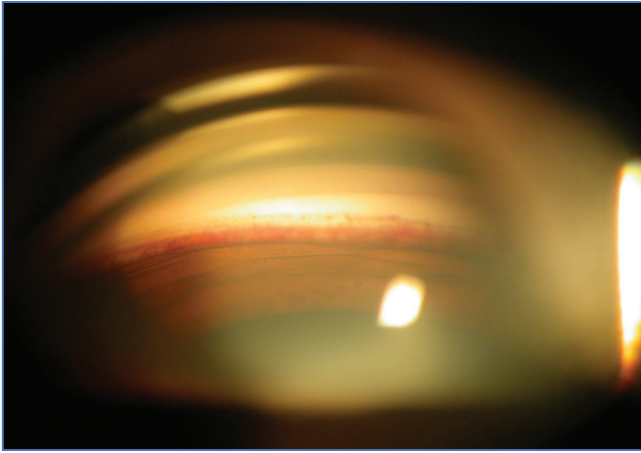


Figure 3: Gonioscopic view of angle showing neovascularization

Gonioscopy

After the age of 40 years, assessment of the angle should routinely be done as part of eye examinations

Gonioscopy is used to examine the angle of the anterior chamber, [Figure 3] a four-mirror indentation gonioscope is chosen due to the lack of need for coupling fluid. The other options can be a two-mirror/three-mirror gonioscope.

The optimal testing circumstances include low slit-lamp illumination intensity, low slit-beam height so that light does not impinge on the pupil and no gonioscope pressure on the eye. Then, wait 30–45 s for the pupil to dilate before determining whether the angle is open. The patient is instructed to look in the direction of the mirror to get a “over the (iris) hill view” of the angle if the posterior trabecular meshwork (PTM) cannot be seen in these circumstances. The angle is regarded as open if $>180^\circ$ of the PTM is visible with such a “over-the-hill view” within the stipulated testing circumstances, without any pressure on the eye.

Optic Disc Examination

Stereo-photographs are the current gold standard, but the optic disc findings should at least be documented, preferably with a drawing or imaging for comparison with future examinations. A magnified,

preferably stereoscopic, and examination of the optic disc using a 60–90 diopter (D) lens is the ideal method of examining the optic nerve head.^[15] Out of different structural changes in the optic disc in glaucoma, the most commonly used sign for the diagnosis of glaucomatous damage is an “increased” cup-to-disc ratio (CDR) with a compromised neuroretinal rim. In general, an arbitrary statistical cutoff of 0.7:1 is considered to be suspicious which should be considered in relation to the disc size. Beyond the 0.7:1 cutoff, a large disc is entitled to a very large cup, whereas a small disc may not be entitled to any cups at all. On the slit light with a 60 D/90D lens, the size of the disc can be quickly measured. The magnification factor is 1 for the 60 D lens, 1.13 for the 78 D lens, and 1.41 for the 90 D lens. The vertical height of a narrow slit beam is adjusted until the borders of the optic disc are just covered. In India, a disc of “normal” size has a vertical diameter of about 2.0 mm.^[9]

A little cup, say 0.3, which is typically thought to be within the normal range, could not be physiological in a small disc, whereas a large cup might be in a large disc. In other words, a large cup can be normal for a large disc whereas a small cup might be odd for a little disc [Figure 4]. CDR is helpful in two other circumstances. If the CDR in the two eyes varies by more than >0.2 after adjusting for disc size differences, glaucomatous damage is suspect. Pathognomonic of glaucoma is a progressive loss of rim (increase in the cup).

We prefer to record the rim-to-disc ratio in the superior, superotemporal, inferotemporal, inferior, and nasal portions of the



Figure 4: Physiological cupping

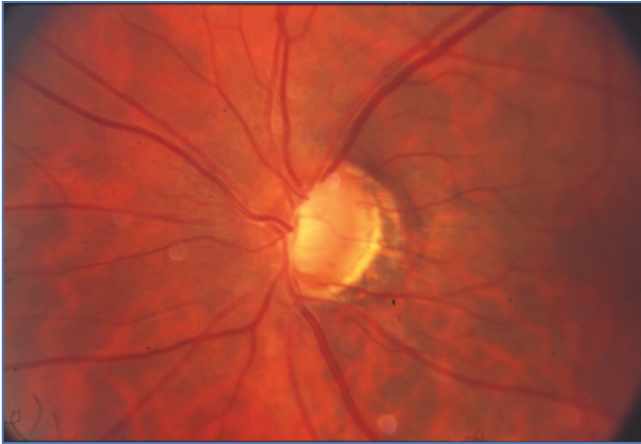


Figure 5: Peripapillary halo

disc rather than the customary CDR. Until shown otherwise, a rim-to-disc ratio of $<0.1:1$ should be regarded as pathology. Rim-to-disc ratio enables improved monitoring as well.^[10,11]

NRR Pattern Modifications: The NRR is typically thickest inferiorly, then superior, nasal, and temporal. This “ISNT” rule is prevalent in 80% of normals. Even though that is not sufficiently detailed and there can be typical variances, any modification to this pattern raises suspicion. It may indicate pathology if the inferior rim is thinner than the superior rim. A superior or inferior rim that is thinner than the temporal rim or equal to it is unquestionably extremely suspicious. It should be narrowest around the temporal rim. It is also suspicious if the inferior or superior rim narrows only locally and not all the way to the rim. A notch is defined as the rim extending one clock hour beyond the disc’s edge. Glaucoma is characterized by a notch, which frequently results in a functional field deficiency as well. Glaucoma can be detected by a hemorrhage that contacts the neuroretinal rim, although it is not sensitive. Glaucoma is not indicated by a pallor of the rim. Other neurological conditions may be the origin of the rim’s pallor, which is out of proportion to the “cupping” or outside the area of loss. A subtle indicator of glaucomatous damage is peripapillary choroidal atrophy [Figure 5]. If it is important, it must be accompanied by other symptoms or grow in size.

Nerve fiber layer defect (NFLD): Red-free photography is the gold standard for examining the nerve fiber layer (NFL), although the NFL can also be clinically assessed with the green slit-lamp filter.

A true glaucomatous NFLD appears as a dark wedge wider than the arteriole apex touching the edge of the disc and follows the pattern of the NFL which increases in width toward the periphery.

Conclusion

Examination in a Glaucoma patient has the light house effect for the appropriate diagnosis that leads to the exact management. This in turn helps to achieve the targeted goal of Minimizing the burden of the Disease.

Suggested Reading

1. Kang JM, Tanna AP. Glaucoma. *Med Clin North Am* 2021;105:493-510.
2. Tham YC, Li X, Wong TY, Quigley HA, Aung T, Cheng CY. Global prevalence of glaucoma and projections of glaucoma burden through 2040: A systematic review and meta-analysis. *Ophthalmology* 2014;121:2081-90.
3. Quigley HA, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. *Br J Ophthalmol* 2006;90:262-7.
4. Thylefors B, Negrel AD. The global impact of glaucoma. *Bull World Health Organ* 1994;72:323-6.
5. Stein JD, Khawaja AP, Weizer JS. Glaucoma in adults-screening, diagnosis, and management: A review. *JAMA* 2021;325:164-74.
6. Mitchell P, Hourihan F, Sandbach J, Wang JJ. The relationship between glaucoma and myopia: The Blue Mountains Eye Study. *Ophthalmology* 1999;106:2010-5.
7. Dandona L, Dandona R, Mandal P, Srinivas M, John RK, McCarty CA, *et al.* Angle-closure glaucoma in an urban population in southern India. The Andhra Pradesh eye disease study. *Ophthalmology* 2000;107:1710-6.
8. Harasymowycz P, Birt C, Gooi P, Heckler L, Hutnik C, Jinapriya D, *et al.* Medical management of glaucoma in the 21st century from a Canadian perspective. *J Ophthalmol* 2016;2016:6509809.
9. Jonas JB, Budde WM, Panda-Jonas S. Ophthalmoscopic evaluation of the optic nerve head. *Surv Ophthalmol* 1999;43:293-320.
10. Harasymowycz P, Davis B, Xu G, Myers J, Bayer A, Spaeth GL. The use of RADAAR (ratio of rim area to disc area asymmetry) in detecting glaucoma and its severity. *Can J Ophthalmol* 2004;39:240-4.
11. Spaeth GL, Lopes JF, Junk AK, Grigorian AP, Henderer J. Systems for staging the amount of optic nerve damage in glaucoma: A critical review and new material. *Surv Ophthalmol* 2006;51:293-315.
12. Bhartiya S, Singh M, Mitra A, editors. *Clinical Handbook of Glaucoma*. Noida: Incessant Nature Science Publishers; 2023.
13. Bhartiya S, editor. *Master Cases in Glaucoma*. New Delhi: United Scientific Solutions; 2023.

CHAPTER

2

Evaluation of the Optic Nerve head

Parul Ichhpujani, Surbhi Kapoor

Summary (Key Points)

- Stereoscopic evaluation of the ONH with sufficient magnification is the essence of optic nerve evaluation in glaucoma.
- Indirect and inverted disc visualization with the +60D, +78D, or +90D fundus lenses can best be obtained when the pupil is dilated.
- Photographs of the ONH are an extremely useful technique for documenting change in the disc over time. The disc drawings made by the clinician are a useful adjunct to disc photographs.
- Eight intrapapillary findings and four associated peripapillary features address the spectrum of glaucomatous alterations of the ONH.
- Size of the disc, refractive status and retinal nerve fibre layer defects are useful adjuncts to neuroretinal rim evaluation.

Importance of Optic Nerve Head (ONH) Evaluation

Introduction

Glaucoma is defined as a chronic, progressive optic neuropathy caused by a group of ocular conditions, which lead to damage to the optic nerve with deterioration of the visual field function. Optic nerve damage precedes visual field loss and thus ONH evaluation is quintessential for the diagnosis of glaucoma. Appropriate techniques for the evaluation of ONH can help us to differentiate between glaucomatous, non-glaucomatous, and normal optic discs.^[1]

Instrumentation

Glaucoma affects the surface contour of the ONH and these are best appreciated with a stereoscopic view. Therefore examinations for surface change should be made through a dilated pupil (at least 4 mm in diameter). Stereoscopic examination of the posterior pole is best performed with a:

Indirect fundus lens

With enough magnification at the slit-lamp, indirect lenses namely, +60D, +78D, or +90D provide a high-magnification stereoscopic view and help in diagnosing even early ONH changes. The +60D lens with appropriate magnification and depth of field makes it the best choice for the examination of ONH. A +90D lens provides a wide field of view but less magnification in comparison to a +60D, which provides a narrower field of view but $\times 1.15$ magnification. A +78D lens lies between these lenses with properties of both.

Direct fundus lens

The central part of Goldmann and Zeiss 4-mirror may also be used.

Characteristic ONH Changes of Glaucoma

The color and contour cup must be delineated. The neuroretinal rim (NRR) is the tissue between the cup and disc margins which represents the location of the bulk of axons and is orange-red because of the associated capillaries. Retinal vessels ride over the nasal wall of the cup, often kinking at the cup margin and then crossing the neural rim to the retina.

A complete ONH evaluation includes intrapapillary and peripapillary features which are described as under:^[2,3]

8 intra papillary features	4 peripapillary features
Optic Disc: Size; shape (2)	Optic disc hemorrhage
NRR: Size; shape (2)	Retinal nerve fiber layer (RNFL) assessment
Cup: Size; shape; cup: disc ratio (3)	Arteriolar diameter
Position of the central retinal vascular trunk (1)	Parapapillary choroidal atrophy

Intra Papillary Changes

Optic disc size

- Optic disc size is independent of age after the first decade and refractive error $< \pm 5.0$ D with little interindividual variability
- The mean area of the ONH ranges from 2.1 to 2.8 mm²
- Estimation of ONH size can be done by.

Direct ophthalmoscope: The 5° aperture of the Welch Allyn direct ophthalmoscope in an emmetropic eye equals an area of 1.7 mm² thereby providing a rough estimation of ONH size

Slit lamp biomicroscopy: Optic disc is evaluated by direct measurement of horizontal and vertical diameters of ONH and the obtained values are corrected with a correction on 1.26 (diameter $\times 1.26$).

$$\text{Optic disc Diameter (mm)} = (X/H) \times D \times C$$

X = height of beam as measured by the millimeter rule (mm)

H = height setting on the beam height indicator when checking with the millimeter rule (mm)

D = diameter of disc as measured by the beam height indicator (mm)

C = correction factor based on high plus lens power

- Corrective factors for different lenses are for Volk +90D: $\times 1.5$; +78 D: $\times 1.3$; +60 D: $\times 1$.
- Optic disc size correlates with a variety of morphological and clinical features.

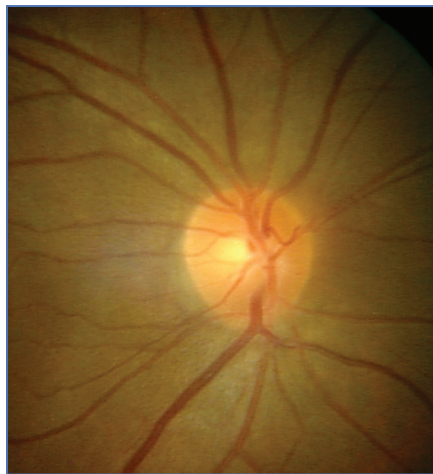


Figure 1: Small disc with a small cup

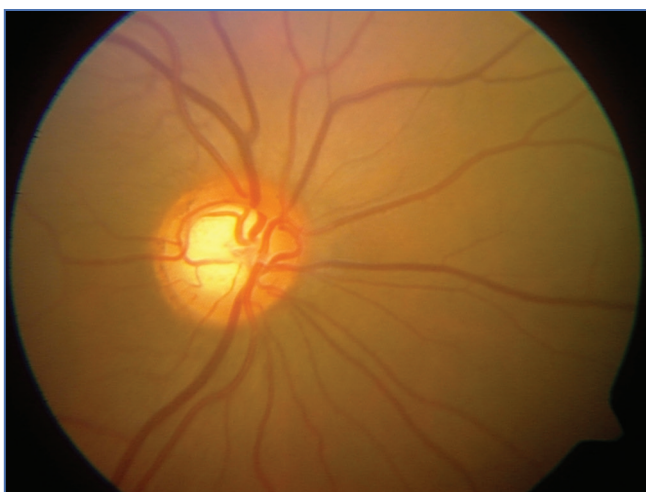


Figure 2: Large disc with a large cup

- Small discs [Figure 1]: Associated with small cups ONH drusen, pseudopapilledema, and non-arteritic anterior ischemic optic neuropathy (NA-AION).
- Intermediate disc size: Associated with arteritic anterior ischemic optic neuropathy (AAION), central retinal vein occlusion, primary open-angle glaucoma, juvenile open-angle glaucoma, and pseudoexfoliation glaucoma
- Large discs [Figure 2]: Associated with morning glory syndrome and congenital optic nerve pit.

Large discs have a greater NRR area, greater axonal fibers, larger size, and the number of laminar pores therefore less susceptible to damage.

Optic disc shape

- The normal optic disc is oval and has a vertical dimension 7–10% larger than the horizontal dimension
- Shape is independent of age, sex, body weight, or height
- Increased ovality of ONH is seen with myopia and astigmatism.

NRR shape

- NRR changes are better predictors of glaucomatous changes as compared to cup disc ratio (CDR).
- ISNT rule: NRR of the normal ONH is the broadest in the inferior quadrant, followed by the superior, then the nasal NRR, with the

temporal rim being the thinnest

- As glaucoma progresses, the NRR is diffusely lost in all sectors. Inferotemporal and superotemporal regions are the earliest to be lost, followed by the temporal sector, and lastly the nasal NRR
- NRR pallor can also act indicator to identify non-glaucomatous optic atrophy which manifests with neither enlargement of the optic cup nor with a decrease in the NRR area but rather with increased NRR pallor and attenuation of the peripapillary retinal vessels.

CDR

- Normally, the optic disc is vertically oval and has a horizontally oval cup with CDRs larger horizontally
- 7% of normal people have a reversed CDR
- There is a symmetric enlargement of the physiologic cup in glaucoma, but usually, some portion of the rim erodes more rapidly than the rest
- In myopic eyes and discs with age-related open-angle glaucoma, the cup tends to be shallow, especially temporally^[4]
- *Contour cup versus Color cup*: The color cup is defined as the extent of the central pallor of the disc and the contour cup is defined as the site at which the vessels change their contour. The contoured cup is a better predictor of NRR loss than the colored cup
- NRR thinning can be localized and appear as a notch or, less frequently, as a pit at the disc rim. When notches are present both inferiorly and superiorly, the cup becomes vertically oval. In glaucoma, the vertical cup always enlarges faster
- *Acquired pit of the optic nerve (APON)*: Discrete, focal area of depression within the optic cup at the level of the lamina cribrosa. APONs are commonly unilateral and inferotemporal, seen in patients with normal-tension glaucoma (NTG)
- Cup deepening:
 - *Overpass cupping*: Blood vessel crossing over an area of NRR loss before sinking in and taking on the bayonet appearance
 - *Laminar dot appearance*: Exposure of the lamina cribrosa.
- Documentation:
 - *CDR system*: This has many drawbacks with variation in cup sizes and imperatively, the disc not showing concentric enlargement and eccentric cups showing localized notching.
 - *Disc Damage Likelihood Score (DDLS)*: DDLS, developed by Dr. George Spaeth is a better indicator of optic nerve damage

in glaucoma as compared to the CDR system.^[5] The DDLS relies on the optic nerve as a direct indicator of disease. The DDLS is based on the radial width of the NRR measured at its thinnest point. The unit of measurement is the *rim/disc ratio* – that is, the radial width of the rim compared to the diameter of the disc in the same axis [Figure 3].

When there is no rim remaining, the rim/disc ratio is 0. The circumferential extent of rim absence (0 rim/disc ratio) is measured in degrees.

Caution must be taken to differentiate the actual absence of the rim from sloping of the rim as, for example, can occur temporally in

New DDLS stage	Narrowest width of rim (rim/disc ratio)			
	For small disc <1.50 mm	For average size disc 1.50-2.00 mm	For large disc >2.00 mm	Old DDLS stage
1	0.5 or more	0.4 or more	0.3 or more	0a
2	0.4 to 0.49	0.3 to 0.39	0.2 to 0.29	0b
3	0.3 to 0.39	0.2 to 0.29	0.1 to 0.19	1
4	0.2 to 0.29	0.1 to 0.19	less than 0.1	2
5	0.1 to 0.19	less than 0.1	0 for less than 45°	3
6	less than 0.1	0 for less than 45°	0 for 46° to 90°	4
7	0 for less than 45°	0 for 46° to 90°	0 for 91° to 180°	5
8	0 for 46° to 90°	0 for 91° to 180°	0 for 181° to 270°	6
9	0 for 91° to 180°	0 for 181° to 270°	0 for more than 270°	7a
10	0 for more than 180°	0 for more than 270°		7b

Figure 3: Disc Damage Likelihood Score



Figure 4: Nasalization of central retinal vessels

some patients with myopia. A sloping rim is not an absent rim. Because rim width is a function of disc size, disc size must be evaluated before attributing a DDLS stage. This is done with a 60D or a 90D lens with appropriate corrective factors.

Position of central retinal vessels and branches

- The rim sector farthest away from the major trunk of the central retinal vessels is vulnerable to damage
- Outward shifting of the bend is associated with NRR thinning. They tend to get nasalized as the glaucomatous changes advance [Figure 4]. In the early stages, their orientation is a vertical bearing of circumlinear vessels common in glaucomatous cups.

Peripapillary disc changes

With the advancement of glaucoma, the following changes occur in the juxtapapillary region: Optic disc hemorrhage, changes in the RNFL; variations in the diameter of retinal arterioles; and patterns of peripapillary choroidal atrophy.

Optic disc hemorrhages

- Located usually within the NRR, commonly seen as flame-shaped hemorrhages [Figure 5]
- Usually seen extending across the disc rim into the retina, but they may occur deep in the disc tissue



Figure 5: Optic disc hemorrhage at 8 o'clock



Figure 6: Red-free photograph showing radial striations of retinal nerve fiber layer in a healthy disc

- May last up to 35 weeks from the time of the presentation
- Other factors such as aspirin and diabetes may also be associated with optic disc hemorrhages
- NTG has a tendency for optic disc hemorrhage
- Strongly associated with progression.

Fiber layer defects

- RNFL evaluation can be done by red-free direct ophthalmoscopy or a wide-angle camera with either blue or green filters [Figure 6]. Serial photographs can assess ongoing glaucomatous changes
- RNFL defects can be localized wedge defects and diffuse loss which alone or in combination of both in glaucoma patients
- Localized loss is easily and almost always recognized. The nerve fibers are seen in the retinal area adjacent to the superior and inferior temporal quadrants of the disc, where the RNFL is thickest
- Diffuse loss is more difficult to assess. In cases where RNFL is poorly visible, if the retinal vessel reflexes are bright and sharp and smaller branches are easily visualized, generalized atrophy may be present.

Diameter of retinal arterioles

- Diffuse narrowing of the retinal vessels on the ONH because of a decrease in peripapillary perfusion.

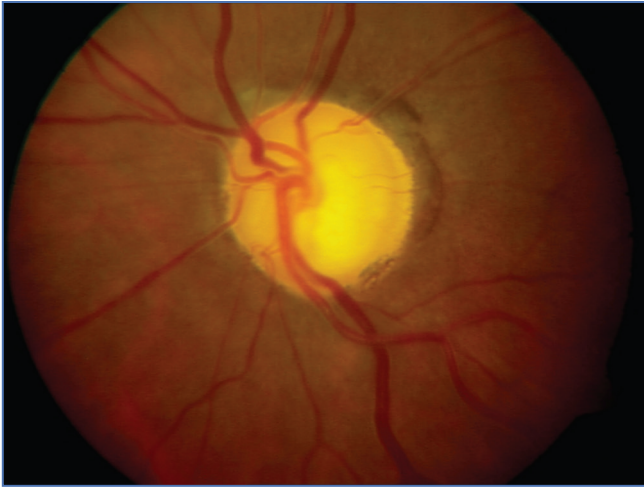


Figure 7: Glaucomatous optic disc with diffuse neuroretinal rim thinning with peripapillary atrophy

Peripapillary choroidal atrophy

- Normal ONH may be surrounded by zones that vary in width, circumference, and pigmentation
- Zones described in conjunction with glaucoma:

Beta zone:

- Broader, irregular, and incomplete areas of depigmentation
- An area of depigmentation is caused by the retraction of retinal pigment epithelium from the disc margin, with a thinning or absence of choroid next to the disc, thereby exposing underneath sclera [Figure 7]
- Commonly seen with a tilted scleral canal, as in myopia
- When zone beta surrounds the ONH 360°, it is called the “*halo glaucomatous*.”

Alpha zone:

- The peripapillary crescent of increased pigmentation that may represent a malposition of the embryonic fold with a double layer or irregularity of retinal pigment epithelium
- Located outside the beta zone but may be seen adjacent to the disc if the zone beta is absent.

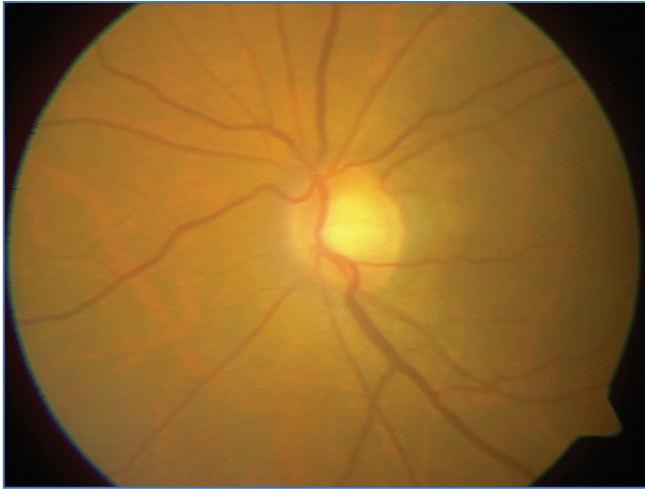


Figure 8: Polar notching



Figure 9: Myopic glaucomatous disc

Nicolela's Patterns of ONH Changes and Subtypes of Glaucoma

Focal glaucomatous optic disc

- Localized NRR loss at inferior/superior pole just temporal to midline [Figure 8]
- Associated with migraine and vasospasm
- Seen more commonly among women
- Scotomas near fixation in the superior visual field are usually seen
- Disc size is smaller than other glaucomatous disc types.

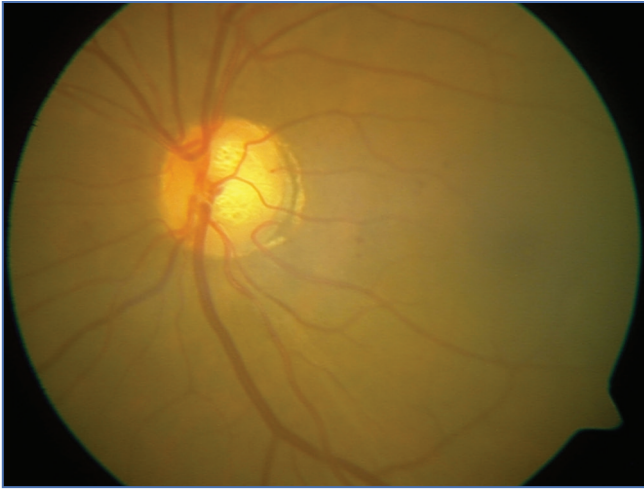


Figure 10: Senile sclerotic disc

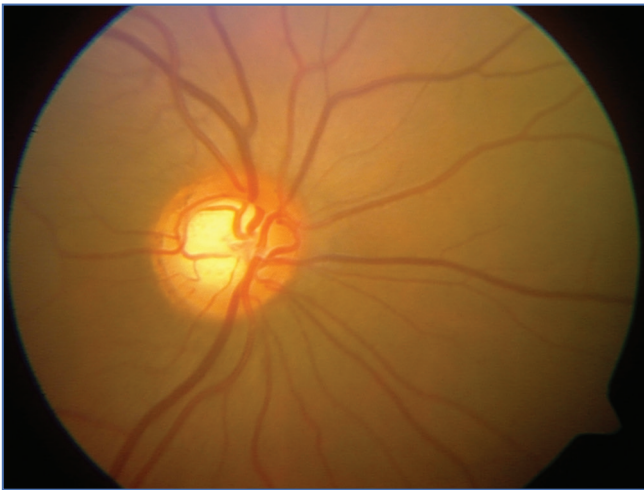


Figure 11: Concentrically enlarging discs

Myopic glaucomatous disc

- Seen in younger male patients
- Appears as a tilted or obliquely inserted optic disc [Figure 9]
- Has a shallow appearance with the presence of a temporal crescent
- Notching may be seen.

Senile sclerotic (atrophic glaucomatous) optic disc

- Shallow and saucerized cup with a gently sloping NRR [Figure 10]
- Shows variable peripapillary atrophy and peripheral visual field loss

- Seen in older patients
- Hypertension and cardiovascular disease are usually associated with it.

Concentrically enlarging discs

- Uniform NRR thinning [Figure 11]
- Commonly associated with diffuse visual field loss
- At presentation, IOP is often significantly elevated.

Causes of Non-Glaucomatous ONH Cupping

- A-AION
- NA-AION
- Posterior ischemic optic neuropathy
- Intracranial tumors
- Optic neuritis
- Dominant optic atrophy
- Methanol toxicity
- Shock optic neuropathy
- Leber hereditary optic neuropathy.

Conclusion

Timely diagnosing glaucoma in earlier stages by careful evaluation of early glaucomatous changes in the ONH can alter the course of the disease and improve the prognosis.

Suggested Reading

1. Sihota R, Sidhu T, Dada T. The role of clinical examination of the optic nerve head in glaucoma today. *Curr Opin Ophthalmol* 2021;32:83-91.
2. Jonas JB, Budde WM, Panda-Jonas S. Ophthalmoscopic evaluation of the optic nerve head. *Surv Ophthalmol* 1999;43:293-320.
3. O'Neill EC, Gurria LU, Pandav SS, Kong YX, Brennan JF, Xie J, *et al.* Glaucomatous optic neuropathy evaluation project: Factors associated with underestimation of glaucoma likelihood. *JAMA Ophthalmol* 2014;132:560-6.
4. Tan NY, Sng CC, Ang M. Myopic optic disc changes and its role in glaucoma. *Curr Opin Ophthalmol* 2019;30:89-96.
5. Spaeth GL, Lopes JF, Junk AK, Grigorian AP, Henderer J. Systems for

staging the amount of optic nerve damage in glaucoma: A critical review and new material. *Surv Ophthalmol* 2006;51:293-315.

6. Bhartiya S, Singh M, Mitra A, editors. *Clinical Handbook of Glaucoma*. Noida: Incessant Nature Science Publishers; 2023.
7. Bhartiya S, editor. *Master Cases in Glaucoma*. New Delhi: United Scientific Solutions; 2023.

CHAPTER

3

Visual Field Analysis and Assessing Progression on Visual Fields

Manju R Pillai, Maghalakshmi Udhayakumar Naidu

Summary (Key Points)

Before interpreting a visual field printout, the following points should be kept in mind:

- Treatment should not be started on the basis of a single visual field. Any defect present should be documented on a repeat examination. It is important to recognize any artefacts if any.
- Other causes of field defects like retinal and neuro ophthalmological diseases should be ruled out.
- Correlate the visual field changes with the optic disc.
- For follow up examinations, same strategy should be used and baseline fields are obtained after a stable management. The baseline field strategy shall depend on the severity of the defect
- Proceed zone wise for a systematic approach.

Introduction

Visual fields are the gold standard in the field of glaucoma which aids in the diagnosis and in setting the target intraocular pressure to arrest progression and onset of new field defects. The device used to perform a visual field test is a perimeter. It is also used to assess visual field loss due to retinal diseases, optic nerve, chiasmal and post-chiasmal damage due to trauma, stroke, compression, and tumors.

The Normal Visual Field

The visual field is everything in the world that the steadily fixed eye can see. 50° above, 60° nasally, 70° below, and 90° temporally are the functional boundaries of a normal visual field, which resemble a spiral [Figure 1].

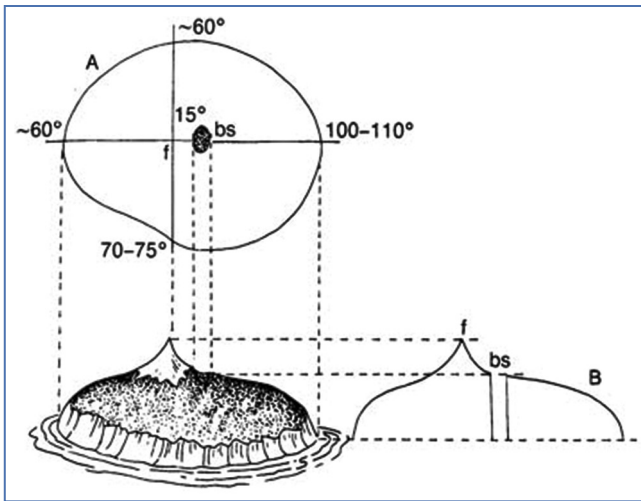


Figure 1: With projections displaying the peripheral limits (A) and the profile (B), the figure represents the normal visual field (right eye) as the Traquair “island of vision surrounded by a sea of blindness.” The retina’s foveola is represented by fixation (f), while the optic nerve head is represented by blind spot (bs). The position of the blind spot and the approximate measurements of the absolute peripheral edge of the visual field are displayed (A)

The Hill of Vision

The sensitivity of light is not uniform across the spatial extent of the visual field. For normal eyes and typical daytime illumination, sensitivity is highest in the central area of the visual field (point of fixation) and decreases rapidly in the 10° around fixation and then decreasing very gradually for locations further in the periphery which represents as a three-dimensional structure as a hill and hence the name. At the optic nerve head, nerve fibers enter the sclera and travel through, usually $10-15^\circ$ nasal to the fixation. This is a typical absolute scotoma because there are no photoreceptors at this site.

Cellular Basis for the Field of Vision

Detection of visual stimuli relies on an intact neural pathway beginning with the retinal photoreceptors through bipolar neurons, RGCs, and LGB to the occipital cortex. Bipolar cells synapse with the different types of RGCs and each type of RGC completely covers the field of vision. Certain RGC types are more susceptible to glaucoma-related damage, and as a result, visual stimuli that these types preferentially detect may help identify glaucoma early on.

The three different types of RGCs are called parvocellular, which transmits information about color and form; magnocellular, which transmits information about motion and flicker; and koniocellular, which transmits blue light or short wavelengths.

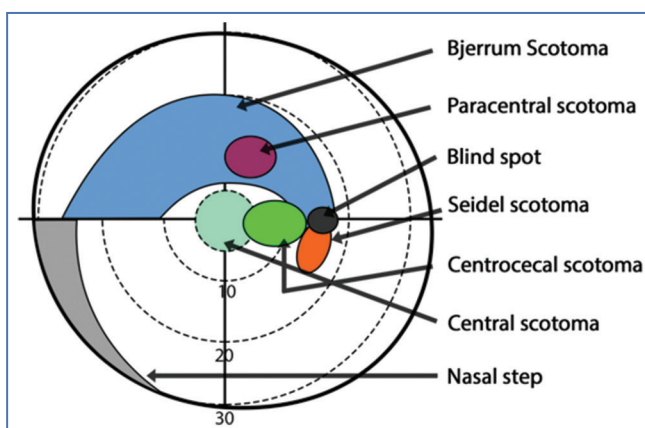
The non-selective nature of the standard automated perimetry (SAP) is caused by this ganglion cell redundancy, and histology investigations have demonstrated that a sizable number of ganglion cells are destroyed before visual field problems manifesting on SAP. This justification led to the creation of frequency doubling perimetry and short wavelength automated perimetry, which are designed to measure a certain subset of RGCs with a sparse distribution.

Visual Field Loss in Glaucoma

The retinal nerve fiber layer, which is made up of axons from RGCs that stretch towards the optic nerve, divides the superior and inferior hemifields of vision into three sections:

1. Nasal fiber supporting the retina nasal to the optic nerve head.
2. The maculopapillary bundle proceeding directly from the macula to the temporal optic nerve head.
3. The arcuate fibers – These fibers take the arcuate course from the peripheral macula and the temporal retina outside the macula to the superior and inferior optic nerve head.

Characteristic Visual Field Defects in Glaucoma



Measurement of the Visual Field

The visual field is a three-dimensional structure which can be measured in the following ways:

Manual versus automated perimetry

Advantages of Automated Perimetry are:

- Provides more sensitive and reproducible results
- Provides quantitative information
- Provides results in a more timely manner
- Experienced Perimetrist is not required
- Early detection of glaucomatous damage is possible.

Kinetic versus static perimetry

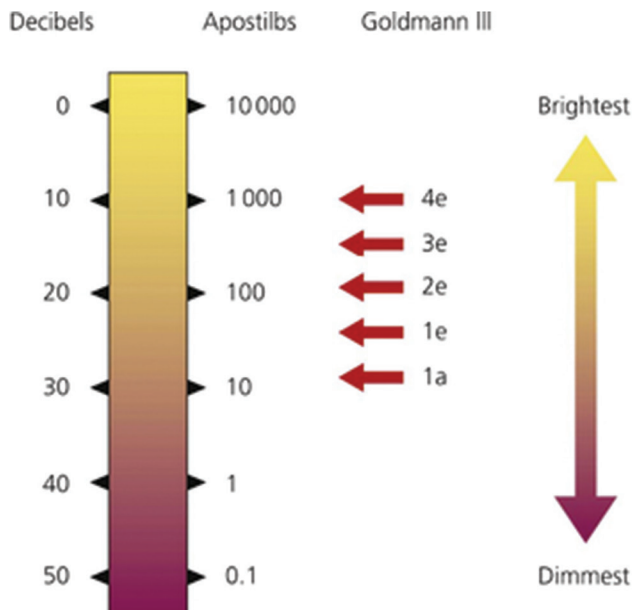
Kinetic Perimetry – Measurement is done along the X-Y axes and the object is moved from the non-seeing area to the seeing area.

In static perimetry, the patient looks into a white hemispherical bowl with a small fixation point in the center. The patient presses a response button when the stimulus is detected. Visual field stimuli are briefly presented at fixed stationary locations, usually lasting 200 ms. Typically, the stimulus's brightness, size, and background lighting determine how visible the stimulus is. Static perimetry typically involves keeping the stimulus size and background illumination constant while varying the light intensity in accordance with a staircase (bracketing) approach to determine the minimum intensity required for stimulus detection.

Background illumination: 31.5 asb in Humphrey perimetry.

Size of the stimulus: Goldmann Size III is the standard stimulus size that applies to all perimeters. However, based on the specific clinical circumstances, the stimulus's magnitude can be altered. Size V can be substituted for size III in the categories related to macular diseases. However, the stimulus's size-whether it is Size III or Size V-as well as the ambient lighting will stay the same for the duration of the test, even though the stimulus's light intensity will change.

Stimulus intensity: Attenuation filters are used to vary the strength of the stimuli. Attenuation of light is measured in logarithmic terms, often represented as tenths of log units, or decibels (dB). Ten log units of attenuation of the greatest stimulus available equal one decibel. Ten thousand asb units are used for the present Humphrey perimeters.



In the Humphrey system, a stimulus of 40 dB is equivalent to 1 asb unit, which is the lowest projected stimulus intensity, while a stimulus of “0” dB is equivalent to 10,000 asb units, which is the highest light intensity projected by the Humphrey field analyzer. dB are relative measures of light intensity, while amps are absolute ones.

As the decibel value increases (that means the attenuation of light increases), the brightness of the light decreases. Hence, higher the decibel value, the lower the light intensity in asb units and the higher the retinal sensitivity.

Definition of Threshold: If a particular intensity of light is shown 100 times and if it is appreciated 50 times that particular intensity of light is termed as threshold. If the stimulus intensity is seen 90% of the times, it is termed as suprathreshold and if it is seen 15% of the times, it is termed as infrathreshold.

How Perimetry is Done

1. Perimetry should be done in a distraction-free environment – the room should be quiet and at a comfortable room temperature.
2. The patient-related data such as name, age, date of birth, and refraction should be entered correctly. The trial lenses with a narrow metal rim should be used and in case of multiple lenses,

spherical lenses should be closest to the eye of the patient, and cylindrical lenses oriented in the angle of astigmatism.

3. The patient should be seated comfortably with a translucent eye patch for the untested eye. The testing eye should be well aligned with the fixation target and should be relatively closer to the trial lens.
4. The patient should be explained to maintain a steady fixation throughout the test which can be done using different fixation targets such as cross mark, central point, or ring.
5. With their head and fixation steady, the patient is asked to indicate seeing a stimulus anywhere in their visual field by pressing a response button.

Common Perimetric Errors

1. Incorrect patient name
2. Incorrect Patient age: As threshold values are compared to the age-adjusted normal values, incorrect age entry will lead to comparisons with the incorrect set of normal values.
3. Inappropriate correction of refractive errors: Failure to properly correct for refractive error will cause stimuli to become visually defocused.
4. Lens rim artifacts: Thick rims for correcting refractive error or inappropriate head positioning which causes the lens rim to block peripheral stimuli can cause artifactual depression of the peripheral points.
5. Cloverleaf field defects: This pattern of visual field defects reflects poor visual attention and/or malingering. Field results typically show high rates of false negative responses.
6. Miotic pupils or Cataracts: Ocular features that allow less light to reach the retina can cause depression of the visual field along with statically significant decrease in mean deviation. A small pupil may simulate a glaucomatous field defect by generalized depression because of miosis or exacerbate an already constricted field, giving a false impression of the progression of glaucoma. In cases of concomitant cataract, attention should be paid to the pattern deviation plot as it adjusts for the generalized depression caused by the cataract.

Classification of Humphrey Visual Field Tests

1. Threshold tests
 - Central tests: 10–2, 24–2, 30–2, Macular program
 - Peripheral tests: Peripheral 60–4, Nasal step, Temporal crescent
 - Special tests: Neurological 20, Neurological 30.

Test pattern	Point density (degrees)	Test points
10-2	2	68
24-2	6	54
30-2	6	76
Macular program	2	16
Nasal step	-	14
24-1	6	56
30-1	6	71

2. Screening tests

Threshold Testing Strategies: Two Types

- Old standard threshold strategies – Full Threshold Strategy
- New threshold strategy – FASTPAC, Swedish Interactive Threshold Algorithm (SITA) Standard and SITA Fast
- SITA.

Which Strategy to Select?

It depends on the time taken for the test.

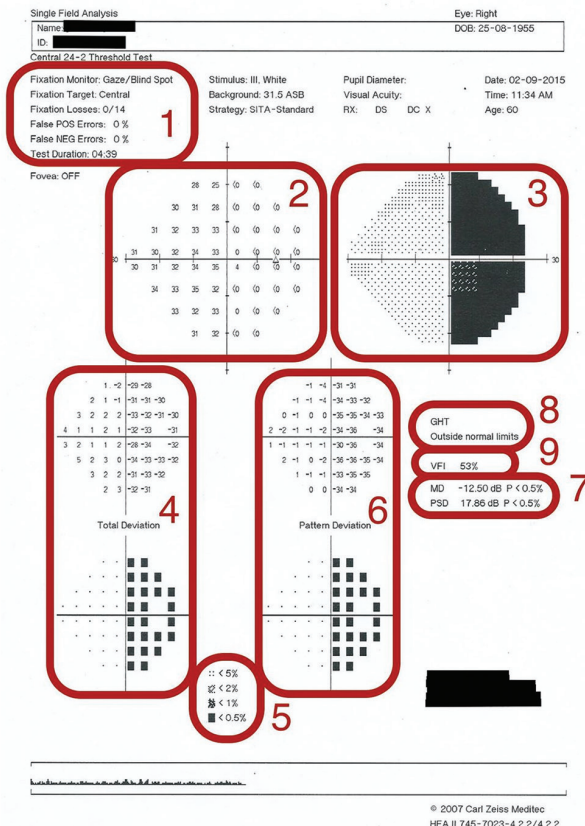
1. 30-2 Full Threshold-20 min
2. 30-2 FAST PAC, 24-2 FULL Threshold-14 min
3. 24-2 FAST PAC, 30-2 SITA Standard-10 min
4. 24-2 SITA Standard-7 min
5. 24-2 SITA fast-5 min

Which Point Patterns to Select?

It is selected according to the stage of glaucoma

1. 30-2 central is the first field to be selected.
2. If no pathology is seen and peripheral 30° is free of scotoma, 24-2 central field can be selected.
3. For advanced glaucoma, the 10-2 central field should be selected.
4. If the field is so advanced and most of the points sensitivity is <10-15 dB and if macular split is present, the selection test would be – 10-2 central field with Size V stimulus or macular program with Size V stimulus. The presence of a macular split indicates poor prognosis after filtering surgery.

Single Field Analysis



Zone 1:

- Age of the patient and DOB
- Size of the pupil
- Refractive error
- Stimulus size usually set at III
- Fixation targets.

Zone 2:

- Foveal threshold and vision
- Reliability indices:- Fixation losses >20% is unreliable, False positives >33% and false negatives >33% is unreliable
- Check for blind spot position.

Zone 3: Raw data

- Exact retinal sensitivity in dB units of selected points is calculated.

- 0 = Lowest retinal sensitivity to the brightest (10,000 asb) stimulus
- 40 = Highest sensitivity to the dimmest (1 asb) stimulus.
- Highest at fovea

Zone 4: Gray scale

- All the values obtained from raw data are grouped into 10 groups and given shades with 5 dB difference
- High sensitivity is given a lighter shade and lower sensitivity is given a darker shade.
- False positive = more white areas and false negative = cloverleaf pattern
- Should not be used to interpret. But can be used to explain the severity to the patient.

Zone 5: Total Deviation Numerical Plot

- The measured retinal sensitivity of each point in raw data is compared with age-matched control and deviation values are plotted where 0 refers to no change, “-” sign refers to lower patient sensitivity and no sign refers to better patient sensitivity than age-matched controls
- Forms the basis for calculation of global indices.

Zone 6: Total Deviation Probability Plot

- The loss of sensitivity at each point is expressed as a probability value.
- Darker the symbol, the greater the probability of abnormality.

Zone 7: Pattern deviation numerical plot (PDNP)

To know the extent of localized scotomas in a generalized defect in TDPP.

Zone 8: Pattern Deviation Probability Plot (PDPP)

It also provides the extent of localized defect in a generalized field loss.

Analysis of TDPP and PDPP

- If same, then can indicate either Glaucoma, AION, ON pathway defects, or occipital lobe infarcts.
- Irregular Generalized defect – TDPP shows generalized defect and PDPP shows localized defect – seen in pure advanced stage of glaucoma, cataract with glaucoma.
- Uniform Generalized defect – TDPP shows generalized defect and PDPP is Normal – seen in media opacities, small pupil, advanced glaucoma, and optic neuritis.

Zone 9: Global indices

1. Mean Deviation
2. Pattern Standard Deviation (PSD)
3. Short Term Fluctuations (SF)
4. Corrected PSD (CPSD)
5. Visual field index-useful in estimating rate of progression.

Defects	TDNP	PDPP	MD	PSD
Localized defect	Dissimilar	Localized	Normal	Increased
Irregular generalized	-	Localized	Increased	Increased
Uniform generalized	Similar	Normal	Increased	Normal

Zone 10: Glaucoma hemifield defect

Compares mirror images of superior and inferior retina for 5 points.

Anderson's and Patella's Criteria for diagnosis of glaucoma in the absence of retinal and neurological defects.

1. PDPP in 30-2
 - Three contiguous non-edge points having $P < 5\%$ of being normal and 1 of which should have $P < 1\%$
 - These points are clustered in the arcuate area
 - In 24-2, even edge points are considered.
2. CPSD $< 5\%$
3. GHT-Outside Normal limits

Glaucoma Progression Analysis (Gpa)

To analyze glaucoma progression, Humphrey introduced a new software-GPA. The PDNP of the follow-up test and the baseline PDNP are compared in terms of GPA. The GPA option is available for SITA strategies.

Step 1 is creating the baseline data (PDNP).

The creation of baseline data (a numerical plot representing the pattern deviation) is the initial stage in the investigation of glaucoma progression. The field analyzer creates the baseline printout based on the data from the first two tests if the patient completes the field test three or more times.

Step 2: Obtain the printout for the decibel deviation plot in the follow-up test.

The PDNP of the follow-up test is now compared to the PDNP of the baseline test, and the difference between the two is calculated.

The difference is then plotted as a deviation from the baseline plot in the follow-up test printout.

Step 3: Creating the progression analysis plot on the printout of the follow-up examination.

At this point, every variation from the baseline is compared to the inter-test variability typical of patients with stable glaucoma, and any significant changes are shown by point positions in the progression analysis plot.

The criteria for identifying progression in visual fields:

- Minimum of three tests required: Two baseline and one follow-up examination
- Each follow-up compared to average thresholds of two baseline examinations
- Additional follow-up compared both to baseline and two most recent follow-ups.

Conclusion

- Even in an era of rapidly advancing imaging technology, perimetry remains instrumental in the care of the glaucoma patient, as it provides valuable data for functional vision assessment
- The clinician must possess a solid understanding of the technology in order to make sound clinical decisions regarding diagnosis and progression of glaucoma
- Recent changes in testing strategies, and the introduction of home-based testing, may improve our ability to assess visual function in the clinic and patient acceptance of the test.

Suggested Reading

1. GR Reddy, Jayamadhury G. Practical Guide to Interpret Visual Field. 4th ed. India: Jaypee Brothers Medical; 2020.
2. Allingam RR, Damji KF, Shields MB. Shields Text Book Glaucoma. 6th ed. Philadelphia, PA: Wolters Kluwer Health/Lippincott Williams and Wilkins; 2010.
3. Nayak BK, Dharwadkar S. Interpretation of autoperimetry. J Clin Ophthalmol Res 2014;2:31-59.
4. Smita P, Ronnie G, Ariga M. Interpreting HFA single field reports. TNOA J Ophthalmic Sci Res 2019;57:220-30.
5. Chaglasian M. Sharpen your visual interpretation skill. Review of Optometry; 2013.

6. Anderson DR, Drance SM. Natural history of normal tension glaucoma. *Ophthalmology* 2001;108:247-53.
7. Bhartiya S, Singh M, Mitra A, editors. *Clinical Handbook of Glaucoma*. Noida: Incessant Nature Science Publishers; 2023.
8. Bhartiya S, editor. *Master Cases in Glaucoma*. New Delhi: United Scientific Solutions; 2023.

CHAPTER

4

Gonioscopy: The Basics

Arnav Panigrahi, Viney Gupta, Shikha Gupta

Summary (Key Points)

- Gonioscopy refers to visualization of angle structures with the help of a gonio lens.
- Gonioscopy must be done in every patient with elevated IOP and/or shallow peripheral AC.
- The angles need to be visualized at the thinnest and dimmest illumination possible, to establish the risk of angle closure.
- Angle closure is suspected when the scleral spur is not seen over $>180^\circ$ in such an illumination.
- Additional features, such as iris configuration, insertion, angulation, and angle pigmentation, should also be examined.
- Undue pressure on the eye and bright illumination might falsely open the angle.

Introduction

Gonioscopy remains an important tool in the field of ophthalmology. It enables us to visualize the anterior chamber (AC) angle for its abnormalities, with the help of a gonio lens. These lenses are of various types [Figure 1] and may involve either direct or indirect optics. Structures seen on gonioscopy provide important clues to the diagnosis of glaucoma, especially primary angle closure disease (PACD), and should be performed in every patient with a suspicion of glaucoma.

Technique of Gonioscopy

The routine gonioscopic examination involves the use of a Goldmann-type lens, which employs indirect optics and has a base

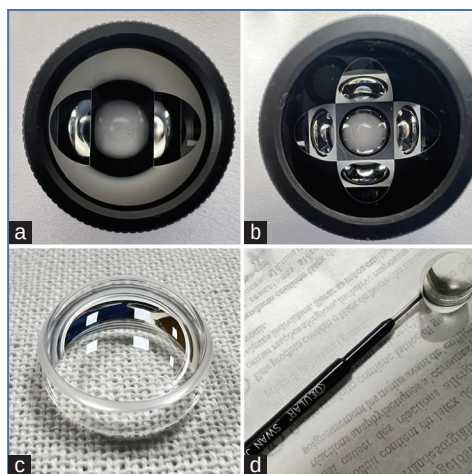


Figure 1: Various types of gonio lenses. (a) Goldmann 2 mirror gonio lens, (b) Thorpe 4 mirror gonio lens, (c) Koeppel lens, (d) Swan Jacob lens

larger than the corneal diameter. These lenses are meant to be used with a coupling agent, like CMC or HPMC, placed on their concave surface. After anesthetizing the eye, the patient is asked to look down, and the lens is placed on the cornea after lifting the eyelid up. The structures seen are oriented in a vertically, but not horizontally, inverted manner, i.e., the inferior angle is seen in the superior mirror, with the nasal half of the image seen in superior mirror corresponding to the nasal half of the inferior angle. The structures seen in a wide-open angle are, from anterior to posterior, Schwalbe's line (SL), anterior trabecular meshwork, posterior trabecular meshwork (PTM), scleral spur (SS), and the ciliary body band (CBB) [Figure 2]. The inferior angle is usually wider than the superior angle. In patients with PACD, all the structures may not be seen. The reason for this closure may either be appositional or synechial; these may be differentiated with manipulation or indentation gonioscopy. In manipulation gonioscopy, the angle can be opened by asking the patient to look toward the mirror being visualized, along with gentle counter pressure given by the examiner. For example, an inferior gaze results in the inferior limbus pressing against the rim of the gonio lens, which pushes aqueous up into the superior angle, thereby opening it up, which can in turn be seen in the inferior mirror. Indentation gonioscopy uses a modified indirect gonio lens which has a base diameter smaller than the cornea and does not require the use of a coupling agent. Pressing the gonio lens against the cornea displaces the central aqueous into the angle,

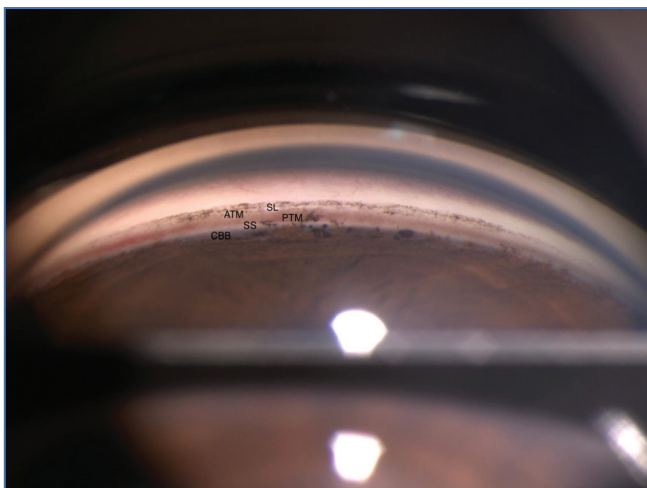


Figure 2: Goniophotography of a normal angle. From anterior to posterior, the structures are Schwalbe's line, anterior trabecular meshwork, posterior trabecular meshwork, scleral spur, and ciliary body band

thereby opening them up. Mastery of either of these techniques is essential to unlock the full potential of gonioscopy.

Gonioscopy Grading Systems

The number of structures seen on gonioscopy can be used to grade the occludability of the angle. Various such grading systems have been devised, including the Scheie, Shaffer, and Spaeth systems. The Spaeth system is the most detailed of the lot, taking the iris insertion, angulation, configuration, and pigmentation of PTM into account.^[1] The most convenient for routine use is Shaffer system, where iris angulation and visibility of angle structures are considered.^[2] Iris angulation $\leq 20^\circ$ and/or invisibility of SS put the patient at risk of developing PACD. It is important to note that these findings must be recorded at the thinnest slit and dimmest illumination possible to enable visualization. This causes pupillary relaxation, thereby increasing the iridotrabecular contact (ITC), resistance to aqueous outflow, and thus, the intraocular pressure (IOP) in anatomically predisposed eyes. This closely simulates the nighttime conditions, especially when performed in a dark room, when IOP spikes are frequently seen in patients with angle closure glaucoma.

Doing it the Right Way

A detailed gonioscopic evaluation is paramount in every patient with glaucoma, as it plays a massive role in deciding the management course of the patient. A schematic documentation of gonioscopic findings is given in Figure 3. The angle is first visualized at the dimmest illumination with the thinnest slit in the primary position, followed by visualization with bright illumination and maximal manipulation, to make note of all the structures seen when the angle is rendered open to the maximal possible extent. In patients with occludable angles, defined by non-visibility of SS $>180^\circ$, the effort required to open the angle up is also noted. The primary cause of occludability is looked for. In the pupillary block mechanism, a convex iris configuration is present [Figure 4a]; these eyes are usually amenable to laser iridotomy, especially when synechial closure has not developed. Plateau iris configuration can be diagnosed with a characteristic sine wave configuration and sudden peripheral iris dip [Figure 4b]. The AC may appear deep in these eyes, often being misdiagnosed as open-angle glaucoma, the occludability being made obvious only on gonioscopy. This configuration can also be caused due to the presence of multiple iris cysts, where a lumpy bumpy appearance is noted [Figure 4c]. In

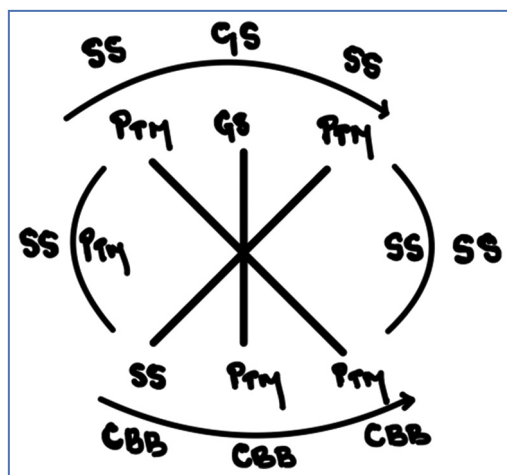


Figure 3: Schematic representation of gonioscopy in an angle closure patient. The structures within the inner zone indicate those seen on minimal illumination on the primary position. Those outside indicate the structures seen on incremental illumination and manipulation. Special features, like goniosynechiae and neovascularization of angle, should also be indicated against their corresponding locations

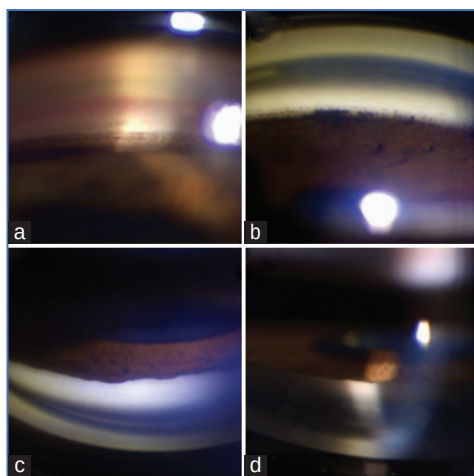


Figure 4: Various mechanisms of primary angle closure disease. Convex iris configuration could be seen in (a), suggestive of pupillary block mechanism. The iris is flat in configuration, but the scleral spur is not visible in (b), suggestive of plateau iris. Numerous ciliary body cysts have resulted in a lumpy bumpy appearance in (c). Anterior bulge of lens with a central pupillary dip resulting in Mount Fuji sign, suggestive of lens-induced mechanism, can be seen in (d)

lens-induced causes, Mount Fuji sign may be seen [Figure 4d]. All the causes other than pupillary block do not respond to laser iridotomy. Lens extraction, combined with angle surgery, can be attempted in these cases if optimal medical control is not achieved.

It is important to note that in many patients of PACD, the IOP may be normal on presentation, or the angles may not appear closed. A dim light examination is paramount in these patients to elucidate the maximum extent of occludability.^[3,4] If the angle still appears open, the presence of subtle signs of ITC, like blotchy irregular pigmentation of angle, must be looked for. Running a diurnal IOP variation should be considered in these patients, as high IOP spikes are usually recorded during the night, which are never seen during office visits. These forms of PACD are usually missed during routine eye examinations and are detected late, when salvaging the patient's vision becomes extremely difficult. Considering the blinding repercussions and high prevalence in the Indian population, PACD should be the default diagnosis in adults with asymmetrical glaucoma with age >40 years, unless ruled out on gonioscopy.

In case of open angles, iris configuration, insertion, and pigmentation of PTM are noted. Dense regular pigmentation of PTM and SL with a concave iris configuration is suggestive of pigment dispersion syndrome (PDS) [Figure 5a]. Anterior insertion of iris

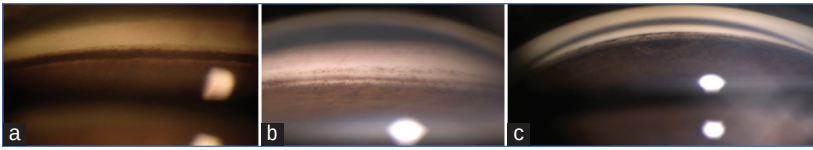


Figure 5: Various types of open angle glaucoma, diagnosed on gonioscopy. Dense regular pigmentation of PTM, suggestive of pigment dispersion syndrome, can be seen in (a). A normal-appearing angle with prominent iris processes, as seen in (b), is suggestive of juvenile open-angle glaucoma. Irregular widening of CBB, as seen in central areas of (c), is indicative of angle recession glaucoma

may be seen in juvenile open-angle glaucoma. A normal-looking angle with a deep cup and very high IOP may be suggestive of JOAG or steroid-induced glaucoma (SIG), although prominent iris processes are more suggestive of the former [Figure 5b]. Irregular asymmetrical widening of the CBB in eyes post-blunt trauma is suggestive of angle recession glaucoma [Figure 5c]. Differentiating one from the other is necessary, considering the difference in natural course and prognosis. For example, misdiagnosing PDS as SIG based on the history of steroid use may limit the options available to the surgeon. Angle surgery and laser trabeculoplasty, although of limited use in SIG, have high success in PDS. By ruling out these modalities, the surgeon limits himself to filtration surgery as his only option. Hence, routine gonioscopy is advised even in eyes where the AC is obviously deep.

Conclusion

To conclude, gonioscopy is a tool which empowers every ophthalmologist. Glaucoma management, a battle against a lifelong disease, hinges on the clinician making the correct diagnosis, which paves the way to an appropriate stepwise management regimen. Gonioscopy, to this day, remains at the very core of it.

Suggested Reading

1. Spaeth GL. Gonioscopy: Uses old and new. The inheritance of occludable angles. *Ophthalmol* 1978;85:222-32.
2. Shaffer RN. Primary glaucomas. Gonioscopy, ophthalmoscopy and perimetry. *Trans - Am Acad Ophthalmol Otolaryngol Am Acad Ophthalmol Otolaryngol* 1960;64:112-27.

3. Gupta B, Angmo D, Yadav S, Dada T, Gupta V, Sihota R. Quantification of iridotrabecular contact in primary angle-closure disease. *J Glaucoma* 2020;29:681-8.
4. Zhang X, Guo PY, Lin C, Li F, Nguyen A, Sakata R, *et al.* Assessment of iris trabecular contact in eyes with gonioscopic angle-closure. *Ophthalmology* 2023;130:111-9.
5. Bhartiya S, Singh M, Mitra A, editors. *Clinical Handbook of Glaucoma*. Noida: Incessant Nature Science Publishers; 2023.
6. Bhartiya S, editor. *Master Cases in Glaucoma*. New Delhi: United Scientific Solutions; 2023.

CHAPTER

5

Primary Open-Angle Glaucoma

Purvi Bhagat, Margi Panchal

Summary (Key Points)

Primary open-angle glaucoma is a chronic, progressive, commonly bilateral, often asymmetric, anterior optic neuropathy characterized by elevated intraocular pressure, open anterior chamber angles, characteristic optic disc changes, and visual field changes, with no causative ocular or systemic conditions. It is a leading cause of irreversible blindness. The disease is usually asymptomatic in its early stages. The patient may present only later when the disease is advanced and field defects become significant. The diagnosis is made by tonometry, ophthalmoscopy, gonioscopy, perimetry, and pachymetry. Treatment includes topical medications, laser trabeculoplasty, and incisional surgery. The goal of treatment is to prevent further optic nerve and visual field damage by lowering the intraocular pressure (IOP). The target IOP should be 20–40% below the baseline. There is significant inter-individual variation in the susceptibility of the optic nerve to IOP-related damage; therefore, regular monitoring is an important aspect of primary open-angle glaucoma management.

Introduction

Primary open angle glaucoma (POAG) is a chronic, progressive, commonly bilateral, often asymmetric, anterior optic neuropathy characterized by:

- Intraocular pressure (IOP) - elevated above the statistically normal range.
- Glaucomatous optic nerve damage.
- Open anterior chamber angles.
- Characteristic visual field loss.
- No obvious causative ocular or systemic conditions.

Epidemiology

An estimated 57.5 million people worldwide are affected by POAG, with a global prevalence of 2.2%.

In the Baltimore Eye Study, the prevalence of POAG in people aged 40 years and older was higher among blacks than whites.^[1]

In a meta-analysis of global variations of glaucoma prevalence, the black population had the highest POAG prevalence.^[2]

In the Framingham study, the incidence of POAG was 2 cases per 1000 people per year from age 55 to 60 years and 11 cases per 1000 people per year from age 70 to 75 years.^[3]

In India, POAG is estimated to affect 6.48 million people.^[4]

Risk Factors

General

- Age: The prevalence of POAG increases with age.
- Race: The prevalence is 4 times higher in blacks than in whites and has a rapid progression in black patients.^[1]
- Heredity: The risk of developing POAG in first-degree relatives is 4–16%.^[5]

A mutation of the gene GLC1A on chromosome 1q has been found in juvenile POAG and in 3–4% of POAG in adults. Another gene, GLC1B, located on chromosome 2, is associated with adult-onset POAG.^[6]

Ocular

- IOP: The higher the IOP, the greater the likelihood of glaucoma. Asymmetry of 4 mmHg or more is significant.
- Myopia: Large axial myopia has weaker scleral support at the optic nerve, which contributes to greater susceptibility to damage.
- Central corneal thickness (CCT): A thin CCT is associated with increased progression.
- Large discs may be more vulnerable to damage. The incidence of POAG is higher in persons with baseline cup disc ratios of >0.7 than in persons with <0.7.^[7]

Systemic

- Diabetes mellitus.
- Hypothyroidism.
- Vascular diseases: Systemic hypertension, cardiovascular diseases, and migraine lead to poor ocular perfusion, which is a risk factor for glaucoma progression.^[8]
- Contraceptive pills increase the risk of glaucoma by blocking the protective effect of estrogen.
- Sleep apnea: Episodes of transient hypoxia lead to decreased ocular perfusion.
- Translaminar pressure gradient: Differences in levels of IOP and cerebrospinal fluid pressure increase the progression of glaucoma.^[9]

Pathophysiology

Diminished aqueous humor outflow

The main site of resistance to the outflow is juxta-canalicular tissue, which has the greatest concentration of mucopolysaccharides and phagocytic activity.

Theories

- Abnormal levels of TGF- β 2 in the aqueous of patients with POAG decrease the cellularity of the trabecular meshwork and promote the buildup of excessive amounts of extracellular matrix materials, with subsequent increased resistance to aqueous outflow.
- The loss of trabecular endothelial cells is responsible for the phagocytosis of macromolecules.
- The loss of giant vacuoles in the endothelium of Schlemm's canal and the collapse of Schlemm's canal also increases the resistance to aqueous outflow.
- Decrease in the size and density of pores in the inner wall of Schlemm's canal is also found to play a role.

Corticosteroid sensitivity

- There is some amount of IOP elevation in response to potent topical steroids.
- An abnormal response of the hypothalamic-pituitary-adrenal axis may be related to alterations in aqueous humor dynamics in response to corticosteroids.^[10]

- Corticosteroids reduce the phagocytic activity of endothelial cells lining the trabecular meshwork.

Oxidative damage

Glutathione metabolism is intrinsically involved. Glutathione protects the endothelial cells from hydrogen peroxide.

Mechanisms of optic neuropathy

Ischaemic damage

Compression of blood vessels supplying the optic nerve head.

Apoptosis of ganglion cells

Calcium influx into the cell body and an increase in nitric oxide result in astrocyte and glial cell proliferation and alteration of the extracellular matrix of the lamina cribrosa [Figure 1].

Diagnosis

Symptoms

Usually asymptomatic until the late stage of glaucoma. In advanced glaucoma, there is loss of fixation or loss of peripheral vision.

Occasionally, in cases of a severe rise in IOP, there can be eye pain, headache, or haloes.

Signs

Usually none. Relative afferent pupillary defect (RAPD) can be seen in asymmetric or unilateral advanced disease.

History

Past medical history like asthma, heart disease, head injury, migraine, diabetes, psychiatric illness, or neurological disease (to rule out mimicking field defects).

- Ocular history of refractive error and trauma.
- Family history of glaucoma.

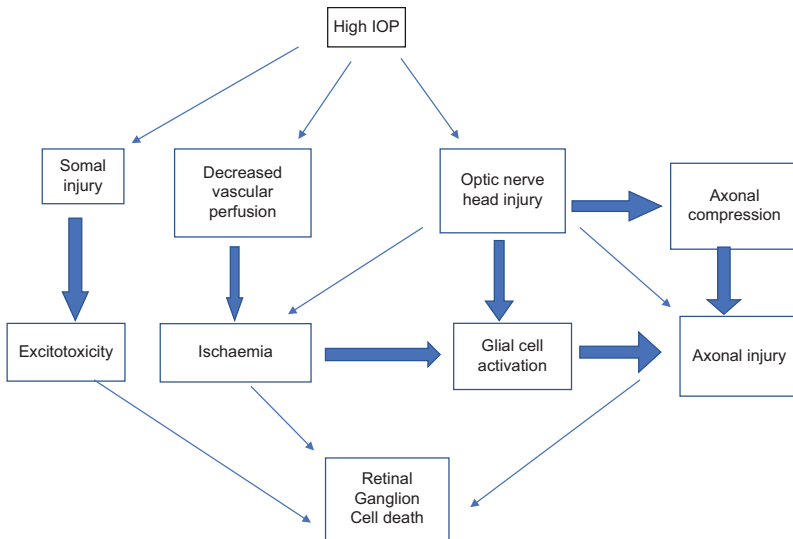


Figure 1: Mechanisms of optic nerve damage

- Medication history for use of topical or systemic steroids, steroid creams or inhalers, oral contraceptive pills, and oral beta blockers.
- Social history includes smoking or alcohol intake.
- Allergy history to sulphonamides or other drugs.

Examination

- Best-corrected visual acuity.
- Pupils (for RAPD).
- Slit lamp examination to exclude features of angle closure and secondary glaucoma.
- Tonometry, preferably by applanation.
- Pachymetry for CCT.
- Gonioscopy.
- Optic nerve head evaluation with a 90D lens and using red-free light is used to detect RNFL defects [Table 1, Figures 2 and 3].

Investigations

- Visual field evaluation: Small paracentral depression in the early stage, nasal step, arcuate defects, ring scotoma, small island of central vision with temporal island [Figure 4].^[11]
- Optic nerve head and RNFL imaging [Figure 5].

Table 1: Optic nerve head findings for glaucoma

Signs	Description
Cup to disc ratio	Raised, usually >0.7 Asymmetry between eyes >0.2 Vertical elongation, denoting loss of superior or inferior rim Deepening of cup
Neuro retinal rim (NRR)	Excavation, notching, or focal loss Pallor
Retinal nerve fiber layer (RNFL)	Localized wedge defects Diffuse in advanced stage
Vascular	Splinter hemorrhage Bayoneting Baring of circumlinear vessels Nasalization of vessels Overpass
Peripapillary changes	Peripapillary atrophy-hyper pigmentation, depigmentation

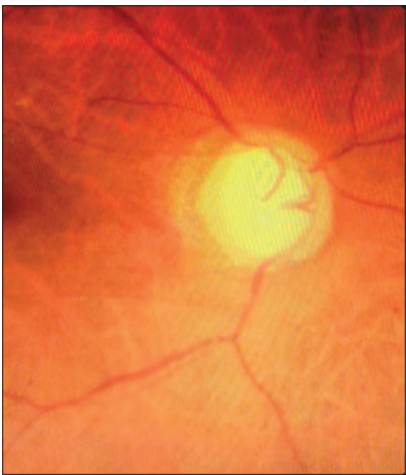


Figure 2: Nasalisation of blood vessels, peripapillary atrophy, inferior and superior rim thinning

MANAGEMENT

Goals

- Control of IOP in the target range.
- Stable optic nerve and RNFL status.
- Stable visual fields.

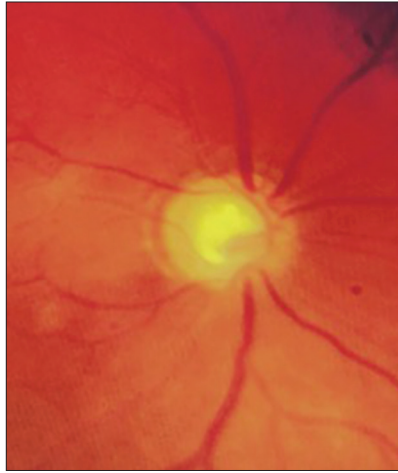


Figure 3: Nasalisation and deepening of cup

Choice of therapy

Medical therapy is the most common initial intervention to lower the IOP [Figure 6]. Prostaglandin analogues are the 1st choice, as these are most efficacious and instilled once daily [Table 2].

Follow-up protocol^[12]

- The interval to review after starting medication depends on the severity of glaucoma but is usually 4–8 weeks.
- Depending on the efficacy and target IOP required, drugs may be added or substituted.
- Fixed-dose combinations offer better compliance, are more cost-effective, and have lesser side effects compared to individual molecules.
- If the response is satisfactory, the patient is reviewed 3–6 monthly.
- Perimetry should be done every 6 months to look for progression, if any.^[11]
- An optic disc examination is performed at each visit.

Causes of treatment failure

- Poor compliance with the therapy.
- Undetected diurnal variation.
- Inappropriate target pressure.

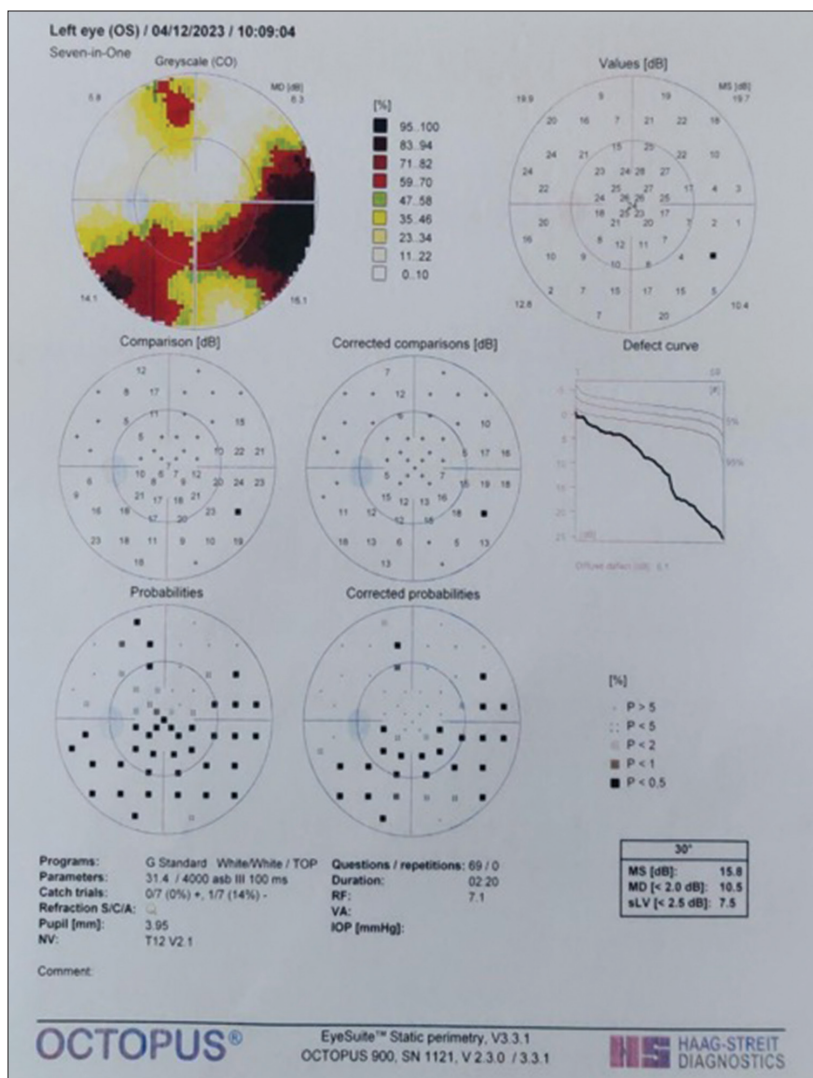


Figure 4: Automated perimetry shows nasal step with inferior arcuate scotoma

Laser trabeculoplasty

Selective LASER Trabeculoplasty may be used as an adjunct or initial therapy (especially in pregnancy). It lowers the IOP by improving aqueous outflow. It may be performed in 180 degrees or 360 degrees of angle in a single visit.

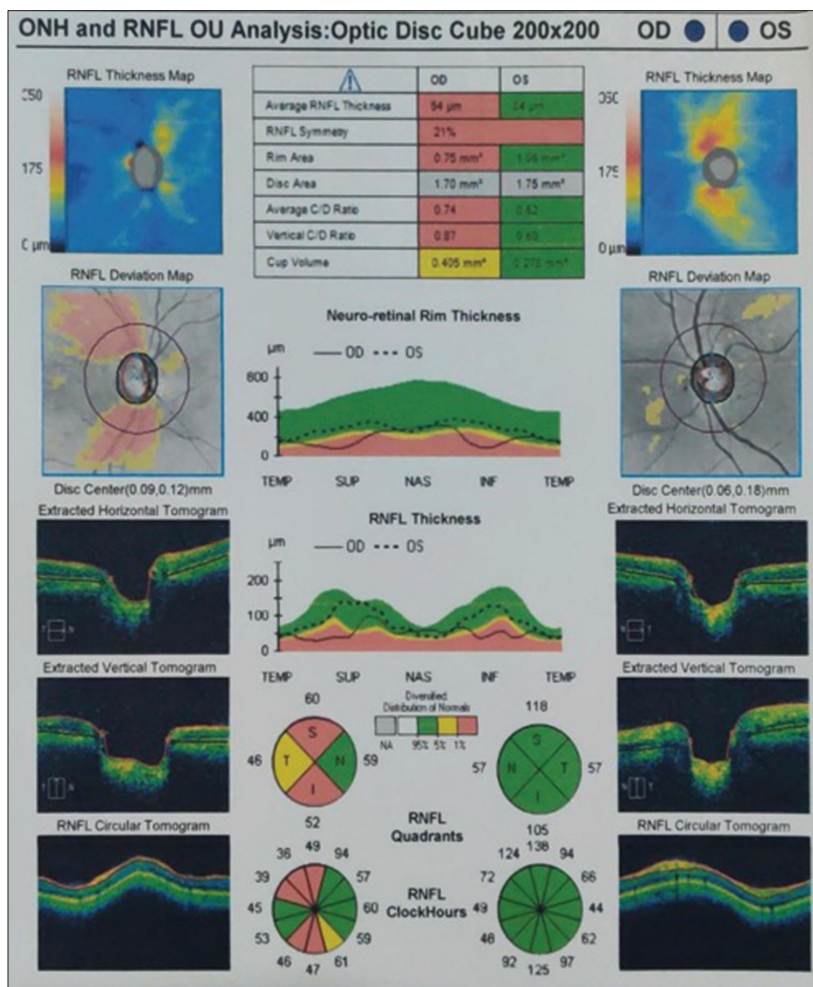


Figure 5: Optical Coherence Tomography showing superior, inferior and temporal thinning of RNFL in right eye

Surgery

Trabeculectomy is the procedure, most commonly performed when maximum medical therapy fails to control IOP, progression is evident, or patients are not compliant or intolerant to the therapy.

It can be combined with cataract surgery in patients with significant cataracts.

Glaucoma drainage devices are used when trabeculectomy has failed to control IOP.

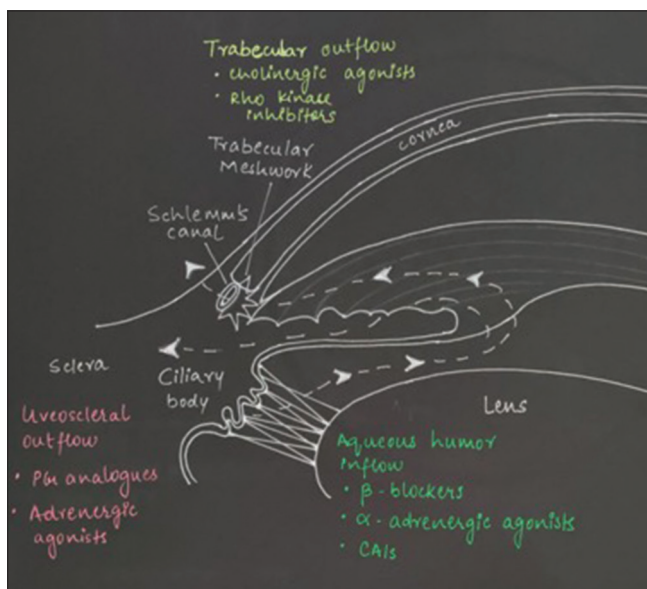


Figure 6: Mechanism of action of antiglaucoma drugs

Table 2: Efficacy of antiglaucoma drugs in lowering IOP

Drugs	Reduction in IOP (%)
Selective beta blockers	20–25
Non selective beta blockers	25–30
Prostaglandin analogues	27–34
Topical carbonic anhydrase inhibitors	15–20
Systemic carbonic anhydrase inhibitors	20–30
Cholinergics	20
Rho kinase inhibitors	10–20
Alpha adrenergic agonists	20–30

Minimally invasive glaucoma surgery (MIGS) can be performed in select cases.

Prognosis

It is determined by (1) the degree of optic nerve damage, (2) peak IOP, (3) the vulnerability of the disc, (4) the presence of systemic vascular disease, (5) compliance with treatment, and (6) ethnic origin

(prognosis better in whites). Age is also a factor, as the older one gets, the more is the disease likely to progress.^[12,13]

Major POAG Clinical Trials

1. Early manifest glaucoma trial (EMGT)^[13]

Aim:

- To compare the effect of immediate therapy versus late or no treatment on the progression of newly detected POAG.
- To determine the extent of IOP reduction attained by treatment and to explore factors influencing glaucoma progression.

Results:

- Progression after 6 years
 - Treatment group: 45%
 - Control-62%
- High risk of progression associated with old age, higher baseline IOP, pseudoexfoliation, bilateral disease, and advanced baseline field changes.

Conclusion:

The risk of progression decreased by 10% with each 1mmHg IOP reduction from baseline.

2. Collaborative initial glaucoma treatment study (CIGTS)^[14]

Aim:

- Determine if glaucoma is better treated by initial medical therapy or trabeculectomy.

Results:

- Significant lowering of IOP in the surgical group.
- Visual field score maintained in surgical group.
- Cataract formation increased after trabeculectomy.
- At 5 yrs follow up, more reduction in visual acuity in surgical group.

Conclusion:

IOP reduction is greater with surgery, but quality of life is worse with surgery.

3. Advanced Glaucoma Intervention Study (AGIS)^[15]

Aim:

- Determine if advanced open-angle glaucoma is better treated by initial argon laser trabeculoplasty or trabeculectomy.

Outcome:

Visual function outcomes better in ATT sequence in blacks and better in TAT sequence in whites.

Suggested Reading

1. 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;266:369-74.

2. Allison K, Patel D, Alabi O. Epidemiology of glaucoma: The past, present, and predictions for the future. *Cureus* 2020;12:e11686.
3. Kahn HA, Leibowitz HM, Ganley JP, Kini MM, Colton T, Nickerson RS, *et al.* The Framingham Eye Study. II. Association of ophthalmic pathology with single variables previously measured in the Framingham Heart Study. *Am J Epidemiol* 1977;106:33-41.
4. George R, Ve RS, Vijaya L. Glaucoma in India: Estimated burden of disease. *J Glaucoma* 2010;19:391-7.
5. Francois J, Heintz-DeBree C. Personal research on the heredity of chronic simple (open-angle) glaucoma. *Am J Ophthalmol* 1966;62:1067-71.
6. Stoilove D, Child A, Trifan OC, Crick RP, Coakes RL, Sarfarazi M. Location of a locus (GLC1B) for adult-onset primary open angle glaucoma to the 2cen-q13 region. *Genomics* 1996;36:142-50.
7. Healey PR, Mitchell P. Optic disk size in open-angle glaucoma: The Blue Mountains Eye study. *Am J Ophthalmol* 1999;128:515-7.
8. Kim SH, Park KH. The relationship between recurrent optic disc hemorrhage and glaucoma progression. *Ophthalmology* 2006;113:598-602.
9. Ren R, Jonas JB, Tian G, Zhen Y, Ma K, Li S, *et al.* Cerebrospinal fluid pressure in glaucoma: A prospective study. *Ophthalmology* 2010;117:259-66.
10. Kass MA, Shin DH, Cooper DG, Becker B. The ocular hypotensive effect of epinephrine in high and low corticosteroid responders. *Invest Ophthalmol Vis Sci* 1977;16:530-1.
11. Chen PP. Correlation of visual field progression between eyes in patients with open-angle glaucoma. *Ophthalmology* 2002;109:2093-9.
12. Kronfeld PC, McGarry HI. Five year follow-up of glaucoma. *JAMA* 1948;136:957-65.
13. Leske MC, Heijl A, Hussein M, Bengtsson B, Hyman L, Komaroff E, *et al.* Factors for glaucoma progression and the effect of treatment: The early manifest glaucoma trial. *Arch Ophthalmol* 2003;121:48-56.
14. Musch DC, Lichter PR, Guire KE, Standardi CL. The Collaborative Initial Glaucoma Treatment Study: Study design, methods, and baseline characteristics of enrolled patients. *Ophthalmology* 1999;106:653-62.
15. Ederer F, Gaasterland DE, Sullivan EK; AGIS Investigators. The Advanced Glaucoma Intervention Study (AGIS): 1. Study design and methods and baseline characteristics of study patients. *Control Clin Trials* 1994;15:299-325.
16. Bhartiya S, Singh M, Mitra A, editors. *Clinical Handbook of Glaucoma*. Noida: Incessant Nature Science Publishers; 2023.
17. Bhartiya S, editor. *Master Cases in Glaucoma*. New Delhi: United Scientific Solutions; 2023.

CHAPTER

6

Ocular Hypertension

Alokesh Ganguly

Summary of Clinical Decision-Making

1. Intraocular pressure (IOP) must be measured three times on separate occasions, preferably at different times of the day during office hours.
2. Essential investigations: Gonioscopy (including indentation), slit lamp biomicroscopy, and/or imaging studies of the optic nerve head (ONH), reliable visual field.
3. No validated nomograms exist for IOP correction on the basis of central corneal thickness (CCT). IOP corrected for CCT does not provide a valid basis for initiating or not initiating therapy.
4. The threshold for starting treatment for OHT is lower for patients with risk factors, including:
 - African or Hispanic ancestry
 - Family history of glaucoma in a first-degree blood relative with or without history of loss of vision due to glaucoma
 - Younger patients
 - Patients with myopia
 - Patients with a high risk of being lost to follow-up due to remote places of residence
 - Patients with decreased corneal thickness, high C: D ratio, and/or visual fields with a high PSD.
5. Consider the economics of glaucoma therapy as also compliance QoL costs of treatment versus no treatment for the individual.
6. Consider selective laser trabeculoplasty versus topical glaucoma therapy.

Introduction

Ocular hypertension (OHT) is defined as elevated intraocular pressure (IOP) measured >21 mmHg on at least three occasions, in subjects

with normal, open anterior chamber angles, no glaucomatous optic nerve changes or retinal nerve fiber layer (RNFL) defects or visual field abnormalities. There should be no history of steroid usage, no history of uveitis, no evidence of neovascularization, etc.

Investigations

Every patient with OHT requires a careful and comprehensive eye examination to rule out early signs of glaucoma or secondary causes of elevated IOP.

Mandatory Tests Include

1. Visual acuity and refraction.
2. Tonometry: Ensure that the baseline eye pressure is checked on at least more than one visit preferably three times, at different times of the day, to establish baseline IOP, before labeling the patient as having high IOP. Goldmann Applanation tonometry still remains the gold standard for measuring IOP. IOP > 21 mmHg is mandatory for diagnosing OHT.
3. Gonioscopy is critical to managing any glaucoma suspect so as to rule out angle closure. Only patients with anatomically normal and open angles qualify as having ocular hypertensives.
4. Optic nerve assessment: Together with a red-free assessment of the peripapillary RNFL, a dilated examination of the ONH is crucial. A manually drawn, labeled diagram with a focus on the cup/disc ratio, notching, RNFL flaws, and/or hemorrhage, as well as a clinical photograph, can be used to record the ONH. For serial follow-up, a color photograph and a red-free shot of the ONH are required.
5. Visual field testing: Reliable visual fields provide a baseline for future follow-up. If abnormal, the first visual field must be repeated to compensate for the learning curve of the machine.
6. CCT, or pachymetry, is required to make therapeutic decisions.
7. The following tests are also contributory to a detailed examination and follow-up of ocular hypertensives, to be done at the discretion of the physician:
8. Stereo-optic disc photographs to confirm normal optic nerve parameters and document baseline
9. Imaging of the optic nerve with RNFL analysis (scanning laser polarimetry, Heidelberg retinal tomography, or ocular coherence

- tomography) offers a statistical comparison with the normative database, offering more data for the management that comes after.
10. Diurnal variation of the IOP curve could impact the course of treatment and offer more details. Water drinking test (WDT): To get a rough notion of IOP changes, a WDT using 10 mL/kg body weight of water over 5 min may be used instead of the 24-h diurnal variation of IOP.

Patient factors favoring treatment versus observation in OHT	
Factors favoring treatment	Factors favoring observation
Young age (longer life expectancy)	Older age (shorter life expectancy)
Older age (higher risk of POAG)	Younger age (lower risk of POAG)
Highly elevated untreated IOP	Borderline elevated untreated IOP
Thin CCT	Thick CCT
Increased vertical cup-to-disc ratio	Inability to afford treatment
Higher pattern standard deviation	Inability to tolerate treatment
Disc hemorrhage	Inability to comply with treatment
Positive family history	Patient preference against treatment
African ancestry	
POAG in fellow eye	
Loss of vision in fellow eye (due to any cause)	
Patients with myopia	
Patients without access to repeat glaucoma investigations	
Low patient risk tolerance	

OHT: Ocular hypertension, IOP: Intraocular pressure, CCT: Central corneal thickness

Role of Risk Calculators for Treatment of OHT

The OHT Treatment Study (OHTS) [Table 1] and the European glaucoma Prevention Study (EPGS) [Table 2] have provided data on the conversion of OHT to primary open-angle glaucoma (POAG) in two independent groups of patients, which have been used to develop risk calculators. These do provide estimates of global risk but cannot definitively determine which individual patients would benefit from

Table 1: OHTS

Objectives: Role of topical IOP lowering agents in preventing the onset of POAG
Risk factors in the development of POAG

Participants: 1636 patients were included between ages of 40–80 years; IOP range was 24–32 mmHg in at least one eye and 21–32 in the fellow eye

Intervention: Participants were randomized to observation versus 20% IOP reduction (to IOP ≤ 24) using topical medication

End point: Optic nerve glaucomatous change or visual field abnormality was the end points.

Conclusions:

- 5-year glaucoma risk is 4.4% in treated eyes versus 9.5% in untreated eyes.
- Risk factors for developing glaucoma include:
 1. Old age: 10 years older $\rightarrow$ 22% more risk
 2. African–American race (only univariate analysis)
 3. Higher IOP: 1 mmHg rise in IOP corresponds to a 10% increase in risk
 4. Thinner CCT (< 555 μm): a 40 μm decrease corresponds to an 81% increase in risk
 5. Higher pattern standard deviation: 0.2 change corresponds to a 22% increase in risk.
 - Higher baseline C/D: an increase in the vertical C: D ratio of 0.1 corresponds to a 32% increase in risk
 6. NOT family history (though most other studies say yes)
- OHTS phase 2–13-year follow-up: Treatment initiated after 7.5 years of observation, monitored for 5.5 more years:
 1. 16% treated versus 22% untreated eyes develop glaucoma.

There is no further increase in risk once treatment is started between the treated and observation groups. Data suggest that patients with $>13\%$ risk for the development of POAG, according to the OHTS/EPGS risk calculator, would benefit from earlier treatment or more frequent observation.

OHT: Ocular hypertension, IOP: Intraocular pressure, POAG: Primary open-angle glaucoma, OHTS: OHT treatment study

treatment. The above table shows the multiple factors to be considered, on top of matching the patient profile to the population studied in the OHTS.

The Level of IOP Elevation to Begin Treatment

Some physicians start treatments at IOPs above 21 mmHg; some do so at levels above 26 mmHg; and some only at 30 mmHg or above. There is no unique accepted evidence-based standard for optimum reduction of IOP in OHT, and one has to be guided by one's clinical

Table 2: EGPS

Objective: The EGPS was conducted to evaluate the efficacy of reducing IOP by topical dorzolamide in prevention or delaying the onset of primary open-angle glaucoma (POAG) in patients affected by OHT (OHT).

1. Design: This was a randomized, double-masked, controlled clinical trial.
2. Participants: One thousand eighty-one patients (age, ≥ 30 years) were part of the study. The inclusion criteria were IOP 22–29 mmHg at baseline; at least 2 normal and reliable visual fields (on the basis of mean deviation and corrected pattern standard deviation or corrected loss variance of standard 30/II performed on both Humphrey and Octopus perimetry); normal optic disc fulfilling optic disc reading center criterion.
3. Intervention: Patients were randomized to treatment with topical dorzolamide or placebo (which was the vehicle of dorzolamide applied topically).
4. Main outcome measures:
 - a. In this study, the endpoints measured were visual field changes, optic disc changes, or both parameters.
 - b. A visual field change during follow-up was confirmed by 2 further positive tests to be considered reliable.
 - c. Optic disc change was determined by the agreement of at least 2 of 3 independent observers evaluating optic disc stereo slides as per the criteria set by the optic disc reading center.
 - d. The safety endpoint was reached if the IOP of more than 35 mmHg on 2 consecutive examinations was measured.
5. Results:
 - a. This study showed that the mean reduction in IOP in percentage in the dorzolamide-treated group was 15% after 6 months which increased to 22% after 5 years.
 - b. Mean IOP in the study observation//placebo group declined as follows - 9% after 6 months and by 19% after 5 years.
 - c. After 60 months, the study showed that the cumulative probability of converting to an efficacy endpoint was 13.4% in the group receiving topical dorzolamide and 14.1% in the placebo group (with a hazard ratio of 0.86; 95% confidence interval [CI], 0.58–1.26; $P=0.45$).
 - d. The cumulative probability of developing an efficacy or a safety endpoint was 13.7% in the group receiving dorzolamide and 16.4% in the placebo group (with a hazard ratio of 0.73; 95% CI: 0.51–1.06; $P=0.1$).
6. Conclusions: Dorzolamide eye drops were seen to reduce IOP by 15–22% throughout the 5 years of the trial in patients with OHT.

The EGPS was unable to detect a statistically significant difference between medical therapy and placebo in reducing the incidence of POAG among a large population of OHT patients at moderate risk for developing POAG.

EGPS: European glaucoma prevention study, OHT: Ocular hypertension, IOP: Intraocular pressure, POAG: Primary open-angle glaucoma

judgment and experience while keeping in mind all the factors noted in the above table.

Relationship of Retinal Vein Occlusion with OHT

Some ophthalmologists prefer to treat OHT patients to prevent future retinal vein occlusions. The incidence of retinal vein occlusions in the OHTS was retrospectively analyzed in a study that showed 26 RVO's (5 BRVOs/14 CRVOs/7 HCRVO's) in 23 study participants out of 1636. The 10-year cumulative incidence of RVO projected in this study was 2.1% in the observation group and 1.4 % in the medication group (log rank $P=0.14$). Older patients with larger horizontal CD ratios at baseline developed relatively more RVOs.

Discussion with Patients

Salient points to be discussed with patients before initiating therapy for OHT should ideally include

1. Making the patient Understand the implications of OHT: The patient must understand that he or she is at risk of glaucoma but is not suffering from the disease yet. The risk of glaucoma is significantly higher in eyes with OHT as compared to the normal population.
2. Freely discussing the risks and benefits of glaucoma therapy in the setting of OHT: The risks and benefits of treatment, as well as its QoL and economic implications, must be discussed with the patient. The associated risk factors that are guiding you to treat or defer treatment must be explained to the patient.
3. When discussing treatment options, the risks of SLT versus medical therapy must be discussed with the patient, in case the former is available.
4. Compliance and adherence: In the case of prescribed treatment for OHT, the patient must be explained that compliance and adherence to therapy are essential. In addition, the patient must be taught how to apply eye drops.
5. Importance of follow-up: The importance of follow-up, just like compliance, in a chronic asymptomatic disease like glaucoma cannot be overemphasized. Ensure clear written guidelines for future follow-up, including probably frequency of investigations.

6. Apprehensive patient: The apprehensive patient may require a little more reassurance, regardless of whether they are being counseled for treatment or not.

Treatment Target

The goal of reducing IOP should target lowering baseline IOPs by 20–30% and below 24 mmHg.

Compliance and follow-up

If the patient is unable to follow-up or understand the implications of the OHT, it may be better to start treatment, rather than not. The risks and benefits of treatment, as well as its QoL and economic implications, must be discussed with the patient.

Follow up protocol

The follow-up protocol has to be customized to the individual patient, depending on the risk of developing glaucoma, the risk factors evident, and whether treatment has been initiated or not. Initially, a follow-up may be scheduled every 4 months for IOP and a complete eye evaluation. Repeat visual field testing may be performed once a year or earlier if optic disc changes are picked up.

Key Evidence Base

The definitive study that influences the management of OHT in the current evidence-based practice of glaucoma is the OHTS and the EPGS.

The studies are described in brief in Tables 1 and 2.

Suggested Reading

1. American Academy of Ophthalmology Glaucoma Panel. Preferred Practice Pattern Guidelines. Primary Open-angle Glaucoma. San Francisco, CA: American Academy of Ophthalmology; 2010. Available from: <https://www.aao.org/ppp> [Last accessed on 2016 Mar 20].
2. Broman AT, Quigley HA, West SK, Katz J, Munoz B, Bandeen-Roche K, *et al*. Estimating the rate of progressive visual field damage in those with

- open-angle glaucoma, from cross-sectional data. *Invest Ophthalmol Vis Sci* 2008;49:66-76.
3. Heijl A, Bengtsson B, Hyman L, Leske MC, Early Manifest Glaucoma Trial Group. Natural history of open-angle glaucoma. *Ophthalmology* 2009;116:2271-6.
 4. Jay JL, Murdoch JR. The rate of visual field loss in untreated primary open angle glaucoma. *Br J Ophthalmol* 1993;3:176-8.
 5. Leske MC, Heijl A, Hussein M, Bengtsson B, Hyman L, Komaroff E, *et al.* Factors for glaucoma progression and the effect of treatment: The early manifest glaucoma trial. *Arch Ophthalmol* 2003;121:48-56.
 6. Leske MC, Heijl A, Hyman L, Bengtsson B, Dong L, Yang Z, *et al.* Predictors of long-term progression in the early manifest glaucoma trial. *Ophthalmology* 2007;114:1965-72.
 7. Lichter PR, Musch DC, Gillespie BW, Guire KE, Janz NK, Wren PA, *et al.* Interim clinical outcomes in the collaborative initial glaucoma treatment study comparing initial treatment randomized to medications or surgery. *Ophthalmology* 2001;108:1943-53.
 8. South East Asia Glaucoma Interest Group. Asia-Pacific Glaucoma Guidelines. 2nd ed. Australia: South East Asia Glaucoma Interest Group; 2008.
 9. Barnett EM, Fantin A, Wilson BS, Kass MA, Gordon MO, Ocular Hypertension Treatment Study Group. The incidence of retinal vein occlusion in the ocular hypertension treatment study. *Ophthalmology* 2010;117:484-8.
 10. Miglior S, Zeyen T, Pfeiffer N, Cunha-Vaz J, Torri V, Adamsons I, *et al.* Results of the European glaucoma prevention study. *Ophthalmology* 2005;112:366-75.
 11. Bhartiya S, Singh M, Mitra A, editors. *Clinical Handbook of Glaucoma*. Noida: Incessant Nature Science Publishers; 2023.
 12. Bhartiya S, editor. *Master Cases in Glaucoma*. New Delhi: United Scientific Solutions; 2023.

CHAPTER

7

Normal-tension Glaucoma

Sachin Dharwadkar

Summary of the Clinical Decision-making:

- Normal tension glaucoma is a more common condition than thought and should not be missed
- It is a slowly progressive disease in most of the cases
- It is a diagnosis of exclusion requiring extensive due diligence and checklist verification
- Essential investigations in addition to the diagnosis of glaucoma will be dictated by systemic comorbidity with a detailed history
- Threshold for starting treatment is high as majority of the cases do not progress or progress slowly
- Immediate treatment is to be considered for cases with scotomas near or threatening fixation
- Progressive cases of normal tension in glaucoma surgery, more frequently than high tension glaucomas
- It is very important to rule out. Non-glaucomatous optic neuropathy in this subset of cases.

Introduction

Normal tension glaucoma (NTG) is a form of open-angle glaucoma (OAG) or a continuum characterized by glaucomatous optic neuropathy wherein the intraocular pressure (IOP) measurements are consistently lower than 21 mmHg on all occasions (by applanation tonometry).

Based on the prevalence and incidence in various population-based studies, it is now found to be as common as $\frac{1}{3}$ – $\frac{2}{3}$ of all OAGs.

The difficult part here is to isolate the etiology, which can often be elusive even after significant due diligence.

Conventionally, vascular and ischemic factors as well as abnormal responses to normal mechanical stressors are said to predispose the optic nerve to damage at otherwise normal IOP ranges. Associations with vasospastic phenomena such as migraine, Raynaud's, and cerebral ischemic events are known as ones with autoimmunity.

Investigations

Besides the basic glaucoma investigations such as visual acuity, applanation tonometry, gonioscopy, stereo disc photographs, central corneal thickness, field tests, and OCT that are mandatory for all patients, this subset requires systemic investigations as dictated by risk profile and leading questions on history.

Medication history has to be in full detail enumerating all clinical events in the lifetime and current medications, addictions, substance abuse, alternative therapies (YOGA, Homeopathy, Ayurveda).

Ophthalmic history specifically should rule out steroid usage and trauma.

Special attention is to be paid to gonioscopy to rule out subtle angle closure elements, central corneal thickness is mandatory, and diurnal variation of IOP is very informative not to miss out a masquerading OAG.

Optic disc photographs of disc hemorrhages are a must to be documented to assess the progression of the disease.

In post-refractive surgery status, most cases will need a baseline AS OCT of the cornea for interface status and corneal thickness.

As vascular and hypoxic risk factors predispose to NTG certain systemic investigations and interdisciplinary consults are necessitated from time to time.

1. 24-h BP monitoring/Holter: Patients who have a history of unsupervised anti-hypertensive regimens for a long time, especially those who suffer from postural hypotension.
2. Sleep study for patients that have a history of snoring and associated sleep disturbances with a high STOP BANG score (Sleep apnea screening score). These patients need to be investigated for AHI as well as the effect of continuous positive airway pressure (CPAP) titration to elicit improvement.

3. Neuroimaging in certain cases where the field defects or the nerve head appearance deem it necessary
4. Carotid and ophthalmic artery Doppler: In high-risk individuals with signs of ocular ischemia.

Differential diagnosis:

1. Burnt out OAG
2. Old steroid response
3. Subtle secondary glaucoma
4. Post-refractive surgery false low IOP
5. Ischemic optic neuropathy
6. Compressive optic neuropathy
7. Drug-induced optic neuropathy.

Post-inflammatory - multiple sclerosis, tuberculosis, syphilis, etc.

Red flags that suggest alternative diagnosis:

1. Fast progression
2. Field defects not in the arcuate area or non-glaucomatous in appearance
3. Pallor more than cupping
4. Unilateral disease/markedly asymmetric disease
5. Younger patient (<65 years age).

Key Evidence Base

Collaborative NTG study (CNTGS):

- Largest and most extensive trial for NTG, progression based on VF and Disc photographs compared treatment (30% IOP reduction) to observation
- 12% treated and 35% untreated eyes progressed
- 65% untreated DID NOT progress, cataracts being more common in treated.

LoGTS study:

- Compared brimonidine to timolol for the treatment of NTG
- At 30 months, with similar IOP reduction, brimonidine patients progressed less (9.1 v/s 39.2%)
- The high dropout rate of brimonidine patients due to side effects, however, affected the power of the study
- Circumstantial evidence shows that timolol may not be the first choice pharmacotherapy for NTG.

Management

Patient communication

Points that need to be put across:

1. Importance of systemic assessment and its contribution - helps in eliciting prompt systemic testing
2. Allay apprehension - slow nature of the disease
3. Need for regular follow-ups - protocol similar to OAG for frequency of testing (dynamic testing) with fields/imaging.
4. Motivation for following systemic therapy – CPAP, etc.

Pharmacotherapy

Targets: 30% IOP lowering from baseline (CNTGS)

PGA, alpha agonist, and CAI preferred drugs, timolol to be avoided.

IOP lowering at low baseline IOP is not easy to achieve and measure.

Episcleral venous pressure limits IOP-lowering effects of SLT/drugs.

Surgical treatment

Progression in spite of IOP lowering/inability to lower IOP to target levels and associated progression may require trabeculectomy with mitomycin C.

Suggested Readings

1. Leung DY, Tham CC. Normal-tension glaucoma: Current concepts and approaches-a review. Clin Exp Ophthalmol 2022;50:247-59.
2. Killer HE, Pircher A. Normal tension glaucoma: Review of current understanding and mechanisms of the pathogenesis. Eye (Lond) 2018;32:924-30.
3. Reza Razeghinejad M, Lee D. Managing normal tension glaucoma by lowering the intraocular pressure. Surv Ophthalmol 2019;64:111-6.
4. Adeghate J, Rahmatnejad K, Waisbourd M, Katz LJ. Intraocular pressure-independent management of normal tension glaucoma. Surv Ophthalmol 2019;64:101-10.
5. Mercer R, Mathew RG, Henein C. Infographic: Collaborative normal-tension glaucoma study (CNTGS). Eye (Lond) 2021;35:2667-8.

6. Bhartiya S, Clement C, Dorairaj S, Kong G, Albis O, editors. Clinical Decision Making in Glaucoma. 1st ed. New Delhi: Jaypee Brothers Medical Publishers; 2019.
7. Bhartiya S, Icchpujani P, editors. Manual of Glaucoma. 1st ed. New Delhi: Jaypee Brothers Medical Publishers; 2015.
8. Bhartiya S, Singh M, Mitra A, editors. Clinical Handbook of Glaucoma. Noida: Incessant Nature Science Publishers; 2023.
9. Bhartiya S, editor. Master Cases in Glaucoma. New Delhi: United Scientific Solutions; 2023.

CHAPTER

8

Medical Management of Glaucoma

Trupti Sudhir Patil

Summary (Key Points)

- Glaucoma medications are started when there is a risk of glaucomatous optic nerve damage
- The aim is to achieve the target intraocular pressure (IOP) range with stable retinal nerve fiber layer and visual field status.
- Points to be considered before starting medical therapy – life expectancy, severity of disease, baseline IOP presence of ocular and systemic comorbidities.
- The presence of additional risk factors such as thinner pachymetry, family history of glaucoma, age, IOP, presence of pseudoexfoliation, and disc hemorrhage needs to be considered before starting treatment for glaucoma suspect^[1-4] Target IOP – dynamic IOP ranges at which rate of progression of glaucomatous damage is minimized so that it does not affect quality of life.^[1-4]
- Target IOP should be maintained with minimum medications with the least side effects with maximum efficacy. Target IOP is adjusted as per the patient's condition during follow-up.
- IOP-lowering medications reduce IOP by inhibiting aqueous production or increasing aqueous outflow through conventional or uveoscleral pathways. Potential side effects and contraindications for individual drugs are given in Table 1.
- The first drug of choice is prostaglandin analogs in most of the cases.^[1-4]
- With monotherapy expected IOP reduction is 20%, >10% IOP drop is considered a non-responder.
- With initial treatment at least 20 % lower IOP than pretreatment IOP is expected. Need lower target IOP as severity increases.
- Percentage of IOP reductions^[3]
- 20% ocular hypertension treatment study

- 25% early manifest glaucoma trial
- 37% collaborative normal tension glaucoma study
- 38% collaborative initial glaucoma treatment study
- Combination therapy with a fixed-dose combination is started if monotherapy fails to reach the target IOP.
- Maximal glaucoma therapy – more than 3 glaucoma medications.^[5] A fourth medication is considered effective if an additional drop in IOP by at least 15% is achieved.
- Carbonic anhydrase inhibitor are available as topical and systemic medication. Oral Carbonic anhydrase inhibitor and oral hyperosmotic medications are usually used to reduce IOP immediately, or patient awaiting for glaucoma surgery (Table 2).
- Treatment should be cost-effective with minimum side effects and least concentration. Systemic side effects can be reduced using reduced frequency dose, eyelid closure, and nasolacrimal duct occlusion.
- For PG analog peak effect is seen 12 h after administration; for remaining eye drops, it is 2 h. PG analog effect lasts for 24 h.^[4]
- PG analog and topical CIA inhibitors reduce nocturnal IOP while beta blockers and alpha agonists have no effect on nocturnal IOP.^[6]
- When combined with PG analog, IOP-lowering efficacy is similar to beta blockers, alpha agonists, and carbonic anhydrase inhibitors.^[4]

Special Condition

Pregnancy

Drug Pregnancy categories

- Class A-A-controlled studies showed no risk to the fetus
- Class B-No risk to humans, no risk based on human study but animal studies show risk
- Class C-Can be a risk to humans, animal studies show risk, human studies lacking
- Class D-Positive evidence of risk to infant.

Brimonidine is the only class B medication available, the rest of the medications are class 3.

In the first 8 weeks of pregnancy, organogenesis happens, so IOP-lowering medications should be avoided. Later on, brimonidine and beta-blockers can be used. Fetal growth and heart rate need to be

Table 1: Topical IOP-lowering medication mechanism of action, side effects, and contraindications^[1,4,7]

Drug	Mechanism of action	Dose	Peak%	Trough%	Ocular side effects	Systemic side effects	Contraindications
Timolol Maleate 0.5% Non-selective beta-adrenergic antagonist (Block beta 1 and 2 receptor)	Decrease aqueous production	Twice daily	27	26	Stinging, burning itching, dry eye, superficial punctate keratitis, corneal anesthesia, blepharoconjunctivitis	Bradycardia, hypotension, bronchospasm, syncope, nocturnal hypotension, hypoglycemia, mask sign of hypoglycemia, depression, erectile dysfunction	Heart failure, COPD, asthma, sinus bradycardia
Betaxolol 0.5% B1 selective beta-adrenergic antagonist	Decrease aqueous production	Twice daily	23	20	Same as Timolol	Less cardiac and pulmonary side effect	Heart failure, sinus bradycardia
Dorzolamide 2% Topical carbonic anhydrase inhibitor	Decrease aqueous production	Twice or thrice daily	22	17	Burning (more with dorzolamide due to acidic PH 5.6), allergic dermatitis/conjunctivitis, superficial punctate keratitis, burring of vision	Bitter taste	Ocular low endothelial count, sulfonamide allergy, sickle cell disease

(Contd...)

Table 1: (Continued)

Drug	Mechanism of action	Dose	Peak%	Trough%	Ocular side effects	Systemic side effects	Contraindications
Brinzolamide 1% Topical carbonic anhydrase inhibitor			17	17			
Brimonidine 0.1%, 0.15%, and 0.2% alpha 2 adrenergic agonist	Decrease aqueous production Increase uveoscleral outflow	Twice daily	25	18	Blepharoconjunctivitis, contact dermatitis	Dryness of mouth, fatigue, dizziness, weakness, hypotension	with MAO inhibitor, children
Pilocarpine 1%, 2%, 4% Parasympathomimetic cholinergic agonist	Increases trabecular outflow through muscarinic receptors	Thrice or four times	25	20	Blurring of vision transient myopia Constriction field of vision Breakdown of blood-aqueous barrier	Brow-ache Increased Nausea Vomiting Diarrhea Bronchial spasm Bradycardia salivation Abdominal cramps Pulmonary edema	Neovascular glaucoma, retinal hole/detachment, inflammatory glaucoma

(Contd...)

Table 1: (Continued)

Drug	Mechanism of action	Dose	Peak%	Trough%	Ocular side effects	Systemic side effects	Contraindications
Latanoprost 0.005% Prostaglandin analog	Increased uveoscleral outflow once daily at night once a day		31	28	Conjunctival hyperemia, eyelashes thickening and increased growth, increased iris and eye lashes pigmentation, periorbitopathy, cystoid macular edema, possible reactivation of herpes virus, uveitis	Flue-like symptoms, migraine-like headache, muscle pain	Macular edema, history of herpetic keratitis, pregnancy
Travoprost 0.004% Prostaglandin analog			31	29			
Bimatoprost-0.03% 0.01% Prostamide			33	28			
Tafluprost 0.0015% Prostaonid FP receptor agonist		Same as other PG analogs					

(Contd...)

Table 1: (Continued)

Drug	Mechanism of action	Dose	Peak%	Trough%	Ocular side effects	Systemic side effects	Contraindications
Netarsudil 0.02% Rho-kinase inhibitor and norepinephrine transport inhibitor	Increase trabecular outflow; decrease episcleral venous pressure, decrease aqueous production	Once a day	20	10	Conjunctival hyperemia, conjunctival hemorrhage, cornea verticillate, pain at the installation site, keratitis	nil	Nil
Ripasudil 0.4% Rho-kinase inhibitor		Twice a day					
Latanoprost bunod 0.024% Nitrous oxide donating Prostaglandin analog	Increased uveoscleral outflow, increased trabecular outflow ⁽⁸⁾	Once a day	26	22	Conjunctival hyperemia, eye irritation, eye pain, increased iris pigmentation	nil	nil

Table 2: Systemic medications for IOP reductions^[1-3]

Drug	Mechanism of action	% of IOP reduction	Side effects	Contraindications
Oral carbonic anhydrase inhibitor Acetazolamide	Decrease IOP	20–30%	Anorexia, malaise, depression, serum electrolyte imbalance, metallic taste, enuresis, Steven–Johnson syndrome, blood dyscrasia, paresthesia, diarrhea, abdominal cramps	Sulfonamide allergy, renal disease, sickle cell anemia, aplastic anemia, thrombocytopenia
Hyperosmotic agent Glycerol Mannitol	Dehydrate vitreous		Dehydration, nausea, vomiting, diarrhea, headache, mental confusion, chest pain, congestive cardiac failure	Renal failure, congestive heart failure, CNS pathology

monitored. Second-trimester PG analog can be added as a third line along with Brimonidine and beta-blocker. (The risk of abortion due to uterine contraction should be kept in mind.) During the third trimester B blocker, PG analog and topical carbonic anhydrase inhibitor can be used (With topical CAI fetal acidosis should be monitored). Systemic CIA should be avoided during pregnancy as limb malformation has been noted in animal studies.^[9,10]

Lactation

All except alpha agnostic can be used.

Neonates

Brimonidine should be avoided due to the risk of CNS depression, hypotension, apnea.

Avoid B blockers in fetuses with cardiac problems. B blockers can cause bradycardia, arrhythmia, hypotension, and CNS depression.

Pediatric Group

B blockers and carbonic anhydrase inhibitors are drug choices. Brimonidine should be avoided among children younger than 6 years. PG analogs are third-line therapy. In Juvenile glaucoma, PG analog can be considered first-line therapy.^[11,12]

Newer Glaucoma Medications

Sustained release Implant-

- a. Punctal plugs - Travoprost and Latanoprost
- b. Surface implant - Bimatoprost ring and Latanoprost eluting contact lens
- c. Intrasceral implant - Ophthalmic micropump
- d. Subconjunctival implant - Durysta Bimatoprost implant – FDA approved^[13,14]
- e. Intracameral implant - Bimatoprost SR, iDose Glaukos drug eluting membrane, travoprost intracameral implant.

Preservatives in Glaucoma Medications

Benzalkonium chloride (BAK) is the most common preservative used in glaucoma medication with concentrations varying from 0.02 to 0.04%. It is bactericidal and enhances drug penetration. Other preservatives available are Polyquad, Purite, and Sofzia.^[15] Drug allergy can be due to type I or IV hypersensitivity reaction to active drug compounds or preservatives used. Better adherence is noted with preservative-free eye drops. Preservative-free eye drops are more costly as compared BAK-free eye drops.

Prescribing medical therapy can be a complex process. Side effects and contraindications should be considered before starting medications.

Suggested Reading

1. World Glaucoma Association. Medical Management of Glaucoma (WGA Consensus Series 7). Netherlands: Kugler Publications; 2010.
2. World Glaucoma Association. Asia Pacific Glaucoma Guidelines. Netherlands: Kugler Publications; 2016.
3. Gedde SJ, Vinod K, Wright MM, Muir KW, Lind JT, Chen PP, *et al.* Primary open-angle glaucoma preferred practice pattern®. *Ophthalmology* 2021;128:P71-50.
4. van der Valk R, Webers CA, Schouten JS, Zeegers MP, Hendrikse F, Prins MH. Intraocular pressure-lowering effects of all commonly used glaucoma drugs: A meta-analysis of randomized clinical trials. *Ophthalmology* 2005;112:1177-85.
5. Fechtner RD, Singh K. Maximal glaucoma therapy. *J Glaucoma* 2001;10(5 Suppl 1):S73-5.
6. Gulati V, Fan S, Zhao M, Maslonka MA, Gangahar C, Toris CB. Diurnal and nocturnal variations in aqueous humor dynamics of patients with ocular hypertension undergoing medical therapy. *Arch Ophthalmol* 2012;130:677-84.
7. Cheng JW, Cheng SW, Gao LD, Lu GC, Wei RL. Intraocular pressure-lowering effects of commonly used fixed-combination drugs with timolol: A systematic review and meta-analysis. *PLoS One* 2012;7:e45079.
8. Kawase K, Vittitow JL, Weinreb RN, Araie M; JUPITER Study Group. Long-term safety and efficacy of latanoprostene bunod 0.024% in Japanese subjects with open-angle glaucoma or ocular hypertension: The JUPITER study. *Adv Ther* 2016;33:1612-27.
9. Strelow B, Fleischman D. Glaucoma in pregnancy: An update. *Curr Opin Ophthalmol* 2020;31:114-22.

10. Drake SC, Vajaranant TS. Evidence-based approaches to glaucoma management during pregnancy and lactation. *Curr Ophthalmol Rep* 2016;4:198-205.
11. Lingham G, Thakur S, Safi S, Gordon I, Evans JR, Keel S. A systematic review of clinical practice guidelines for childhood glaucoma. *BMJ Open Ophthalmol* 2022;7:e000933.
12. Sacchi M, Lizzio RA, Villani E, Monsellato G, Lucentini S, Cremonesi E, *et al*. Medical management of pediatric glaucoma: Lessons learned from randomized clinical trials. *Graefes Arch Clin Exp Ophthalmol* 2020;258:1579-86.
13. Ostler E, Rhee D, Burney E, Sozeri Y. Advances in medical therapy for glaucoma. *Curr Opin Ophthalmol* 2021;32:129-33.
14. Aref AA. Sustained drug delivery for glaucoma: Current data and future trends. *Curr Opin Ophthalmol* 2017;28:169-74.
15. Steven DW, Alagband P, Lim KS. Preservatives in glaucoma medication. *Br J Ophthalmol* 2018;102:1497-503.
16. Bhartiya S, Singh M, Mitra A, editors. *Clinical Handbook of Glaucoma*. Noida: Incessant Nature Science Publishers; 2023.
17. Bhartiya S, editor. *Master Cases in Glaucoma*. New Delhi: United Scientific Solutions; 2023.

Rho Kinase Inhibitors in Glaucoma

Surajit Sen, Asim Ghosh

Summary (Key Points)

- Newer class of topical intraocular pressure (IOP)-lowering agent
- Primarily increases aqueous outflow through the trabecular meshwork
- Approximately 15–20% IOP drop may be achieved in primary open-angle glaucoma and ocular hypertension
- Shows additive effect on IOP lowering when combined with other anti-glaucoma medications (AGMs) like latanoprost and timolol
- Conjunctival hyperemia is the most common side effect. Systemic side effects are rare.

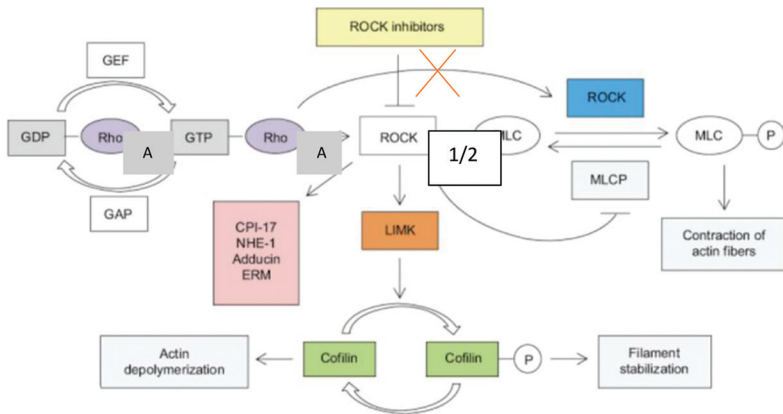
Introduction

In the mid and late 90s, there was a paradigm shift in the medical management of glaucoma, primarily because of the US Food and Drug Administration (FDA) approval of various newer AGMs and fixed-dose combinations. All these glaucoma medications lower IOP either by reducing aqueous production or by increasing uveoscleral outflow. Almost after 21 years of FDA approval of latanoprost, netarsudil, a Rho kinase-associated protein kinase (ROCK) inhibitor received FDA approval as IOP-lowering agent in 2017. Before that another ROCK inhibitor, ripasudil received approval in Japan in 2014. ROCK inhibitors work in a different pathway to lower IOP. It primarily increases aqueous outflow through trabecular meshwork (TM). Apart from IOP lowering its role has been described in neuroprotection and bleb modulation also.

Mechanism of Action

The mechanism of ROCK inhibitors' ability to decrease IOP is through the direct action of relaxation on the TM and Schlemm's canal cells causing increased permeability, which reduces the resistance of aqueous humor outflow.

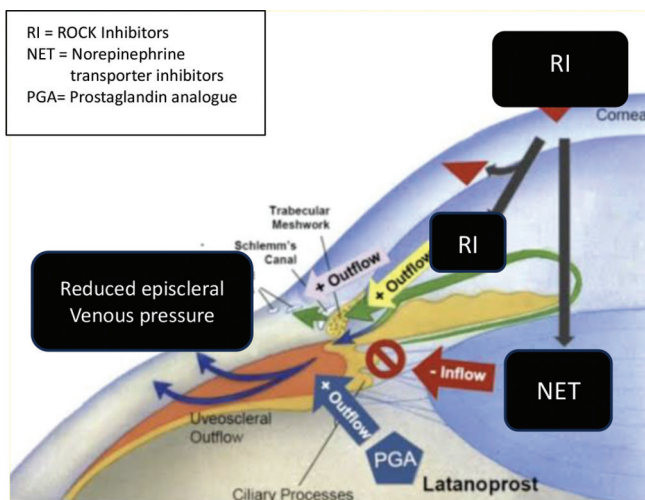
The Rho family (RhoA, RhoB, RhoC) are small guanosine triphosphate (GTP) binding proteins. They regulate cell morphology, proliferation, adhesion, cytokinesis, and apoptosis. Rho kinases are downstream regulators of GTPase involved in calcium-independent regulation of smooth muscle contraction. After activation of RhoA, the coiled-tail serine/threonine kinase becomes active. The Rho kinase has two isoforms, ROCK1 and ROCK 2. Although both isoforms share similar effects, they also fulfill some isoform-specific roles. Once active, Rho kinase phosphorylates the myosin light chain, myosin phosphatase substrate 1, LIM kinase, CP1-17, calponin, and the ERM proteins. These factors serve a number of cellular roles including cell adhesion, actomyosin contraction, cell migration, and cell proliferation.



Apart from this, netarsudil reduces aqueous production by inhibition of norepinephrine transporters at ciliary processes and reduces episcleral venous pressure by vasodilatation.

Ripasudil has shown axon regenerative properties in animal models, which is suggestive of its neuroprotective property. It also showed increased blood flow to the optic nerve head in monkey and rat eyes but there is limited data on these effects on human eyes.

In a mouse model, ripasudil has been shown to cause inhibition of the transdifferentiation of tenon fibroblast into myofibroblast which



may have a potential effect on reduced scar formation after glaucoma filtration surgery.

Rock Inhibitors in Clinical Use for Glaucoma Therapy

Various clinical studies have shown approximately 15–20% IOP reduction from baseline with netarsudil once a day dosing at night in primary open-angle glaucoma (OAG) and ocular hypertensive patients. Peak effect is seen after 2 h of instillation and effect is maintained for 24 h.

The efficacy of netarsudil has been compared to both timolol and latanoprost in clinical trials. Rho Kinase Elevated IOP Treatment Trial (ROCKET) observed clinically relevant and statistically significant IOP reductions in netarsudil 0.02% solution dosed once daily at night which was non-inferior to timolol twice a day in patients with a maximum baseline IOP up to 30 mmHg (Rocket 4).

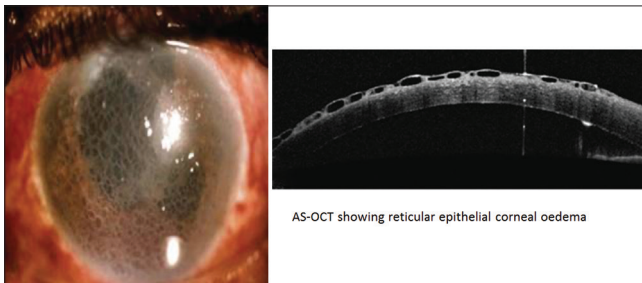
When compared with latanoprost, netarsudil once a day at night dose showed significant IOP drop but was inferior to latanoprost once a day at night dose.

The fixed-dose combination (FDC) of netarsudil 0.02%/latanoprost 0.005% was approved by FDA in 2019, for the reduction of IOP in patients with OAG and ocular hypertension (OHT). Two phase III clinical trials, MERCURY-1 and MERCURY-2, confirmed

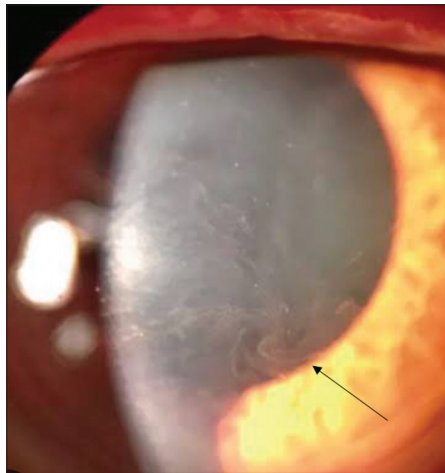
significantly greater efficacy of the FDC than the individual components, with IOP reductions of 30% or greater observed in 59–65% of subjects treated with FDC compared with 29–37% of subjects treated with latanoprost alone and 21–29% of subjects treated with netarsudil alone.

Ripasudil twice a day dosing has shown almost similar IOP reduction as netarsudil. Peak effect was seen after 2 h of use.

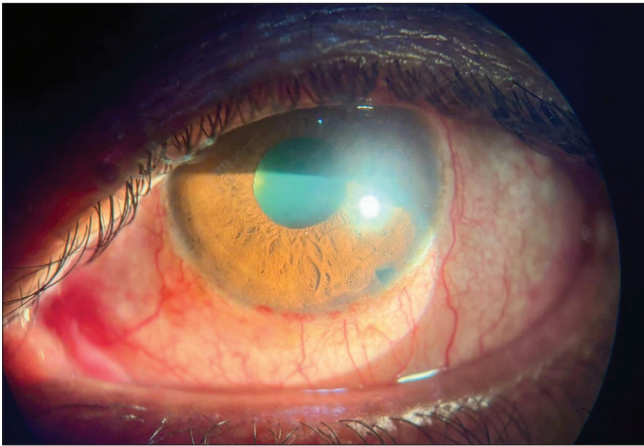
Ripasudil when added with timolol, brimonidine, and latanoprost has shown statistically significant additional IOP drop.



Reticular epithelial corneal oedema



Corneal verticillata



Rho kinase induced conjunctival congestion

Indications

1. Primary OAG
2. Normal-tension glaucoma
3. OHT
4. Steroid-induced glaucoma
5. Glaucoma secondary to uveitis
6. Raised episcleral venous pressure
7. Pseudoexfoliation glaucoma and pigment dispersion glaucoma
8. Other secondary OAG such as post-keratoplasty glaucoma and silicon oil-induced glaucoma.

There is no definite ocular or systemic contraindication of this medication.

Side Effects

The commonest side effect is conjunctival hyperemia due to the vasodilatory effect of ROCK inhibitors, seen in more than 50% of patients. Hyperemia usually resolves after long-term use of the medication. Other documented side effects are subconjunctival hemorrhage, corneal verticillata, reticulate corneal epithelial edema, allergic conjunctivitis, blepharitis, eye pruritus, punctate keratitis, and blurred vision. Although systemic side effects are rare, blood pressure reduction, increased heart rate, and headache have been reported.

Conclusion

Rock inhibitors are the most recent IOP-lowering drugs which work on the area of maximum outflow resistance in OAG; the TM. It is most effective when the baseline IOP is in the mid or late twenties. At present, ROCK inhibitors are mostly used as a 2nd or 3rd-line pharmacotherapy in the medical management of glaucoma but can be used as first-line therapy as well.

All glaucoma medications have certain side effects which ultimately cause discontinuation of the therapy. Hence, newer class of IOP-lowering agents like rock inhibitors has a definite role in different subsets of patients.

Suggested Reading

1. Wang J, Wang H, Dang Y. Rho-kinase inhibitors as emerging targets for glaucoma therapy. *Ophthalmol Ther* 2023;12:2943-57.
2. Thomas NM, Nagrale P. Rho kinase inhibitors as a neuroprotective pharmacological intervention for the treatment of glaucoma. *Cureus* 2022;14:e28445.
3. Moura-Coelho N, Tavares Ferreira J, Bruxelas CP, Dutra-Medeiros M, Cunha JP, Pinto Proença R. Rho kinase inhibitors-a review on the physiology and clinical use in ophthalmology. *Graefes Arch Clin Exp Ophthalmol* 2019;257:1101-17.
4. Tanna AP, Johnson M. Rho kinase inhibitors as a novel treatment for glaucoma and ocular hypertension. *Ophthalmology* 2018;125:1741-56.
5. Moshirfar M, Parker L, Birdsong OC, Ronquillo YC, Hofstedt D, Shah TJ, *et al.* Use of rho kinase inhibitors in ophthalmology: A review of the literature. *Med Hypothesis Discov Innov Ophthalmol* 2018;7:101-11.
6. Clement Freiberg J, von Spreckelsen A, Kolko M, Azuara-Blanco A, Virgili G. Rho kinase inhibitor for primary open-angle glaucoma and ocular hypertension. *Cochrane Database Syst Rev* 2022;6:CD013817.
7. Gopalakrishna M, Kavitha S. Rho-kinase inhibitors in ophthalmology. *TNOA J Ophthalmic Sci Res* 2021;59:56-60.
8. Serle JB, Katz LJ, McLaurin E, Heah T, Ramirez-Davis N, Usner DW, *et al.* Two phase 3 clinical trials comparing the safety and efficacy of netarsudil to timolol in patients with elevated intraocular pressure: Rho kinase elevated IOP treatment trial 1 and 2 (ROCKET-1 and ROCKET-2). *Am J Ophthalmol* 2018;186:116-27.
9. Araie M, Sugiyama K, Aso K, Kanemoto K, Iwata R, Hollander DA, *et al.* Phase 3 clinical trial comparing the safety and efficacy of netarsudil to ripasudil in patients with primary open-angle glaucoma or ocular

- hypertension: Japan rho kinase elevated intraocular pressure treatment trial (J-ROCKET). *Adv Ther* 2023;40:4639-56.
10. Asrani S, Bacharach J, Holland E, McKee H, Sheng H, Lewis RA, *et al*. Fixed-dose combination of netarsudil and latanoprost in ocular hypertension and open-angle glaucoma: Pooled efficacy/safety analysis of phase 3 MERCURY-1 and-2. *Adv Ther* 2020;37:1620-31.
 11. Bhartiya S, Singh M, Mitra A, editors. *Clinical Handbook of Glaucoma*. Noida: Incessant Nature Science Publishers; 2023.
 12. Bhartiya S, editor. *Master Cases in Glaucoma*. New Delhi: United Scientific Solutions; 2023.

CHAPTER

10

Management of Coexisting Cataract and Glaucoma

Arup Chakrabarti, Nirupama Kasturi, Subashini Kaliaperumal

Summary (Key Points)

- Cataract and glaucoma are the two major causes of blindness worldwide and often coexist as the prevalence of both diseases increases with age.
- A combined single surgical intervention can be considered when the glaucoma is moderate to severe in patients with visually significant cataracts.
- While traditional filtering surgeries or glaucoma drainage devices are the surgery of choice for advanced glaucoma, minimally invasive glaucoma surgeries have an increasing role in managing mild to moderate glaucoma with coexisting cataract.
- The operating surgeon must understand the advantages and disadvantages of combined procedures versus sequential staged procedures and individualize the decision for each patient.

Introduction

Glaucoma is a chronic progressive optic neuropathy characterized by optic disc cupping and visual field defects for which intraocular pressure (IOP) is the only modifiable risk factor. Glaucoma can coexist with cataracts in the following clinical situations requiring management.

- Both cataract and primary glaucomas are age-related processes and can occur together in patients above 50–60 years of age
- Lens-induced glaucoma is seen in advanced cataracts (Phacomorphic, Phacolytic, Phacoanaphylactic)
- Other situations causing secondary glaucoma (subluxation, post-traumatic, uveitis, neovascular, pseudoexfoliation, etc.).

While the cataract can be treated by lens extraction either by phacoemulsification or manual small incision surgery with intraocular lens (IOL) implantation, there are various choices for the management of glaucoma depending on the severity of glaucoma and patient preference.

Pre-operative Evaluation and Counseling for Patients with Glaucoma Undergoing Cataract Surgery Only

- Patients must be explained that the visual outcome of cataract surgery may be poor if the glaucoma is advanced.
- There is a risk of snuff-out phenomenon, risk of bleb failure, and need for continuation of anti-glaucoma medications following the surgery.

Considerations for Sequential Staged Surgery versus Combined Surgery

- The decision for surgery must be individualized for each case.
- Initiating cataract surgery as the primary intervention is a viable option in cases of mild, stable glaucomatous damage (evaluated through fundoscopy and standard automated perimetry), effective control with a single antiglaucoma medication, or when the patient's primary concern revolves around impaired vision attributed to cataracts. Additionally, cataract surgery may be indicated when a voluminous cataractous crystalline lens results in increased intraocular pressure (IOP) due to a forward shift of the iris-lens diaphragm, leading to secondary angle closure.
- If extensive glaucomatous damage or very high intraocular pressure (IOP) is observed, and there is a risk of the cataract operation affecting the success of the glaucoma filtering procedure (such as zonular instability due to pseudoexfoliation), trabeculectomy is the primary consideration. The primary goal in such cases is to control IOP and prevent blindness caused by glaucoma. Once glaucoma is stabilized, cataract surgery becomes a subsequent consideration. In instances of mild, non-visually significant cataracts, trabeculectomy alone might be an option. However, studies indicate that trabeculectomy increases the likelihood of cataract progression, with approximately

50% of patients requiring cataract surgery within the first few years post-trabeculectomy surgery.

The combined procedure becomes a suitable option in situations where a patient exhibits both significant cataract and substantial glaucomatous damage. This approach is particularly appropriate when the cataract operation is expected to be straightforward. Alternatively, it is a viable choice when a patient prefers to undergo a single comprehensive procedure rather than two separate ones, or when the surgeon deems it potentially risky to bring a specific patient to the operating theatre on two separate occasions.

Indications for combined surgery

1. Presentation with advanced open-angle glaucoma or angle-closure glaucoma with coexisting significant cataracts.
2. In cases where a patient, prescribed with more than two antiglaucoma medications, experiences the development or presence of a significant cataract, it is noteworthy. Compelling evidence indicates that prolonged use of antiglaucoma eye drops is associated with an elevated count of inflammatory cells, subconjunctival fibrosis, and dry eye. Additionally, this long-term medication approach is linked to a decreased success rate of trabeculectomy.
3. Cataract surgery alone is likely to increase the IOP in patients with poorly controlled glaucoma and/or severe visual field loss. Although removal of the cataractous lens alone can deepen the anterior chamber and improve aqueous filtration, studies have shown that cataract surgery causing a reduction in IOP is inconsistent.
4. Cost-efficient to do combined surgery (payment for a single surgery and/or a reduction in the number of glaucoma medications used). Many patients in developing countries cannot afford the lifelong use of expensive antiglaucoma medications. Adherence and persistence to glaucoma medications are a major issue even among the literate and therefore combined surgery tries to resolve this problem to a great extent.
5. When patients are considered unlikely to return for a second operation due to potential loss of follow-up, it is advisable to perform the cataract and glaucoma operations together.
6. An opportunity arises to offer glaucoma surgery for patients who initially hesitated but reconsidered their decision due to vision impairment caused by cataracts.
7. Anesthetic/surgical risks for repeated surgeries due to systemic conditions.

8. The risk of bleb failure increases when cataract surgery is performed after the glaucoma surgery.

Combined surgical techniques

Cataract surgery like phacoemulsification or manual small incision cataract surgery (SICS) can be combined with any surgical glaucoma technique or laser procedure.

The various surgical techniques for glaucoma that can be combined with cataract surgery include:

1. Penetrating techniques (trabeculectomy and its variations)
2. Non-penetrating techniques (deep sclerectomy, viscocanalostomy, canaloplasty)
3. Glaucoma drainage devices
 - a. With valve (Ahmed, Krupin)
 - b. Without valve (Molteno, Baerveldt)
 - c. Mini-shunt (Ex-PRESS).
4. Minimally invasive glaucoma surgeries (MIGS)
 - a. Increasing outflow through the trabeculum (canaloplasty)
 - b. Increasing outflow through collector channels (trabectome, Glaukos iStent, Eyepass)
 - c. Increasing outflow through suprachoroidal space (CyPass, Solx Gold micro shunt, Aqua-shunt).
5. Laser procedures such as endoscopic cyclophotocoagulation or subliminal transscleral cyclophotocoagulation
 - Trabeculectomy can be combined with phacoemulsification or manual SICS.
 - Non-penetrating techniques have been developed to avoid entering the eye but provide a less controlled reduction of IOP.
 - The utilization of antifibrotic agents has enhanced the success rates of these procedures, yet it has also heightened the occurrence of complications such as scleral necrosis, hypotony, bleb leak, blebitis, and endophthalmitis. The advent of newer minimally invasive glaucoma surgeries has effectively decreased surgical durations. Conversely, the introduction of novel antiglaucoma drops has expanded the array of medical management options available to ophthalmologists for treating glaucoma but has concurrently posed challenges to the outcomes of antiglaucoma surgeries.
 - Glaucoma drainage implants retain their place as a useful tool in many forms of severe glaucoma where the penetrating and

non-penetrating procedures are likely to fail.

- In the past, early glaucoma surgical intervention with traditional glaucoma surgeries was not justified as the inherent risks of the procedure outweighed the medical management. The emergence of MIGS has potentially tipped the risk-benefit scale in favor of early surgery which is beneficial to glaucoma patients with concomitant cataract. There is improved long-term IOP control, reduced need for medications, and potential improved quality of life. A retrospective case series showed that Kahook dual blade goniotomy combined with phacoemulsification showed a higher proportion of eyes able to discontinue 1 or more medications while maintaining IOP ≤ 18 mmHg when compared to eyes undergoing phacoemulsification with iStent.

Complications in Combined Surgeries

- The complications of the combined cataract-glaucoma surgery include those of cataract surgery and those of trabeculectomy.
- The following complications are likely higher with a combined procedure: Hyphema, fibrinous iritis, bleb leak, hypotony, choroidal detachment, posterior capsular opacification, and pupillary capture of IOL.

Advantages and Disadvantages of Combined Procedures/Combined versus Sequential Surgery

- Advantages include patient convenience due to single surgical intervention, reduction in the post-operative need for antiglaucoma medications, and prevention of IOP spikes in the early post-operative period due to cataract surgery alone.
- Disadvantages of the combined procedure include prolonged surgical time and requirement of surgical expertise for the combined technique.
- Cataract surgery in patients with glaucoma may prove to be more challenging due to poor mydriasis from medications, inflammation, trauma or laser and the presence of synechiae or weak zonules due to pseudoexfoliation.
- Cataract surgery complications may compromise the success of the glaucoma procedure.

Single-site Versus Two-site Surgery

- In the single-site approach, both cataract and glaucoma surgery are performed superiorly, thus reducing the surgical time. There is no need for the surgeon to change the position or the microscope. There is more post-operative inflammation and excessive conjunctival manipulation.
- In the two-site approach, trabeculectomy is performed superiorly, and the preferred incision for cataract surgery is done 90° away from the trabeculectomy site as a temporal clear corneal incision for phacoemulsification or temporal scleral tunnel for manual SICS. This involves prolonged surgical time. This may be advantageous in patients with deep-set eyes or shallow anterior chamber but requires change in surgeon's position and adjustment of microscope.
- There is evidence that two-site surgery offers a better IOP lowering effect than single-site surgery as it causes less damage to the filtration area and subsequently less fibrosis with better chances for the survival of the trabeculectomy over time. However, some experienced surgeons have found no significant difference in the IOP control between the two approaches.

IOL Considerations

In the past, the combination of any multifocal intraocular lens (IOL) with glaucoma surgery was deemed unsuitable due to concerns about generating glare, haloes, and diminishing contrast sensitivity by dividing the light directed to the retina. However, advancements in IOL technology have significantly progressed, empowering physicians and patients to consider premium IOL options, even within the realm of glaucoma. The newer premium IOLs including trifocal and extended depth of focus IOLs are a good option for early as well as well-controlled moderate to severe glaucoma patients with good central vision. Toric IOLs can be used to correct any pre-existing corneal astigmatism in a patient undergoing MIGS but are best avoided when the surgery is combined with trabeculectomy or tube-shunt surgery. If a patient is at high risk for progression and declining foveal sensitivity, an enhanced monofocal with aspheric design is the best IOL of choice. Glaucoma patients on chronic medications also suffer from dry eye which may be aggravated

by cataract surgery. It is important to address this condition using preservative-free lubricants and treat any adjoining meibomian gland disease to improve the visual outcome.

Cataract Surgery in Buphthalmos

The co-occurrence of congenital glaucoma and congenital cataracts is a rare phenomenon, often observed in conditions such as congenital rubella syndrome, persistent hyperplastic primary vitreous (PHPV), and Peter's anomaly. In infants with congenital rubella syndrome and microphthalmos, elevated intraocular pressure may manifest despite a seemingly normal-sized cornea. Conditions like oculo-cerebral-renal syndrome of Lowe (OCRL or Lowe syndrome), Patau syndrome, and Homocystinuria can give rise to both cataracts and glaucoma. Moreover, complicated cataracts may develop post-glaucoma surgery, and secondary glaucoma can arise following pediatric cataract surgery. While congenital glaucoma often involves a more extensive angle malformation, these disorders may be linked to partial abnormal angle development and a more favorable prognosis.

Addressing cataracts in buphthalmic eyes during surgery poses several challenges. Utilizing clear corneal incisions is crucial to prevent harm to the conjunctiva, sclera, and bleb area. The use of a high-viscosity ophthalmic viscosurgical device is essential to counter vitreous upthrust. Challenges include low scleral rigidity, elastic anterior capsule, and zonular instability, making capsulorhexis difficult. Migration of trypan blue dye through zonules may obscure the fundal glow. Possible variations in axial length measurements due to intraocular pressure can affect intraocular lens (IOL) power calculations. Children with glaucoma may experience a postoperative myopic shift and an increased risk of retinal detachment.

The enlarged capsular bag, eye expansion with elevated intraocular pressure, and excessive capsular fibrosis pose an additional risk of IOL decentration. To ensure IOL stability and long-term centration, considerations such as using a capsular tension ring, performing optic capture, rhexis fixation, or abstaining from posterior capsulotomy in the same sitting are advisable. Meticulous surgery is imperative to prevent intraocular pressure (IOP) decontrol.

Postoperative care for children entails regular follow-up, aggressive treatment of postoperative inflammation, monitoring signs

of bleb failure, and continuing antiglaucoma medications as prescribed before surgery.

Conclusion

In conclusion, the coexistence of cataract and glaucoma presents significant challenges in managing vision-threatening conditions, particularly as age-related prevalence increases. Combining surgical interventions becomes a viable option, especially in cases of moderate to severe glaucoma with visually significant cataracts. While traditional surgeries remain preferred for advanced glaucoma, minimally invasive procedures are gaining traction for managing mild to moderate glaucoma alongside cataract. Surgeons must carefully weigh the benefits and drawbacks of combined versus staged procedures, tailoring treatment decisions to individual patient needs for optimal outcomes.

Suggested Reading

1. Kozobolis V, Konstantinidis A, Labiris G. Combined cataract-glaucoma surgery. In: Glaucoma-Basic and Clinical Aspects. London: InTechOpen; 2013.
2. Shingleton BJ, Pasternack JJ, Hung JW, O'Donoghue MW. Three and five year changes in intraocular pressures after clear corneal phacoemulsification in open angle glaucoma patients, glaucoma suspects, and normal patients. *J Glaucoma* 2006;15494-8.
3. Hsu CH, Obstbaum SA. Technique and outcome of combined phacoemulsification and trabeculectomy. *Curr Opin Ophthalmol* 1998;9:9-14.
4. Wyse T, Meyer M, Ruderman JM, Krupin T, Talluto D, Hernandez R, *et al.* Combined trabeculectomy and phacoemulsification: A one-site vs a two-site approach. *Am J Ophthalmol* 1998;125:334-9.
5. Lee D, King J, Thomsen S, Hirabayashi M, An J. comparison of surgical outcomes between excisional goniotomy using the kahook dual blade and istent trabecular micro-bypass stent in combination with phacoemulsification. *Clin Ophthalmol* 2019;13:2097-102.
6. Cantor L, Lindfield D, Ghinelli F, Świder AW, Torelli F, Steeds C, *et al.* Systematic literature review of clinical, economic, and humanistic outcomes following minimally invasive glaucoma surgery or selective laser trabeculoplasty for the treatment of open-angle glaucoma with or without cataract extraction. *Clin Ophthalmol* 2023;17:85-101.
7. Lens Options in Glaucoma Patients. Fairfax: Eyeworld; 2023.
8. Sukhija J, Kaur S, Pandav SS, Kaushik S, Raj S, Ram J. Cataract surgery

- in children with buphthalmos. Clin Exp Ophthalmol 2016;44:739-40.
9. Bhartiya S, Singh M, Mitra A, editors. Clinical Handbook of Glaucoma. Noida: Incessant Nature Science Publishers; 2023.
 10. Bhartiya S, editor. Master Cases in Glaucoma. New Delhi: United Scientific Solutions; 2023.

CHAPTER

11

Drug-induced Glaucoma

Ajeet Kumar Dwivedi

Summary (Key Points)

- Open-angle glaucoma, often induced by corticosteroid use, may progressively impair vision without evident symptoms.
- It is crucial to rule out steroid responders, particularly following 3-6 weeks of corticosteroid treatment, even with low-potency steroids like Loteprednol 1%.
- National contraceptive injections should only be administered with glaucoma screening protocols to prevent complications.
- Closed-angle glaucoma, on the other hand, usually presents acutely and symptomatically, triggered by various medications like sulfa drugs including acetazolamide, anticholinergic agents, antimigraine agents, pilocarpine, and even common analgesics like mefenamic acid.
- Early detection and discontinuation of offending agents are pivotal in preventing sight loss.

Introduction

Drug-induced glaucoma (DIG) is a unique type of secondary glaucoma that can be brought on by a variety of regularly prescribed medications, including perphenazine in standard chemotherapy, fluoxetine, paclitaxel, and dexamethasone.^[2,3]

Generally, the DIGs can be classified into two types:

Open-angle glaucoma (OAG) with elevated intraocular pressure (IOP), which is mainly caused by steroids, such as betamethasone, prednisolone, and dexamethasone;

Some antitumor drugs, such as docetaxel and paclitaxel, can also induce OAG via unclear internal mechanisms.^[2-4]

Closed-angle glaucoma (CAG) may occur through two pathways:

1. With blocked trabecular network outflow path, which is mainly caused by non-steroidal drugs, e.g. anticholinergic drugs and epinephrine drugs.
2. Patients with an open or narrow iridocorneal angle (non-pupillary block CAG) may experience choroidal effusion, thickening, and forward displacement of the lens ciliary body rotation. This procedure appears to be a peculiar response to several systemic drugs.^[5]

Drug-induced acute angle closure glaucoma (AACG) is an ophthalmological emergency that ophthalmologists and general practitioners should be familiar with, given its potentially blinding consequences. Thick lenses, anteriorly positioned lenses, plateau iris design, short axial length, anterior chamber depth, and, in rare cases, intraocular tumors are common anatomical risk factors for AACG. Risk variables related to demographics include advanced age, Asian ethnicity, Asian sex, and family history. A prescription or over-the-counter medication is linked to at least one-third of occurrences of acute CAG (ACAG).^[4]

Medications have a direct or secondary effect leading to either sympathetic stimulation or inhibition of parasympathetic pathway activation, causing pupil dilatation, which may precipitate acute CAG (pupillary block glaucoma) in predisposed individuals (short axial length and short anterior chamber).^[5]

Corticosteroids

Steroid-induced glaucoma (SIG), a form of secondary glaucoma, is irreversible optic neuropathy develops with elevated intraocular pressure (IOP).^[1] The term “Steroid Responder” (SR) indicates individuals that show elevated IOP after steroid use, which has been defined in current literature as IOP above 21 mmHg to 24 mmHg and/or an increase of greater than 5 to 10 mmHg compared to baseline with clinical significance.^[12]

Steroid-induced glaucoma is an iatrogenic and preventable disease.^[6] Steroid-induced glaucoma accounts for one-fourth of all acquired glaucomas in children,^[39] with rising trends probably signifying increasing use of unmonitored steroid use.^[40]

Table 1: Studies of Becker and Armaly demonstrating IOP response to steroids^[41-44]

Feature/Parameter	Becker ^[41]	Armaly
Dose frequency	QID	TDS
Duration	6 weeks	4 weeks
Parameter	Final IOP	IOP Change
Type of responder		
Low	<20 mmHg (58%)	<6 mmHg (66%)
Intermediate	20–31 mmHg (36%)	>6 mmHg (29%)
Study agent	Betamethasone	Dexamethasone

IOP: Intraocular pressure

Table 2: Steroid responsiveness in population^[41,45-47]

Population	Incidence of steroid responsiveness (%)		
	Responders		Non-responders
	High	Intermediate	
General population	5	35	60
POAG	90	10	0
Siblings of POAG	30	50	20
Off-springs of POAG	25	70	5

POAG: Primary open-angle glaucoma

Steroid-induced glaucoma is a form of open-angle glaucoma. The precise mechanism for IOP elevation after steroid intake is not very clear, but primarily, it occurs due to the reduced facility of aqueous outflow.^[2]

Becker^[41] and Armaly,^[42-44] categorized the general population into high, intermediate, and low responses according to their pressure responses to topical steroid drops [Table 1].

Risk Factors for Steroid Response

1. Patient-related factors [Table 2]

40% of the normal population and 90% of the primary OAG (POAG) population have >6 mm Hg IOP rise with topical steroid,

Table 3: List of Sulfa medicines related with glaucoma

Antibiotics	Rheumatology drugs	Sulfonyl ureas	Diuretics	Other Drugs
Trimethoprim-sulfamethoxazole	Sulfasalazine	Glyburide	Acetazolamide	Sumatriptan
Sulfadizine	Probenecid	Chlorpropamide	Furosemide	Naratriptan
Sulfisoxazole	Celecoxib	Gliclazide	Hydrochlorothiazide	Topiramate
Dapsone	Valdecoxib	Bumetanide	Chlorothiazide	Ibutilide
Topical sulfa antibiotics		Glimepiride	Chlorthalidone	Sotalol
		Tolbutamide	Indapamide	Zonisamide
			Metolazone	

while 30–50% of populations with Triamcinolone injection develop steroid responses.

2. High myopia

Steroid-induced glaucoma after refractive surgery is masked by a falsely low IOP measurement due to thin central corneal thickness, ocular rigidity changes, corneal edema, and fluid accumulation beneath the LASIK flap.^[48,49]

3. Very young (<10 years of age) or older adults

4. Diabetes mellitus or connective tissue disorders

5. Eyes with pigment dispersion syndrome or traumatic angle recession

6. Endogenous hypercortisolism.

Depot progesterone used in the National Contraceptive Program also induces glaucoma in susceptible females; therefore, IOP checkups at regular intervals should be mandatory after these therapies.

Non-Steroidal Drugs

Anti-glaucoma drugs

Glaucoma can be caused by anti-glaucoma medications through different mechanisms.

Cholinergic agents, topical anticholinesterases, pilocarpine, intraocular acetylcholine, and carbachol can precipitate glaucoma by the forward movement of the iris-lens diaphragm^[7] in zonular weakness and exfoliation syndrome, in addition to a narrow angle in miotic-induced glaucoma.^[8]

Even pilocarpine can induce mydriasis-induced glaucoma sometimes because of impurities, e.g., jaborine. Sometimes, aqueous misdirection syndrome^[9] can also be produced by these agents.

Sympathomimetics like phenylephrine, its prodrug dipivefrine, and apraclonidine can precipitate acute CAG through mydriasis.

Latanoprost has been reported to precipitate ACG by increasing cilio-choroidal effusion in a patient with sturge weber syndrome^[11] and swelling of muscles of ciliary body.^[10]

Acetazolamide has been reported to cause non-pupillary block glaucoma because of sulfa drug reactions.^[17]

Mydriatics

It has been demonstrated that topical cycloplegics significantly raise IOP in 2% of the population that appears normal and in 23% of patients who have POAG.^[13,14]

IOP must be checked after dilation in the highly compromised optic nerve heads of glaucoma patients. Ciliary body paralysis decreases aqueous outflow because of decreased pull on the trabecular meshwork.

Any ointment during the initial post-operative period may precipitate toxic anterior segment syndrome and increase IOP because of trabeculitis; therefore, it should be avoided.

Botulinum toxin injections around the periocular area may block the ciliary ganglion, causing papillary dilatation and precipitating glaucoma in susceptible individuals.

Silicon oil

The IOP increase triggered by silicon oil might be moderate and transitory or severe and long-lasting. Papillary block, mechanical angle obstruction by oil, or inflammation may be the causes of the early IOP spikes. Synechial angle closure, rubeosis iridis, oil droplet emulsification, and silicone oil migrating into the anterior chamber and obstructing the outflow are thought to be the causes of the late-onset spikes.^[5]

Treatment includes the removal of silicon oil, medical therapy, laser, and incisional surgeries.

Sulfa drugs

Glaucoma from Sulfa drugs is usually present with bilateral ACAG that occurs within the first several doses and blurred vision as the first symptoms (forward movement of the lens and increased lens thickness leading to induced myopia). Mechanisms in this type of angle closure include lenticular swelling, retinal edema, choroidal effusion, and secondary shallowing of the anterior chamber associated with elevated IOP. Moreover, the mechanism may involve anterior rotation of the ciliary body and choroidal expansion secondary to the accumulation of serous fluid in the extravascular choroidal space.^[16] It has been documented that HIV-infected individuals have a high risk of hypersensitivity reactions to sulfamethoxazole.^[15] This type of reactions

Table 4: List of antidepressants related with Glaucoma

Mianserin hydrochloride
Paroxetine
Fluoxetine
Maprotiline
Fluvoxamine
Venlafaxine
Citalopram and
Escitalopram

is observed with topiramate, hydrochlorthiazide, acetazolamide, quinine, and tetracycline^[17-20] [Table 3]. Treatment includes Sulfa drug stoppage, including topical or systemic acetazolamide^[21,22] cycloplegics with aqueous suppressants, IV Methylprednisolone,^[23] and IV osmotics, for example, mannitol,^[23] under close observation. Laser iridotomy will only work when the papillary block is the mechanism for glaucoma. Ciliochoroidal effusion drainage can alleviate acute glaucoma if conservative measures fail.^[24,25]

Central nervous system agents

Antidepressants

Selective serotonin reuptake inhibitors (SSRIs) act by producing a gradual increase in postsynaptic levels of serotonin. The pathophysiological mechanism of SSRI-induced ACAG remains unclear, although anticholinergic effects or increased levels of serotonin, which cause partial pupillary dilatation, and increased aqueous production secondary to increased ciliary body blood flow have been implicated.^[28,29] Many antidepressants have been documented to be associated with ACAG attacks [Table 4].

In patients with narrow iridocorneal angles, the anticholinergic activity of these drugs induces mydriasis, which is the cause of ACAG in other classes of antidepressants. Amitriptyline, the tricyclic agent that is most frequently reported, and imipramine^[27] have been linked in the literature to ACAG attacks.

Antiparkinsonians

Carbergoline, a dopamine D2 receptor agonist, produces non-pupillary block glaucoma by increasing choroidal effusion within 5 h of single tablet ingestion, which causes dysfunction associated with hyperprolactinemia.

Trihexyphenidyl, or benzhexol, which has an antimuscarinic effect and a one-third strong activity similar to atropine, can produce ACAG in susceptible persons by a pupillary-block mechanism. Therefore, it is recommended that all patients who are going to start trihexyphenidyl have a gonioscopic assessment.^[26]

Anticonvulsants

Topiramate, a sulfamate-substituted monosaccharide antiseizure medication, is also used in the management of migraine, depression, and neuropathic pain. It is also used off-label as a weight-reduction medication.^[5] It usually presents as bilateral ACAG and blurred vision after seven days of the initiation of treatment or doubling the dose.

Ecstasy (3,4-methylenedioxymethamphetamine)

It releases a monoamine neurotransmitter, causing mydriasis and consequent ACAG in susceptible individuals.

Respiratory agents

While visiting to the ICU for a critically ill patient, you may find mydriasis, which may precipitate pupillary-block glaucoma in susceptible individuals. Enquiring details about medications, Ipratropium bromide, an anticholinergic agent, and salbutamol are common inciting agents.^[30-32] Another similar agent, tiotropium, has a long duration of action and weaker anticholinergic action but has also been absorbed through the cornea and conjunctiva through ill-fitting masks, which may precipitate bilateral glaucoma.

While B-2 agonists relieve reversible bronchospasm by relaxing the bronchial smooth muscles in chronic obstructive pulmonary disease and asthma, they can compound the CAG problem of anticholinergics by increasing aqueous humor production in the ICU.

Cocaine having indirect sympathomimetic activity and mydriasis may precipitate ACAG after therapeutic or abuse intranasal application of cocaine.^[33,34]

Hematologic agents

Anticoagulants have been described as inducing massive spontaneous choroidal hemorrhages.^[5] Warfarin,^[35] phenprocoumon,^[36] and heparin^[36] are reported to have unilateral ACAG in ARMD patients

because of massive suprachoroidal hemorrhage and consequent blindness even after surgical evacuation of blood.

Antineoplastic agents

Docetaxel,^[37] paclitaxel, and Imatinab mesylate^[38] have been reported to cause glaucoma and vision loss after chemotherapy for diffuse bone metastasis after breast carcinoma, chronic myelogenous leukemia, and gastrointestinal stromal tumors, respectively.

Anti-inflammatory agents

Mefenamic acid, a non-steroidal anti-inflammatory agent, has been documented to induce secondary non-pupillary block CAG and 9.00 diopter myopia in a 30-year-old patient. This is the same clinical picture that occurs with sulfa drugs.^[50]

Recent Developments and Future

A glaucoma-related gene network, 55 glaucoma-susceptible genes, and 13 highly glaucoma-associated medications were found in recent studies.^[51] Through an integrated mechanism including intracellular calcium homeostasis disruption, phototransduction failure, and retinal ganglion cell death, these genes most likely played major roles in inducing DIGs. Additional pathogenic risk analysis revealed that a group of nine genes, including the OTOF gene, may be useful as indicators for the prognosis of early-onset DIG.

For the first time, a systematic explanation of the potential molecular underpinning of DIGs is provided by this recent study.^[51] In addition, it offers early-onset glaucoma prognostic signals, which helps in the development of more effective treatment plans.

Conclusions

Glaucoma, whether open-angle or closed-angle, can result from various drug-induced causes (DIGs), with corticosteroids being a common culprit. While open-angle glaucoma may progress silently, closed-angle glaucoma tends to manifest acutely and symptomatic. Prompt identification and discontinuation of offending medications are paramount to halt disease progression and prevent irreversible sight loss. Healthcare professionals, including ophthalmologists and

primary care physicians, must remain vigilant about the potential ocular side effects of commonly prescribed drugs, facilitating early intervention and preservation of visual function in glaucoma patients.

Summary

Open Angle glaucoma by DIGs may gradually decrease vision as it remain asymptomatic unless investigated or suspected. Steroid Responder (SR) must be ruled out at least once after 3-6 weeks of corticosteroid use although it may present earlier. Low potency steroids such as Loteprednol 1% with good efficacy is now available but should be used with serial IOP measurements to detect occasional Steroid Responders. National Contraceptives especially Depot injections should be given after glaucoma screening only.

Closed Angle Glaucoma by DIGs usually present as acute and symptomatic conditions where sulfa drugs and anticholinergic agents are common culprits. Even Acetazolamide and pilocarpine can precipitate acute glaucoma in susceptible individuals as common anti-migraine drug topiramate in young individuals by different mechanisms. Similarly Antipsychotic and common Respiratory medicines such as Ipratropium bromide, salbutamol may precipitate acute glaucoma. Mefenamic acid, common analgesic has been reported to produce acute glaucoma.

Except Corticosteroids, DIGs are occasional or sporadic with other agents. Nevertheless we should keep ourselves and our speciality colleagues aware about its occurrence. This helps in early detection of Glaucoma and consequent prevention of sight year loss in Glaucoma. Stoppage of offending agent is single most effective treatment making reversal of pathogenic changes which are iatrogenic in many cases.

Suggested Reading

1. Feroze KB, Zeppieri M, Khazaeni L. Steroid induced glaucoma. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2023. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK430903> [Last accessed on 2023 Feb 14].
2. Phulke S, Kaushik S, Kaur S, Pandav SS. Steroid-induced glaucoma: An avoidable irreversible blindness. *J Curr Glaucoma Pract* 2017;11:67-72.
3. Wijnants D, Stalmans I, Vandewalle E. The effects of intranasal, inhaled and systemic glucocorticoids on intraocular pressure: A literature review. *J Clin Med* 2022;11:2007.

4. Boland MV, Quigley HA. Risk factors and open-angle glaucoma: Classification and application. *J Glaucoma* 2007;16:406-18.
5. Razeghinejad MR, Pro MJ, Katz LJ. Non-steroidal drug-induced glaucoma. *Eye (Lond)* 2011;25:971-80.
6. Razeghinejad MR, Myers JS, Katz LJ. Iatrogenic glaucoma secondary to medications. *Am J Med* 2011;124:20-5.
7. Lachkar Y, Bouassida W. Drug-induced acute angle closure glaucoma. *Curr Opin Ophthalmol* 2007;18:129-33.
8. Ritch R, Lowe R. Angle-closure glaucoma: Clinical types. In: Shields M, Krupin T, editors. *The Glaucomas*. Mosby: St Louis; 1996. p. 829-30.
9. Rieser JC, Schwartz B. Miotic-induced malignant glaucoma. *Arch Ophthalmol* 1972;87:706-12.
10. Yalvac IS, Tamcelik N, Duman S. Acute angle-closure glaucoma associated with latanoprost. *Jpn J Ophthalmol* 2003;47:530-1.
11. Sakai H, Sakima N, Nakamura Y, Nakamura Y, Hayakawa K, Sawaguchi S. Ciliochoroidal effusion induced by topical latanoprost in a patient with sturge-weber syndrome. *Jpn J Ophthalmol* 2002;46:553-5.
12. Sheppard JD, Comstock TL, Cavet ME. Impact of the Topical Ophthalmic Corticosteroid Loteprednol Etabonate On Intraocular Pressure. *Adv Ther* 2016;33:532-52.
13. Portney GL, Purcell TW. The influence of tropicamide on intraocular pressure. *Ann Ophthalmol* 1975;7:31-4.
14. Harris LS. Cycloplegic-induced intraocular pressure elevations a study of normal and open-angle glaucomatous eyes. *Arch Ophthalmol* 1968;79:242-6.
15. Slatore CG, Tilles SA. Sulfonamide hypersensitivity. *Immunol Allergy Clin North Am* 2004;24:477-90, vii.
16. Sankar PS, Pasquale LR, Grosskreutz CL. Uveal effusion and secondary angle-closure glaucoma associated with topiramate use. *Arch Ophthalmol* 2001;119:1210-1.
17. Fan JT, Johnson DH, Burk RR. Transient myopia, angle-closure glaucoma, and choroidal detachment after oral acetazolamide. *Am J Ophthalmol* 1993;115:813-4.
18. Beasley FJ. Transient myopia and retinal edema during hydrochlorothiazide (hydrodiuril) therapy. *Arch Ophthalmol* 1961;65:212-3.
19. Segal A, Aisemberg A, Ducasse A. Quinine, transient myopia and angle-closure glaucoma. *Bull Soc Ophthalmol Fr* 1983;83:247-9.
20. Edwards TS. Transient myopia due to tetracycline. *JAMA* 1963;186:69-70.
21. Rauscher FM, Parrish RK 2nd. Atypical angle closures. *Curr Opin Ophthalmol* 2008;19:107-14.
22. Ponka D. Approach to managing patients with sulfa allergy: Use of antibiotic and nonantibiotic sulfonamides. *Can Fam Physician* 2006;52:1434-8.
23. Rhee DJ, Ramos-Esteban JC, Nipper KS. Rapid resolution of topiramate-induced angle-closure glaucoma with methylprednisolone and mannitol.

- Am J Ophthalmol 2006;141:1133-4.
24. Postel EA, Assalian A, Epstein DL. Drug-induced transient myopia and angle-closure glaucoma associated with supraciliary choroidal effusion. Am J Ophthalmol 1996;122:110-2.
 25. Parikh R, Parikh S, Das S, Thomas R. Choroidal drainage in the management of acute angle closure after topiramate toxicity. J Glaucoma 2007;16:691-3.
 26. Friedman Z, Neumann E. Benzhexol-induced blindness in Parkinson's disease. Br Med J 1972;1:605.
 27. Ritch R, Krupin T, Henry C, Kurata F. Oral imipramine and acute angle closure glaucoma. Arch Ophthalmol 1994;112:67-8.
 28. Tripathi RC, Tripathi BJ, Haggerty C. Drug-induced glaucomas: Mechanism and management. Drug Saf 2003;26:749-67.
 29. Costagliola C, Parmeggiani F, Sebastiani A. SSRIs and intraocular pressure modifications: Evidence, therapeutic implications and possible mechanisms. CNS Drugs 2004;18:475-84.
 30. Shah P, Dhurjon L, Metcalfe T, Gibson JM. Acute angle closure glaucoma associated with nebulised ipratropium bromide and salbutamol. BMJ 1992;304:40-1.
 31. Cox AR, Gilmartin B. Drug-induced ophthalmic adverse reactions. Adverse Drug React Bull 2006;241:923-6.
 32. Ortiz Rambla J, Hidalgo Mora JJ, Gascón Ramón G, Navarro Arambudo B. Acute angle-closure glaucoma and ipratropium bromide. Med Clin (Barc) 2005;124:795.
 33. Hari CK, Roblin DG, Clayton MI, Nair RG. Acute angle closure glaucoma precipitated by intranasal application of cocaine. J Laryngol Otol 1999;113:250-1.
 34. Mitchell JD, Schwartz AL. Acute angle-closure glaucoma associated with intranasal cocaine abuse. Am J Ophthalmol 1996;122:425-6.
 35. Chandra A, Barsam A, Hugkulstone C. A spontaneous suprachoroidal haemorrhage: A case report. Cases J 2009;2:185.
 36. Schlote T, Freudenthaler N, Gelissen F. Anticoagulative therapy in patients with exudative age-related macular degeneration: Acute angle closure glaucoma after massive intraocular hemorrhage. Ophthalmologe 2005;102:1090-6.
 37. Fabre-Guillevin E, Tchen N, Anibali-Charpiat MF, Calluau L, Ravau A. Taxane-induced glaucoma. Lancet 1999;354:1181-2.
 38. Fraunfelder FW, Solomon J, Druker BJ, Esmali B, Kuyl J. Ocular side-effects associated with imatinib mesylate (Gleevec). J Ocul Pharmacol Ther 2003;19:371-5.
 39. Kaur S, Dhiman I, Kaushik S, Raj S, Pandav SS. Outcome of ocular steroid hypertensive response in children. J Glaucoma 2016;25:343-7.
 40. Gupta S, Shah P, Grewal S, Chaurasia AK, Gupta V. Steroid-induced glaucoma and childhood blindness. Br J Ophthalmol 2015;99:1454-6.
 41. Becker B. Intraocular pressure response to topical corticosteroids. Invest

- Ophthalmol 1965;4:198-205.
42. Armaly MF. Statistical attributes of the steroid hypertensive response in the clinically normal eye. I. The demonstration of three levels of response. Invest Ophthalmol 1965;4:187-97.
 43. Armaly MF. The heritable nature of dexamethasone-induced ocular hypertension. Arch Ophthalmol 1966;75:32-5.
 44. Armaly MF. Inheritance of dexamethasone hypertension and glaucoma. Arch Ophthalmol 1967;77:747-51.
 45. Armaly MF. Effect of corticosteroids on intraocular pressure and fluid dynamics. II. The effect of dexamethasone in the glaucomatous eye. Arch Ophthalmol 1963;70:492-9.
 46. Becker B, Chevrette L. Topical corticosteroid testing in glaucoma siblings. Arch Ophthalmol 1966;76:484-7.
 47. Becker B, Hahn KA. Topical corticosteroids and heredity in primary open-angle glaucoma. Am J Ophthalmol 1964;57:543-51.
 48. Najman-Vainer J, Smith RJ, Maloney RK. Interface fluid after LASIK: Misleading tonometry can lead to end-stage glaucoma. J Cataract Refract Surg 2000;26:471-2.
 49. Hamilton DR, Manche EE, Rich LF, Maloney RK. Steroid-induced glaucoma after laser *in situ* keratomileusis associated with interface fluid. Ophthalmology 2002;109:659-65.
 50. Vishwakarma P, Raman GV, Sathyan P. Mefenamic acid-induced bilateral transient myopia, secondary angle closure glaucoma and choroidal detachment. Indian J Ophthalmol 2009;57:398-400.
 51. Ding RF, Yu Q, Liu K, Du J, Yin HJ, Ji ZL. Gene network analyses unveil possible molecular basis underlying drug-induced glaucoma. BMC Med Genomics 2021;14:109.
 52. Bhartiya S, Singh M, Mitra A, editors. Clinical Handbook of Glaucoma. Noida: Incessant Nature Science Publishers; 2023.
 53. Bhartiya S, editor. Master Cases in Glaucoma. New Delhi: United Scientific Solutions; 2023.

CHAPTER

12

The Role of Artificial Intelligence in Glaucoma: A Promising Pathway for Early Diagnosis and Management

Prasanna Venkatesh Ramesh

Summary (Key Points)

- Glaucoma is a complex and progressive eye disease that can lead to irreversible vision loss if not detected and managed early. Traditional methods of glaucoma diagnosis and monitoring rely heavily on the experience and expertise of a clinician and can be time-consuming.
- However, the emergence of artificial intelligence (AI) in ophthalmology has brought about exciting advancements in patient care.
- AI algorithms can analyze large datasets, detect subtle patterns, and provide objective assessments, offering the potential for early detection, accurate diagnosis, and personalized treatment strategies.
- This chapter explores the applications of AI in glaucoma, including early detection and screening, imaging and diagnostics, disease progression monitoring, personalized treatment and risk stratification, and telemedicine and remote monitoring.
- By leveraging AI technologies, the field of glaucoma care stands to benefit from improved patient outcomes, reduced burden on health-care systems, and enhanced accessibility to quality eye care.

Introduction

Glaucoma is a chronic eye condition characterized by progressive damage to the optic nerve, often associated with elevated intraocular

pressure (IOP). It is a leading cause of irreversible blindness worldwide, affecting millions of individuals. The challenge in managing glaucoma lies in its asymptomatic nature in the early stages, making early detection and intervention crucial for preserving vision.

Artificial intelligence (AI), a branch of computer science that involves the development of intelligent algorithms, has the potential incorporated in several platforms, and it is inevitable that AI will become a routine part of our medical practice to revolutionize patient care. AI algorithms can process vast amounts of data, identify patterns, and make predictions based on learned information. Interestingly, ophthalmology is adapted to the application of AI as there is a lot of clinical imaging, scanning process, and clinical ophthalmic tests that need interpretation. Moreover, glaucoma in particular has a huge potential for AI-related advances such as glaucoma diagnosis, monitoring disease progression, and enabling personalized treatment strategies. In addition, data from multiple modalities can be combined together in a meaningful way to arrive at an appropriate treatment and improving adherence to treatment.

This chapter aims to provide an overview of the applications of AI in glaucoma care, focusing on early detection and screening, imaging and diagnostics, disease progression monitoring, personalized treatment and risk stratification, and telemedicine and remote monitoring.

The Need for a Gold Standard

Building AI algorithms to identify the presence or absence of glaucoma needs a neat and concrete definition of the disease with strong certainty. An appropriate machine learning is utmost needed to identify the early detection of a disease and its disease process.

Currently, multiple professional health-care societies and associations provided definitions for “glaucoma,” such as Glaucoma Research Foundation, The National Institute for Health and Care Excellence, the American Academy of Ophthalmology, European Glaucoma Society, and World Glaucoma Association, and agreed with the word “progressive” in the definition of glaucoma.

Some important points are followed to identify the progression of glaucoma:

- Rate of progression: Despite no cutoff point, glaucomatous progression in optic nerve fiber layer loss is faster than expected from age-related changes.
- Pattern of damage: Glaucomatous damage typically starts in the parapapillary area and progress from the peripheral to the central visual field.
- Risk factors: Increased IOP, aging, thin corneas, and family history of glaucoma.

Various documented articles have already tried to establish a gold standard definition for early detection of glaucoma and its progression.

- Iyer *et al.* documented objective criteria from optical coherence tomography (OCT) and perimetry that could denote a specific definition of GON in eyes with open-angle glaucoma.
- Ramesh *et al.* developed an explainable AI, which can detect intricate findings along with the diagnosis in fundus photographs.

Early Detection and Screening

- Early detection of glaucoma is crucial for timely intervention and preventing irreversible vision loss. However, conventional screening methods can be time-consuming, subjective, and reliant on the expertise of health-care professionals.
- AI algorithms offer the potential to automate and enhance the screening process by analyzing the various types of data, including retinal images and optic nerve assessments [Table 1].
- One area where AI has shown promise is in analyzing retinal images obtained through fundus photography or fundus imaging, and OCT imaging. AI algorithms can identify subtle changes in

Table 1: Deep learning models to detect glaucoma in early stage

Authors	Modalities	Accuracy
Li <i>et al.</i> (2018)	Fundus Images	High accuracy in detecting glaucoma
Smith <i>et al.</i>	Fundus Images	High accuracy of 95% in detecting glaucoma
Johnson <i>et al.</i>	Optic disc and retinal nerve fiber layer (RNFL) segmentation	High accuracy

the optic disc and retinal nerve fiber layer, which are indicative of glaucomatous damage.

- In addition, AI algorithms can analyze visual field data to identify early signs of glaucomatous visual field loss. By comparing an individual's visual field test results to large databases, AI algorithms can detect abnormalities that may indicate the presence of glaucoma. This approach can enhance the sensitivity and specificity of glaucoma screening.

Imaging and Diagnostics

- Imaging modalities play a vital role in diagnosing and monitoring glaucoma [Table 2].
- Fundus photography and OCT are a broadly used imaging technique that gives cross-sectional high-resolution images of the retina.
- AI algorithms can analyze OCT data to extract quantitative measurements, such as retinal nerve fiber layer thickness and optic disc parameters.
- This objective and subjective (visual field) analysis can aid in diagnosing glaucoma, monitoring disease progression, and assessing treatment efficacy.

Disease Progression Monitoring

- Monitoring disease progression is crucial for determining the effectiveness of treatments and making informed clinical decisions [Table 3].

Table 2: Deep learning models to detect glaucoma from different imaging modalities

Authors	Imaging modalities	Accuracy
Liu <i>et al.</i> (2017)	OCT	The algorithm could differentiate between healthy individuals and glaucoma patients with high accuracy.
Lee <i>et al.</i>	Fundus Images	The proposed model achieved high sensitivity and specificity in detecting glaucoma.
Wang <i>et al.</i>	Visual Field Data	High accuracy in differentiating glaucomatous and healthy eyes, providing a potential tool.

Table 3: Deep learning models to detect glaucoma progression

Authors	Imaging modalities	Accuracy
Medeiros <i>et al.</i> (2018)	Visual Field Data	AI algorithm that predicted glaucoma progression up to 2 years in advance using longitudinal visual field data, highlighting the potential for early intervention and tailored treatment plans.
Zhang <i>et al.</i>	OCT Images	The deep learning model achieved high accuracy in identifying progressive changes in the retinal nerve fiber layer (RNFL) and optic disc, providing a potential tool for monitoring glaucoma progression.
Chen <i>et al.</i>	Fundus Photographs	The model utilizes convolutional neural networks (CNNs) to analyze longitudinal image data and accurately identify progressive changes associated with glaucoma.

- AI algorithms can analyze longitudinal data, such as serial imaging or functional tests, to detect subtle changes that may indicate disease progression. This analysis can help identify patients at higher risk of vision loss and guide treatment strategies.

Personalized Treatment and Risk Stratification

- Glaucoma is a heterogeneous disease, and patient characteristics can vary significantly.
- AI algorithms can analyze large datasets and identify relevant risk factors associated with disease progression.
- This information can assist in tailoring treatment strategies to individual patients, improving therapeutic outcomes.
- For instance, Asaoka *et al.* (2019) developed an AI model that predicted the rate of visual field progression in glaucoma patients.
- By considering various clinical factors, such as baseline visual field parameters, age, and IOP, the AI model could provide personalized predictions. This approach can help clinicians make informed decisions regarding treatment intensity and frequency of follow-up visits.

Telemedicine and Remote Monitoring

- Telemedicine, driven by AI technologies, has the potential to transform glaucoma care by enabling remote monitoring and reducing the need for frequent in-person visits.
- AI algorithms can analyze patient-generated data, such as visual field tests, IOP measurements, and medication adherence, to provide real-time feedback and alerts to both patients and health-care providers.
- By integrating AI into telemedicine platforms, glaucoma patients can conveniently monitor their condition from home. Remote monitoring systems equipped with AI algorithms can detect significant changes in patient data and alert health-care providers, enabling timely interventions.
- Patel *et al.* present an AI-based system for remote glaucoma screening using fundus image analysis. The system utilizes deep learning algorithms to analyze retinal fundus images captured remotely by patients using a smartphone or a dedicated fundus camera. The AI model automatically detects characteristic features of glaucoma, such as optic disc cupping and retinal nerve fiber layer thinning. The system achieved high accuracy and sensitivity in detecting glaucoma remotely, providing a convenient and cost-effective solution for early glaucoma screening in underserved populations or remote areas with limited access to specialized eye care.

Challenges and Limitations

- Despite the immense potential, several challenges exist in implementing AI in glaucoma care. Data availability, especially annotated and well-curated datasets, remains a limitation. The development and training of accurate AI models require large and diverse datasets that encompass various disease stages, demographics, and imaging modalities.
- Another challenge is the interpretability and transparency of AI algorithms. Deep learning models, particularly those with complex architectures like deep neural networks, often operate as black boxes, making it difficult to understand the decision-making process.
- Ethical considerations and regulatory frameworks surrounding the use of patient data for AI are also important challenges. AI algorithms heavily rely on large-scale datasets, including patient information, imaging data, and treatment records. Ensuring the

privacy and security of patient data, as well as obtaining informed consent, is crucial to maintain trust between patients, health-care providers, and AI-driven systems.

Future Directions

- The future of AI in glaucoma holds exciting prospects. Advancements in deep learning, including explainable AI and federated learning, can address the interpretability and privacy concerns associated with AI models.
- Integration of multimodal data, such as genetic information, environmental factors, and patient-reported outcomes, can enhance the predictive capabilities of AI algorithms.
- By incorporating a broader range of data sources, AI models can provide a more comprehensive understanding of glaucoma and its underlying mechanisms. For example, genetic data can help identify individuals at high risk of developing glaucoma or predict the response to specific treatments.
- Patient-reported outcomes can provide valuable insights into the impact of glaucoma on daily life and help tailor treatment plans accordingly.
- Collaborative efforts between ophthalmologists, AI researchers, and regulatory bodies are essential to foster the development and adoption of AI technologies in routine glaucoma care.

Conclusion

- AI holds great promise in revolutionizing glaucoma care by enhancing early detection, improving diagnostics, enabling disease progression monitoring, facilitating personalized treatment strategies, and supporting telemedicine initiatives.
- By leveraging AI technologies, health-care providers can harness the power of data analytics and automation to detect glaucoma at an early stage, monitor disease progression, and provide personalized treatment strategies, ultimately leading to better visual outcomes for patients with glaucoma.

Suggested Reading

1. American Academy of Ophthalmology (AAO). American Academy of Ophthalmology. Available from: <https://www.aao.org> [Last accessed on

- 2023 May 25].
2. The National Institute for Health and Care Excellence. NICE. Available from: <https://www.nice.org.uk> [Last accessed on 2023 May 25].
 3. World Glaucoma Association (WGA). World Glaucoma Association. Available from: <https://wga.one> [Last accessed on 2023 May 25].
 4. European Glaucoma Society (EGS). Available from: <https://www.eugs.org/eng/default.asp> [Last accessed on 2023 May 25].
 5. Glaucoma Research Foundation is Dedicated to Finding a Cure; 2021. Available from: <https://glaucoma.org> [Last accessed on 2023 May 25].
 6. Mariottoni EB, Jammal AA, Berchuck SI, Shigueoka LS, Tavares IM, Medeiros FA. An objective structural and functional reference standard in glaucoma. *Sci Rep* 2021;11:1752.
 7. Iyer JV, Boland MV, Jefferys J, Quigley H. Defining glaucomatous optic neuropathy using objective criteria from structural and functional testing. *Br J Ophthalmol* 2021;105:789-93.
 8. Ramesh PV, Ramesh SV, Aji K, Ray P, Tamilselvan S, Parthasarathi S, *et al.* Modeling and mitigating human annotations to design processing systems with human-in-the-loop machine learning for glaucomatous defects: The future in artificial intelligence. *Indian J Ophthalmol* 2021;69:2892-4.
 9. Li Z, He Y, Keel S, Meng W, Chang RT, He M. Efficacy of a deep learning system for detecting glaucomatous optic neuropathy based on color fundus photographs. *Ophthalmology* 2018;125:1199-206.
 10. Ramesh PV, Subramaniam T, Ray P, Devadas AK, Ramesh SV, Ansar SM, *et al.* Utilizing human intelligence in artificial intelligence for detecting glaucomatous fundus images using human-in-the-loop machine learning. *Indian J Ophthalmol* 2022;70:1131-8.
 11. Bhartiya S, Singh M, Mitra A, editors. *Clinical Handbook of Glaucoma*. Noida: Incessant Nature Science Publishers; 2023.
 12. Bhartiya S, editor. *Master Cases in Glaucoma*. New Delhi: United Scientific Solutions; 2023.

POAG, Ocular Hypertension, Post YAG



^{Rx} **BIDIN LS**

(Brimonidine Tartrate 0.1% w/v) Eye Drops

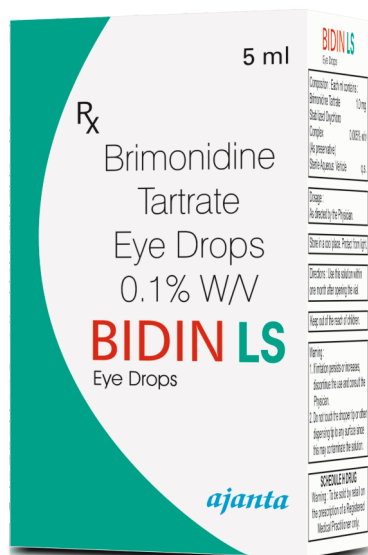
Efficacy, Safety & Neuroprotection



25% IOP reduction



**Safe in cardiac, diabetic
& asthmatic patients**



About the Book:

The "Clinical Insights into Glaucoma Management" aspires to become an essential resource for glaucoma practitioners, eye doctors, and residents in training, navigating the ever-evolving landscape of clinical practice. This collaborative compendium goes beyond traditional boundaries, providing a detailed examination of the complexities surrounding glaucoma diagnosis, management, and innovative treatment approaches.

Authored by esteemed experts in the field, each chapter reflects their collective dedication to advancing the understanding and application of glaucoma management. From foundational principles to the latest advancements, this book serves as a guiding light, directing clinicians towards evidence-based strategies and optimal practices.

The integration of clinical insights, research discoveries, and practical expertise renders this handbook an invaluable tool. It not only encapsulates the current state of glaucoma care but also anticipates future developments, empowering practitioners to remain at the forefront of their discipline.

In the spirit of collaboration and knowledge-sharing, this handbook transcends mere reference material – it becomes a trusted companion for every glaucoma practitioner committed to enhancing the vision and quality of life for their patients.

May this volume serve as a source of inspiration, fostering a community of professionals dedicated to the unwavering pursuit of excellence in glaucoma care.

