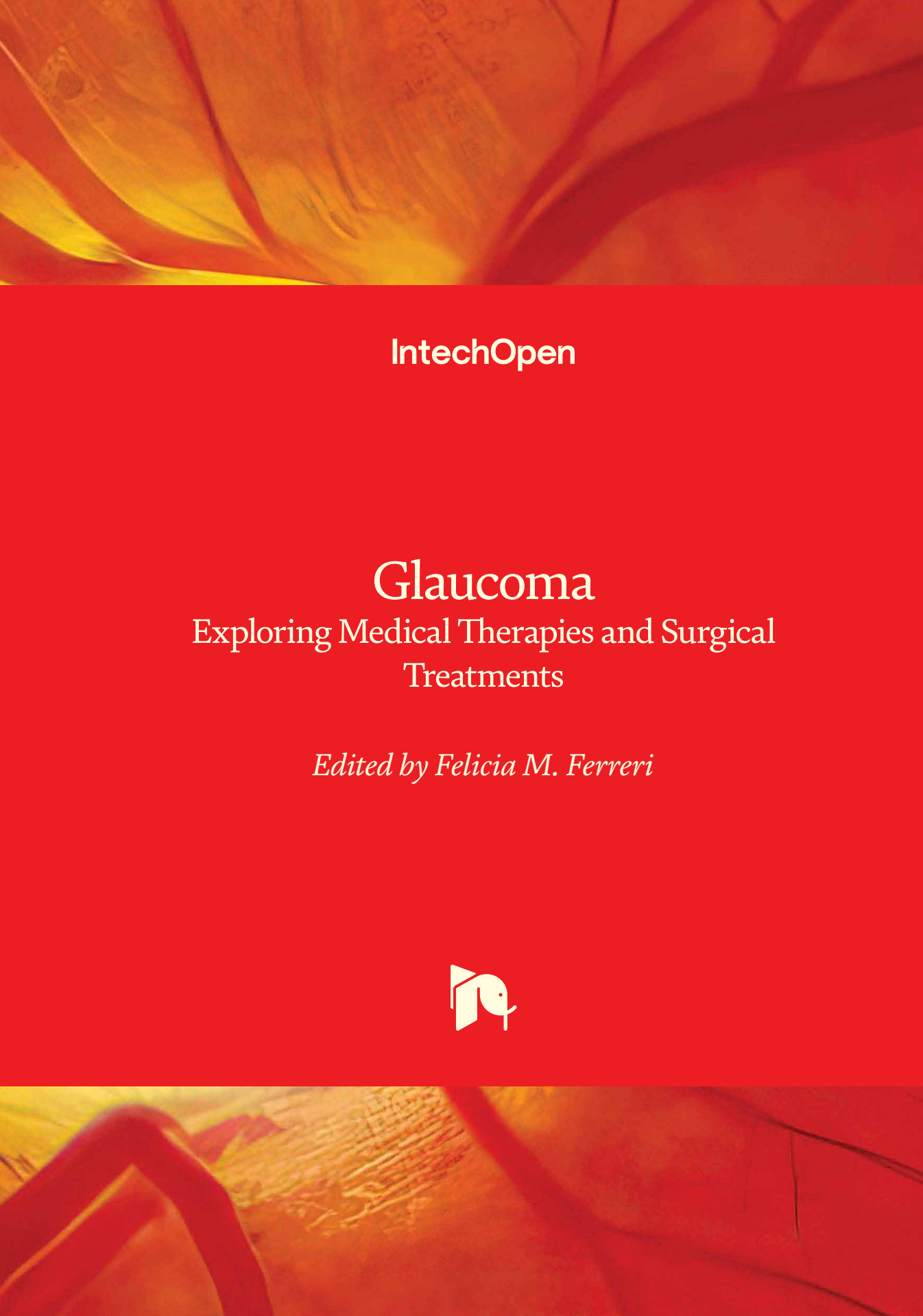




IntechOpen

Glaucoma

Exploring Medical Therapies and Surgical
Treatments

Edited by Felicia M. Ferreri



Glaucoma - Exploring Medical Therapies and Surgical Treatments

Edited by Felicia M. Ferreri

Published in London, United Kingdom

Glaucoma - Exploring Medical Therapies and Surgical Treatments

<http://dx.doi.org/10.5772/intechopen.1008600>

Edited by Felicia M. Ferreri

Contributors

Amitendu Saha, Ashutosh Dayal, Carolyn Aitken, Debdas Mukhopadhyay, Fatma Merve Bektaş, Francesco Stringa, Karl Mercieca, Kingsley Ekemiri, Lays Fernanda Nunes Dourado, Paolo Brusini, Tamal Roy

© The Editor(s) and the Author(s) 2026

The rights of the editor(s) and the author(s) have been asserted in accordance with the Copyright, Designs and Patents Act 1988. All rights to the book as a whole are reserved by INTECHOPEN LIMITED. The book as a whole (compilation) cannot be reproduced, distributed or used for commercial or non-commercial purposes without INTECHOPEN LIMITED's written permission. Enquiries concerning the use of the book should be directed to INTECHOPEN LIMITED rights and permissions department (permissions@intechopen.com).

Violations are liable to prosecution under the governing Copyright Law.



Individual chapters of this publication are distributed under the terms of the Creative Commons Attribution 4.0 License which permits commercial use, distribution and reproduction of the individual chapters, provided the original author(s) and source publication are appropriately acknowledged. If so indicated, certain images may not be included under the Creative Commons license. In such cases users will need to obtain permission from the license holder to reproduce the material. More details and guidelines concerning content reuse and adaptation can be found at <http://www.intechopen.com/copyright-policy.html>.

Notice

Statements and opinions expressed in the chapters are these of the individual contributors and not necessarily those of the editors or publisher. No responsibility is accepted for the accuracy of information contained in the published chapters. The publisher assumes no responsibility for any damage or injury to persons or property arising out of the use of any materials, instructions, methods or ideas contained in the book.

First published in London, United Kingdom, 2026 by IntechOpen

IntechOpen is the global imprint of INTECHOPEN LIMITED, registered in England and Wales, registration number: 11086078, 167-169 Great Portland Street, London, W1W 5PF, United Kingdom

For EU product safety concerns: IN TECH d.o.o., Prolaz Marije Krucifikse Kozulić 3, 51000 Rijeka, Croatia, info@intechopen.com or visit our website at intechopen.com.

British Library Cataloguing-in-Publication Data

A catalogue record for this book is available from the British Library

Glaucoma - Exploring Medical Therapies and Surgical Treatments

Edited by Felicia M. Ferreri

p. cm.

Print ISBN 978-1-83635-403-1

Online ISBN 978-1-83635-402-4

eBook (PDF) ISBN 978-1-83635-404-8

If disposing of this product, please recycle the paper responsibly.

IntechOpen

intechopen.com

Built by scientists, for scientists



Explore all IntechOpen books

Meet the editor



Felicia M. Ferreri graduated summa cum laude from the University of Messina, Italy, in 1998, and completed her ophthalmology residency at the Policlinico Universitario di Messina in 2002. She interned in the Corneal Section at San Raffaele Hospital in Milan and in the Pediatric Ophthalmology Diseases Section at Careggi Hospital in Florence. She spent research periods at Virgen del Rocio Hospital in Seville, San Carlos Hospital in Madrid, the Royal Bolton Hospital in Manchester, and Universidade Fluminense in Rio de Janeiro. She served as a co-investigator of many national and international clinical trials. Since 2002, she has been an Assistant Professor in Ophthalmology at the University of Messina. Her research interests are glaucoma, neuro-ophthalmology, pediatric ophthalmology, and cataract. She authored more than 50 scientific papers and edited two IntechOpen books. Dr. Ferreri is a member of the American Academy of Ophthalmology (AAO), the Italian Society of Ophthalmology (S. O. I-A. M. OI), and the Italian Glaucoma Society (S. I. GLA), among others.

Contents

Preface	IX
Chapter 1	1
The Application of Animal-Derived Peptides for Glaucoma Control <i>by Lays Fernanda Nunes Dourado</i>	
Chapter 2	15
Identifying Risk Factors for Glaucoma through Iris Images <i>by Carolyn Aitken</i>	
Chapter 3	41
Living with Glaucoma: Challenges in Daily Activities <i>by Fatma Merve Bektaş</i>	
Chapter 4	57
Techniques in Trabecular Meshwork and Canal Surgery <i>by Francesco Stringa, Karl Mercieca and Paolo Brusini</i>	
Chapter 5	73
Objective Evaluation of Anterior Chamber Characteristics in Angle Closure Disease Diagnosis and Treatment <i>by Debdas Mukhopadhyay, Tamal Roy and Amitendu Saha</i>	
Chapter 6	95
Glaucoma Pharmacotherapy – Principles and Practice <i>by Ashutosh Dayal</i>	
Chapter 7	113
Systematic Review on the Modern Strategies in Glaucoma Treatment – The Role of Optometrists <i>by Kingsley Ekemiri</i>	

Preface

This Edited Volume is a collection of reviewed and relevant research chapters on developments in glaucoma research. The book includes scholarly contributions by various authors, edited by an expert in ophthalmology. Each contribution is a separate chapter, complete in itself but directly related to the book's topics and objectives.

The book includes the following chapters:

1. The Application of Animal-Derived Peptides for Glaucoma Control
2. Identifying Risk Factors for Glaucoma through Iris Images
3. Living with Glaucoma: Challenges in Daily Activities
4. Techniques in Trabecular Meshwork and Canal Surgery
5. Objective Evaluation of Anterior Chamber Characteristics in Angle Closure Disease Diagnosis and Treatment
6. Glaucoma Pharmacotherapy – Principles and Practice
7. Systematic Review on the Modern Strategies in Glaucoma Treatment - The Role of Optometrists

The target audience comprises scholars and specialists in the field.

IntechOpen

Chapter 1

The Application of Animal-Derived Peptides for Glaucoma Control

Lays Fernanda Nunes Dourado

Abstract

Glaucoma remains a leading cause of irreversible blindness, characterized by retinal ganglion cell degeneration and progressive optic nerve damage. Although intraocular pressure (IOP) remains the primary modifiable risk factor, disease progression often occurs despite adequate IOP control, indicating the need for novel therapeutic strategies. Thus, recent research has turned attention to neuroprotective approaches that target oxidative stress, excitotoxicity, and impaired vascular perfusion. Among these, animal-derived peptides, particularly those obtained from the venom of the Brazilian armed spider, *Phoneutria nigriventer*, have shown promising therapeutic properties. The synthetic peptide PnPP-19, inspired by the venom's bioactive components, demonstrates significant potential by promoting nitric oxide release, enhancing ocular blood flow, and preserving retinal ganglion cells. Because of this, this chapter explores the potential of animal-derived peptides, particularly those isolated or inspired by the venom of the spider *Phoneutria nigriventer*, in the treatment of glaucoma. Furthermore, it explores the anatomical and molecular basis of glaucomatous damage, emphasizing the relevance of nitric oxide and glutamate pathways, and presents preclinical evidence supporting the use of venom-derived peptides for neuroprotection in glaucoma. Moreover, it explores the integration of innovative drug delivery systems and biologically active peptides, highlighting the future challenges of integrating peptide-based therapies into clinical ophthalmology.

Keywords: eye neuroprotection, nitric oxide, *Phoneutria nigriventer*, venom-derived peptides, retinal ganglion cells, peptide delivery systems

1. Introduction

Glaucoma is a progressive neurodegenerative disease and a leading cause of irreversible blindness worldwide, affecting over 76 million people globally, with projections suggesting more than 111 million cases by 2040 [1]. The prevalence of this disease is particularly pronounced in aging populations and regions with limited access to early diagnostic and therapeutic resources [2, 3]. It is primarily characterized by the loss of retinal ganglion cells (RGCs), degeneration of the optic nerve, and associated visual field defects. Although elevated intraocular pressure (IOP) is the most significant risk factor, glaucomatous damage can continue to progress even

when IOP is adequately controlled [4, 5]. This clinical observation has prompted the search for therapeutic strategies that go beyond IOP regulation, focusing instead on neuroprotection, mitochondrial preservation, and molecular modulation of disease pathways such as oxidative stress and excitotoxicity [6, 7].

Recent advances in biotechnology and pharmacology have identified a wide array of biomolecules with therapeutic potential, particularly peptides derived from animal venoms [8]. These peptides often possess highly specific biological activities and have been shown to modulate ion channels, neurotransmitter release, oxidative stress, and inflammatory responses—all of which are involved in the pathogenesis of glaucoma [9, 10]. The specificity and potency of these compounds make them attractive candidates for drug development, especially in ophthalmology, where local delivery methods can maximize efficacy and minimize systemic exposure.

Among the most promising bioactive compounds are peptides derived from the venom of the Brazilian armed spider (*Phoneutria nigriventer*), which have demonstrated neuroprotective effects in models of retinal and optic nerve injury [11]. These peptides are capable of modulating neuronal signaling pathways, influencing nitric oxide release, and potentially counteracting excitotoxic mechanisms. Their small size, structural stability, and functional versatility provide a unique platform for engineering targeted ocular therapies [12].

In this chapter, we explore the current understanding of glaucoma pathophysiology, with an emphasis on ocular anatomy, key molecular targets such as nitric oxide (NO) and glutamate, and the emerging role of antimicrobial and venom-derived peptides. Special attention is given to the PnPP-19 peptide, a synthetic derivative from *P. nigriventer*, which has shown potential for topical application in glaucoma therapy through NO-mediated mechanisms [8]. Furthermore, findings from recent studies, peptide delivery platforms, and formulation strategies to enhance ocular bioavailability are also discussed [13].

2. Anatomy of the eye and pathophysiology of glaucoma

The human eye is a complex sensory organ composed of multiple specialized tissues, each playing a crucial role in maintaining homeostasis, regulating intraocular dynamics, and facilitating phototransduction [14]. The integrity and functionality of these structures are essential for maintaining both visual acuity and visual field, which are progressively compromised in glaucomatous disease [15].

Glaucoma predominantly affects the optic nerve and the inner retinal layers, particularly the retinal ganglion cells (RGCs), whose axons converge to form the optic nerve [16]. These neurons are highly sensitive to changes in pressure, ischemic conditions, metabolic stress, and excitotoxic insults [17].

A comprehensive understanding of glaucoma pathophysiology requires familiarity with the anatomical structures involved in intraocular pressure regulation, visual signal transduction, and neural pathways connecting the eye and the brain [18].

Thus, from a clinical standpoint, the disease is typically categorized into open-angle glaucoma, characterized by an anatomically unobstructed anterior chamber angle but dysfunctional outflow pathways, and angle-closure glaucoma, in which physical obstruction at the angle leads to rapid IOP elevation [19]. Subtypes such as pigmentary, pseudoexfoliative, and congenital glaucoma each involve distinct anatomical anomalies and pathophysiological mechanisms, underscoring the need for tailored diagnostic and treatment approaches [20, 21].

Moreover, the interplay between ocular anatomy and systemic factors, such as vascular dysregulation, nocturnal hypotension, and aging-related structural changes, further complicates the disease landscape [22]. Therefore, a detailed appreciation of the anatomical features of the eye is foundational to understanding not only the onset and progression of glaucoma but also the rationale behind emerging peptide-based neuroprotective interventions discussed in this chapter.

2.1 Ocular structures relevant to glaucoma

The anterior segment of the eye contains the cornea, aqueous humor, iris, and trabecular meshwork—structures critical for maintaining IOP homeostasis. Aqueous humor is produced by the ciliary body and flows through the posterior chamber into the anterior chamber, exiting primarily *via* the trabecular meshwork and Schlemm's canal. Dysfunction or obstruction in this outflow pathway is a central event in the elevation of IOP [23].

Posteriorly, the retina and optic nerve are particularly vulnerable to pressure-related and molecular insults. The optic nerve head (or optic disc), where retinal ganglion cell axons converge to exit the eye, is a focal point of damage in glaucoma. Characteristic changes in this region, including cupping and thinning of the neuro-retinal rim, are hallmarks of disease progression [17].

Retinal ganglion cells (RGCs) are essential for visual processing, transmitting electrical impulses from photoreceptors to the brain *via* the optic nerve. In glaucoma, RGCs undergo apoptosis triggered by a combination of mechanical stress, impaired axonal transport, oxidative damage, and excitotoxicity. The selective vulnerability of these neurons underlies the progressive and irreversible nature of the disease [19, 24].

Axonal degeneration typically precedes soma loss, suggesting a distal-to-proximal pattern of neuronal injury. This process shares features with other central nervous system (CNS) neurodegenerations, reinforcing the need for neuroprotective interventions in glaucoma management [25].

Although elevated IOP remains a pivotal risk factor, normal-tension glaucoma (NTG) highlights the complexity of the disease, in which neurodegeneration occurs without measurable IOP elevation. In such cases, systemic vascular dysregulation, mitochondrial dysfunction, and local inflammatory responses contribute to disease development [22].

This multifactorial nature underscores the limitations of pressure-lowering therapies and bolsters the rationale for novel pharmacological strategies aimed at molecular and cellular targets within the retina and optic nerve.

3. Molecular targets in glaucoma therapy

3.1 Nitric oxide (NO): A pleiotropic molecule in ocular physiology

Nitric oxide (NO) plays a dual role in ocular health and disease. On one hand, it contributes to aqueous humor outflow by relaxing the trabecular meshwork and Schlemm's canal, thereby lowering IOP [23, 26]. On the other hand, excessive or dys-regulated NO production can lead to oxidative damage and inflammation. NO is synthesized from L-arginine by the enzyme nitric oxide synthase (NOS), of which there are three isoforms: neuronal (nNOS), endothelial (eNOS), and inducible (iNOS) [27]. Under physiological conditions, eNOS-derived NO is vasoprotective, promoting

vascular relaxation, improving perfusion, and regulating ocular blood flow. However, during ischemic or glaucomatous conditions, upregulation of iNOS and nNOS may contribute to neuronal toxicity, oxidative stress, and tissue degeneration.

The therapeutic potential of NO in glaucoma has been reinforced by the development of NO-donating prostaglandin analogs, such as latanoprostene bunod, which demonstrate enhanced IOP-lowering effects [28]. More recently, peptide-based approaches have emerged as novel strategies for NO delivery. These systems aim to modulate local NO release without triggering systemic side effects or inducing inflammatory cascades [8].

In this context, the PnPP-19 peptide, derived from *Phoneutria nigriventer* venom, has shown promising results [29]. In preclinical studies, topical administration of PnPP-19 promoted NO release in ocular tissues, leading to a significant and sustained reduction in IOP without cytotoxic effects [8]. This mechanism is particularly valuable in neuroprotective approaches, as NO also enhances ocular blood flow, stabilizes mitochondrial function, and modulates synaptic activity [30]. Importantly, studies have indicated that PnPP-19 selectively induces NO synthesis *via* eNOS pathways without triggering inflammatory responses associated with iNOS activation, distinguishing it from other NO donors that may have deleterious side effects in ocular tissues [8].

Moreover, as NO plays a key role in angiogenesis and vascular remodeling, controlled modulation of its levels offers additional advantages in preventing ischemia-related retinal degeneration [31]. The dual vasodilatory and neuroprotective actions of NO place it at the forefront of emerging strategies for comprehensive glaucoma therapy, especially in cases of normal-tension glaucoma or those unresponsive to conventional IOP-lowering treatments in ocular health and disease. This effect contributes to aqueous humor outflow by relaxing the trabecular meshwork and Schlemm's canal, thereby lowering IOP. However, excessive or dysregulated NO production can lead to oxidative damage and inflammation [26].

3.2 Glutamate excitotoxicity: A key driver of RGC death

Glutamate, the primary excitatory neurotransmitter in the retina, plays a pivotal role in normal synaptic transmission between photoreceptors, bipolar cells, and retinal ganglion cells (RGCs) [32]. Under physiological conditions, glutamate release is tightly regulated by calcium-dependent exocytosis, and extracellular levels are controlled by glial uptake mechanisms, particularly through Müller cells, which convert glutamate into glutamine *via* glutamine synthetase. This homeostasis is crucial, as there are no extracellular enzymes capable of degrading glutamate [33].

In glaucomatous and ischemic conditions, impaired glutamate reuptake and excessive release lead to elevated extracellular concentrations, overstimulation of ionotropic glutamate receptors—especially N-methyl-D-aspartate (NMDA) receptors—and a consequent influx of calcium into neurons. This calcium overload triggers a cascade of events, including mitochondrial dysfunction, generation of reactive oxygen species (ROS), activation of apoptotic pathways, and ultimately, neuronal death. These processes are collectively referred to as excitotoxicity [34, 35]. NMDA receptors are particularly implicated due to their high permeability to Ca^{2+} . Their overactivation not only initiates cell death pathways but also exacerbates oxidative stress by activating nitric oxide synthase (nNOS), which further contributes to retinal damage. Research has shown that experimental models of glaucoma exhibit upregulated NMDA receptor expression and downregulated glutamate transporter activity, exacerbating the toxic environment within the inner retina [36].

Therapeutic efforts to modulate glutamatergic toxicity have included the use of NMDA receptor antagonists, such as memantine and ketamine [37, 38]. While effective in animal models, their translation to human therapy has been limited by side effects and lack of sustained efficacy. Noncompetitive antagonists that selectively block NMDA receptor subtypes or target specific binding sites have shown better tolerability and may offer neuroprotective benefits without impairing normal neurotransmission [39].

Interestingly, some venom-derived peptides demonstrate neuromodulatory and neuroprotective properties potentially useful in mitigating glutamate-induced damage. For instance, components of *Phoneutria nigriventer* venom—such as PnTx4(5-5)—have shown the capacity to inhibit glutamate uptake and NMDA receptor overactivation, possibly *via* allosteric modulation or indirect calcium regulation [10]. Although the PnPP-19 peptide does not directly antagonize glutamate receptors, its ability to stimulate nitric oxide production *via* eNOS and improve retinal perfusion may help reduce ischemia-related glutamate accumulation [40].

Altogether, targeting the glutamatergic cascade represents a promising strategy for neuroprotection in glaucoma [41]. Future developments may focus on combination therapies that integrate glutamate receptor antagonism, antioxidant support, and vascular modulation, mechanisms potentially synergized through the action of venom-derived peptides.

4. Antimicrobial peptides and their pharmacological potential

Antimicrobial peptides (AMPs) are naturally occurring molecules found across diverse species, ranging from bacteria to mammals. Initially characterized by their ability to disrupt microbial membranes, AMPs have more recently been recognized for their broader immunomodulatory and cytoprotective properties. These include roles in tissue repair, inflammation control, chemotaxis, and neuroprotection—making them attractive candidates for therapeutic application in both infectious and noninfectious diseases [42, 43].

Structurally, AMPs are generally small (less than 50 amino acids), amphipathic, and cationic, enabling them to interact with negatively charged microbial membranes and cellular targets. The classification of antimicrobial peptides varies depending on their phylogenetic origin, with distinct schemes used across different kingdoms. This structural diversity supports a wide range of biological activities and target specificities [44].

In the context of ocular diseases, AMPs present several appealing characteristics. Their small size facilitates penetration into ocular tissues, and their amphipathic structure allows interaction with both lipid membranes and specific molecular targets. Some AMPs have been shown to reduce oxidative stress, inhibit pro-inflammatory cytokine release, promote angiostasis, and modulate apoptotic signaling, which can represent potential therapeutic effects in glaucoma treatment [45].

Experimental models of retinal injury and neurodegeneration have demonstrated that selected AMPs can attenuate retinal ganglion cell loss and preserve visual function [8, 46]. These peptides exert protective effects either directly on neurons—by stabilizing membrane integrity and modulating ionic conductance—or indirectly by modulating glial responses, reducing microglial activation, and preserving blood-retinal barrier function [46, 47].

In this context, while not all venom peptides are strictly classified as AMPs, many share similar structural motifs and biological properties. For instance, the venom of *Phoneutria nigriventer* contains peptides with α -helical structures and cationic surfaces, reminiscent of classical AMPs. These peptides, in addition to their antimicrobial effects, can also modulate ion channels and neurotransmitter systems, providing neuromodulatory and anti-inflammatory benefits [8, 48].

Furthermore, recent advances in peptide engineering have enabled the design of hybrid molecules that combine antimicrobial activity with tissue-targeting or receptor-modulating features. These rationally designed AMPs offer high specificity, reduced immunogenicity, and improved stability, overcoming some of the traditional limitations of peptide therapeutics [49].

5. Peptides from *Phoneutria nigriventer*: Discovery and characterization

The venom of the Brazilian armed spider, *Phoneutria nigriventer*, has long intrigued neuroscientists and pharmacologists due to its rich composition of bioactive peptides capable of interacting with a wide range of ion channels and molecular targets in the nervous system [48]. Historically, research on *P. nigriventer* venom identified multiple peptide fractions—such as PhTx1, PhTx2, PhTx3, and PhTx4—each with unique pharmacological effects [10, 48]. These fractions contain toxins that act on voltage-gated sodium, calcium, and potassium channels, and some exhibit inhibitory effects on neurotransmitter release or modulate excitatory synaptic signaling. Several toxins from these fractions have demonstrated either excitatory or inhibitory neurotoxicity in mammals, suggesting a delicate balance of therapeutic potential and safety challenges [50].

Among these, the synthetic peptide PnPP-19 has emerged as a promising therapeutic candidate for ocular diseases. Derived from the neurotoxin PnTx2-6, PnPP-19 was rationally designed to retain the beneficial nitric oxide-releasing properties of the parent molecule while eliminating its toxic effects [48]. This peptide includes 19 amino acids representing a discontinuous epitope of PnTx2-6 and was chemically synthesized using Fmoc solid-phase peptide synthesis. Post-synthesis modifications, such as N-terminal acetylation and C-terminal amidation, were employed to enhance solubility and resistance to enzymatic degradation [48, 51].

In animal models of glaucoma, topical application of PnPP-19 led to significant reductions in IOP, preserved retinal ganglion cell integrity, and improved retinal morphology. The mechanism appears to involve NO-mediated relaxation of the trabecular meshwork and vasodilation in ocular microvasculature, facilitating aqueous humor outflow and enhancing ocular perfusion. Unlike many conventional NO donors, PnPP-19 does not trigger cytotoxic oxidative bursts or inflammation, providing a more targeted and biocompatible therapeutic effect [8].

Moreover, repeated administration of PnPP-19 did not cause corneal irritation, conjunctival hyperemia, or systemic side effects, as demonstrated by histological analyses and behavioral assessments in rodent models. These favorable safety findings, combined with its efficacy, suggest a unique therapeutic niche for PnPP-19, particularly in patients requiring adjunct neuroprotection or those with contraindications to current pressure-lowering drugs [8].

To further enhance ocular bioavailability, PnPP-19 has been incorporated into nanowafer-based delivery systems using polyvinyl alcohol (PVA) as the matrix polymer. Nanowafers offer prolonged retention on the ocular surface, sustained drug

release, and improved penetration into target tissues. In experimental settings, PnPP-19-loaded nanowafers delivered the peptide over 24 hours with consistent therapeutic effects and without inducing local inflammation [52].

These developments illustrate a successful case of toxin-inspired drug discovery and provide a framework for future peptide-based interventions in ophthalmology [12]. Ongoing research seeks to refine the peptide's structure, optimize delivery vehicles, and assess its efficacy in larger animal models and human tissues. The ultimate goal is to transition PnPP-19 from bench to bedside, potentially expanding its application beyond glaucoma to other ischemic or degenerative retinal diseases [8].

The exploration of *P. nigriventer* venom and the refinement of its components reflect the broader shift in pharmaceutical science toward biologically derived, mechanism-specific therapies that prioritize both safety and efficacy. Peptides such as PnPP-19, situated at the intersection of neurobiology and drug design, may pave the way for the next generation of targeted treatments in ocular health.

6. Translational potential and future directions

The clinical application of animal-derived peptides presents exciting opportunities and considerable challenges. For venom-derived peptides such as PnPP-19, for example, several technical, regulatory, and biological hurdles must be addressed to ensure successful translation to human glaucoma therapy [12].

One of the major concerns is the inherent instability of peptides in the ocular environment. Peptides are susceptible to degradation by proteolytic enzymes in tear fluid and on ocular surfaces, which can reduce their half-life and efficacy. To overcome this, strategies such as terminal modifications (e.g., acetylation, amidation), cyclization, and incorporation of D-amino acids have been explored to enhance peptide stability without compromising biological activity. These approaches are complemented by advanced drug delivery systems such as hydrogels, liposomes, and nanowafers that protect the peptide and prolong ocular residence time [53, 54].

Topical administration remains the preferred route for ophthalmic therapies due to its noninvasive nature and patient compliance. However, drug bioavailability is limited by precorneal factors, including blinking, lacrimation, and nasolacrimal drainage. Novel formulations, such as mucoadhesive polymers and controlled-release matrices, aim to optimize ocular pharmacokinetics by increasing drug retention and facilitating penetration into target tissues [54, 55].

From a regulatory standpoint, peptide-based ophthalmic therapies must meet rigorous criteria for purity, potency, sterility, and reproducibility. Manufacturing under Good Manufacturing Practices (GMP) is essential to ensure batch consistency. Regulatory agencies like the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have provided guidance for the approval of biologics, but peptide therapeutics still face a relatively complex pathway due to their hybrid nature between small molecules and biologics [56].

A key translational step is the establishment of pharmacodynamic (PD) and pharmacokinetic (PK) profiles in human ocular tissues. This includes assessments of drug absorption, distribution, metabolism, and elimination. Noninvasive imaging technologies, such as optical coherence tomography (OCT), confocal microscopy, and laser speckle flowgraphy, may aid in monitoring drug effects and tissue responses in early clinical trials [57].

Moreover, expanding the preclinical data to include studies in non-rodent models, such as rabbits or nonhuman primates, will provide more relevant information regarding dosing, tolerance, and therapeutic windows. Studies evaluating PnPP-19 in models of normal-tension glaucoma and secondary glaucoma types, such as pigmentary or pseudoexfoliative glaucoma, could further broaden its clinical applicability.

The interdisciplinary nature of this work necessitates strong collaboration between pharmacologists, ophthalmologists, materials scientists, and regulatory experts. It also highlights the importance of intellectual property protection and strategic partnerships with industry to facilitate clinical translation and eventual commercialization.

Importantly, the promise of venom-derived peptides extends beyond glaucoma. Similar neurodegenerative mechanisms, such as excitotoxicity, oxidative stress, and impaired perfusion, are implicated in conditions like diabetic retinopathy, retinal vein occlusion, and age-related macular degeneration. With appropriate delivery modifications, peptides like PnPP-19 may serve as templates for developing therapeutic analogs tailored to these conditions.

Future directions may also explore the potential of combining PnPP-19 with other therapeutic agents. Co-delivery strategies involving antioxidants, anti-inflammatory compounds, or IOP-lowering drugs could produce synergistic effects and enable personalized glaucoma therapy based on patient phenotype and disease stage. Advances in polymer engineering, such as stimuli-responsive systems that release drugs in response to changes in IOP or oxidative markers, could further revolutionize precision ophthalmology.

7. Conclusion

The pathogenesis of glaucoma extends far beyond elevated intraocular pressure (IOP), encompassing a complex interplay of mechanical, vascular, oxidative, excitotoxic, and inflammatory mechanisms. As such, a singular approach focused only on IOP reduction may not suffice to halt disease progression in many patients. This multifactorial nature of glaucoma necessitates the development of complementary strategies that target neuronal survival, perfusion, and cellular resilience.

Within this context, animal-derived peptides—particularly those obtained from the venom of *Phoneutria nigriventer*—represent a compelling avenue for innovation. These peptides, exemplified by PnPP-19, combine specificity, potency, and safety in a therapeutic profile that addresses multiple aspects of glaucomatous degeneration. PnPP-19's ability to promote nitric oxide release, preserve retinal ganglion cell viability, and lower IOP through physiological pathways supports its dual role as both a pressure-lowering and neuroprotective agent.

The exploration of antimicrobial peptides and venom-inspired molecules broadens the pharmacological toolkit for managing glaucoma. Their multifunctionality allows them to act across diverse molecular targets, providing anti-inflammatory, antioxidant, and cytoprotective benefits that may complement or enhance the effects of conventional drugs. Moreover, their small size and modifiable structure make them ideal candidates for incorporation into advanced delivery.

In conclusion, while challenges remain, the translational trajectory of PnPP-19 exemplifies the broader potential of venom-derived therapeutics in ocular diseases.

As research advances and regulatory frameworks adapt, peptide-based interventions may redefine the landscape of glaucoma management, offering new hope for patients at risk of vision loss.

Conflict of interest

The authors declare no conflict of interest.

Author details

Lays Fernanda Nunes Dourado
Faculty of Medicine, Federal University of Vales do Jequitinhonha e Mucuri, Gerais,
Brazil

*Address all correspondence to: laysndourado@gmail.com

IntechOpen

© 2025 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. 

References

- [1] Tham YC, Li X, Wong TY, et al. Global prevalence of glaucoma and projections of glaucoma burden through 2040: A systematic review and meta-analysis. *Ophthalmology*. 2014;**11**:2081-2090. DOI: 10.1016/j.opththa.2014.05.013
- [2] Quigley H, Broman AT. The number of people with glaucoma worldwide in 2010 and 2020. *British Journal of Ophthalmology*. 2006. DOI: 10.1136/bjo.2005.081224
- [3] Flaxman SR, Bourne RRA, Resnikoff S, et al. Global causes of blindness and distance vision impairment 1990–2020: A systematic review and meta-analysis. *The Lancet. Global Health*. 2017. DOI: 10.1016/S2214-109X(17)30393-5
- [4] Braunger BM, Fuchshofer R, Tamm ER. The aqueous humor outflow pathways in glaucoma: A unifying concept of disease mechanisms and causative treatment. *European Journal of Pharmaceutics and Biopharmaceutics*. 2015. DOI: 10.1016/j.ejpb.2015.04.029
- [5] Davis BM, Crawley L, Pahlitzsch M, et al. Glaucoma: The retina and beyond. *Acta Neuropathologica*. 2016;**132**:807–826
- [6] Yu-Wai-Man P, Griffiths PG, Chinnery PF. Mitochondrial optic neuropathies - disease mechanisms and therapeutic strategies. *Progress in Retinal and Eye Research*. 2011. DOI: 10.1016/j.preteyeres.2010.11.002
- [7] Russo R, Rotiroti D, Tassorelli C, et al. Chapter 28 Identification of Novel Pharmacological Targets to Minimize Excitotoxic Retinal Damage. 1st ed. Elsevier Inc; 2009. Epub ahead of print 2009. DOI: 10.1016/S0074-7742(09)85028-9
- [8] da Silva CN, Dourado LFN, de Lima ME, et al. PnPP-19 peptide as a novel drug candidate for topical glaucoma therapy through nitric oxide release. *Translational Vision Science & Technology*. 2020;**9**:33
- [9] Matavel A, Estrada G, De Marco Almeida F. Spider venom and drug discovery: A review. In: *Spider Venoms*. Dordrecht: Springer; 2016. pp. 273–292. Epub ahead of print 2016. DOI: 10.1007/978-94-007-6389-0_9
- [10] Elena M, Lima D, Gomes S, et al. Phoneutria nigriventer venom and toxins: A review. In: *Spider Venoms*. Dordrecht: Springer; 2015
- [11] Cunha Junior A, de Lima Perez Garcia ME, Nunes da Silva C, et al. Method and Use of PnPP-19 for Preventing and Treating Eye Diseases. 62/895252. Estados Unidos: WIPO (PCT); 2019
- [12] Peigneur S, de Lima ME, Tytgat J. Phoneutria nigriventer venom: A pharmacological treasure. *Toxicon*. 2018. DOI: 10.1016/j.toxicon.2018.07.008
- [13] Mandal A, Pal D, Agrahari V, et al. Ocular delivery of proteins and peptides: Challenges and novel formulation approaches. *Advanced Drug Delivery Reviews*. 2018. DOI: 10.1016/j.addr.2018.01.008
- [14] Wald G. The molecular basis of visual excitation. *Nature*. 1968;**219**:800–807
- [15] Weinreb RN, Tee Khaw P. Primary open-angle glaucoma. *Lancet*. 2004. Epub ahead of print 2004. DOI: 10.1016/S0140-6736(04)16257-0
- [16] Nickells RW. Apoptosis of retinal ganglion cells in glaucoma: An update of

the molecular pathways involved in cell death. Survey of Ophthalmology. 1999. Epub ahead of print 1999. DOI: 10.1016/S0039-6257(99)00029-6

[17] Calkins DJ. Critical pathogenic events underlying progression of neurodegeneration in glaucoma. Progress in Retinal and Eye Research. 2012;**31**:702-719

[18] Almasieh M, Wilson AM, Morquette B, et al. The molecular basis of retinal ganglion cell death in glaucoma. Progress in Retinal and Eye Research. 2012. DOI: 10.1016/j.preteyeres.2011.11.002

[19] Weinreb RN, Aung T, Medeiros FA. The pathophysiology and treatment of glaucoma: A review. JAMA - Journal of the American Medical Association. 2014. DOI: 10.1001/jama.2014.3192

[20] Lamb TD, Pugh EN. Phototransduction, dark adaptation, and rhodopsin regeneration the proctor lecture. Investigative Ophthalmology & Visual Science. 2006;**47**:5138

[21] Beykin G, Norcia AM, Srinivasan VJ, et al. Discovery and clinical translation of novel glaucoma biomarkers. Progress in Retinal and Eye Research. 2021;**80**:100875

[22] Kim KE, Park K-H. Update on the prevalence, etiology, diagnosis, and monitoring of normal-tension glaucoma. Asia-Pacific Journal of Ophthalmology. 2016;**5**:23-31

[23] Goel M, Picciani RG, Lee RK, et al. Aqueous humor dynamics: A review. The Open Ophthalmology Journal. 2010. DOI: 10.2174/1874364101004010052

[24] Wang W, Chen L. Update on apoptosis signal pathway of retinal ganglion cell. Zhonghua Shiyan Yanke Zazhi/Chinese Journal of Experimental

Ophthalmology. 2014. DOI: 10.3760/cma.j.issn.2095-0160.2014.04.017

[25] Doozandeh A, Yazdani S. Neuroprotection in glaucoma. Journal of Ophthalmic and Vision Research. 2016. DOI: 10.4103/2008-322X.183923

[26] Cavet ME, DeCory HH. The role of nitric oxide in the intraocular pressure lowering efficacy of Latanoprostene Bunod: Review of nonclinical studies. Journal of Ocular Pharmacology and Therapeutics. 2018;**34**:52-60

[27] Mergler S, Pleyer U. The human corneal endothelium: New insights into electrophysiology and ion channels. Progress in Retinal and Eye Research. 2007;**26**:359-378

[28] Cho JH, Ryoo N-K, Cho KH, et al. Incidence rate of massive submacular Hemorrhage and its risk factors in Polypoidal choroidal vasculopathy. American Journal of Ophthalmology. 2016;**169**:79-88

[29] da Silva CN, Pedrosa KN, da Silva GC, et al. The synthetic peptide PnPP-19 potentiates erectile function via nNOS and iNOS. Nitric oxide : Biology and Chemistry. 2021;**113-114**:23-30

[30] Toda N, Nakanishi-Toda M. Nitric oxide: Ocular blood flow, glaucoma, and diabetic retinopathy. Progress in Retinal and Eye Research. 2007. DOI: 10.1016/j.preteyeres.2007.01.004

[31] Yu J, DeMuinck ED, Zhuang Z, et al. Endothelial nitric oxide synthase is critical for ischemic remodeling, mural cell recruitment, and blood flow reserve. Proceedings of the National Academy of Sciences. 2005;**102**:10999-11004

[32] Bringmann A, Pannicke T, Grosche J, et al. Müller cells in the healthy and

diseased retina. *Progress in Retinal and Eye Research*. 2006;25:397-424

[33] Choi D. Glutamate neurotoxicity and diseases of the nervous system. *Neuron*. 1988;1:623-634

[34] Scharfman HE, Lu SM, Guido W, et al. N-methyl-D-aspartate receptors contribute to excitatory postsynaptic potentials of cat lateral geniculate neurons recorded in thalamic slices. *Proceedings of the National Academy of Sciences*. 1990. DOI: 10.1073/pnas.87.12.4548

[35] Siliprandi R, Canella R, Carmignoto G, et al. N-methyl-D-aspartate-induced neurotoxicity in the adult rat retina. *Visual Neuroscience*. 1992. DOI: 10.1017/S0952523800005666

[36] Cobb CA, Cole MP. Oxidative and nitrative stress in neurodegeneration. *Neurobiology of Disease*. 2015;84:4-21

[37] Gu Z, Yamamoto T, Kawase C, Matsubara M, Kawase K, Sawada A, et al. [Neuroprotective effect of N-methyl-D-aspartate receptor antagonists in an experimental glaucoma model in the rat]. *Nippon Ganka Gakkai Zasshi*. Jan 2000;104(1):11-16 (Japanese)

[38] Sleight J, Harvey M, Voss L, et al. Ketamine - more mechanisms of action than just NMDA blockade. *Trends in anaesthesia and critical care*. 2014. DOI: 10.1016/j.tacc.2014.03.002

[39] Parsons CG, Stöffler A, Danysz W. Memantine: A NMDA receptor antagonist that improves memory by restoration of homeostasis in the glutamatergic system - too little activation is bad, too much is even worse. *Neuropharmacology*. 2007;53:699-723

[40] Freitas ACN, Silva GC, Pacheco DF, et al. The synthetic peptide PnPP-19

induces peripheral antinociception via activation of NO/cGMP/KATP pathway: Role of eNOS and nNOS. *Nitric Oxide: Biology and Chemistry*. 2017. DOI: 10.1016/j.niox.2017.01.004

[41] Tezel G. Oxidative stress in glaucomatous neurodegeneration: Mechanisms and consequences. *Progress in Retinal and Eye Research*. 2006;25:490-513

[42] Bahar AA, Ren D. Antimicrobial peptides. *Pharmaceuticals*. 2013. DOI: 10.3390/ph6121543

[43] da Costa JP, Cova M, Ferreira R, et al. Antimicrobial peptides: An alternative for innovative medicines? *Applied Microbiology and Biotechnology*. 2015. DOI: 10.1007/s00253-015-6375-x

[44] Zhang Q-Y, Yan Z-B, Meng Y-M, et al. Antimicrobial peptides: Mechanism of action, activity and clinical potential. *Military Medical Research*. 2021;8:48

[45] Kang HK, Kim C, Seo CH, et al. The therapeutic applications of antimicrobial peptides (AMPs): A patent review. *Journal of Microbiology*. 2017. DOI: 10.1007/s12275-017-6452-1

[46] Nam M-H, Stankowska DL, Johnson GA, et al. Peptains block retinal ganglion cell death in animal models of ocular hypertension: Implications for neuroprotection in glaucoma. *Cell Death & Disease*. 2022;13:958

[47] Lee S, Silverman N, Gao F-B. Emerging roles of antimicrobial peptides in innate immunity, neuronal function, and neurodegeneration. *Trends in Neurosciences*. 2024;47:949-961

[48] da Silva CN, Nunes KP, Dourado LFN, et al. From the PnTx2-6 toxin to the PnPP-19 engineered peptide: Therapeutic potential in

- erectile dysfunction, nociception, and glaucoma. *Frontiers in Molecular Biosciences*. 2022;**9**:831823. DOI: 10.3389/fmolb.2022.831823
- [49] Mwangi J, Kamau P, Thuku R, et al. Design methods for antimicrobial peptides with improved performance. *Zoological Research*. 2023
- [50] Gomez MV, Kalapothakis E, Guatimosim C, et al. Phoneutria nigriventer venom: A cocktail of toxins that affect ion channels. *Cellular and Molecular Neurobiology*. 2002. DOI: 10.1023/A:1021836403433
- [51] De Lima ME, Figueiredo SG, Matavel A, et al. Phoneutria nigriventer venom and toxins: A review. In: *Spider Venoms*. Dordrecht: Springer Netherlands; 2015. pp. 1-24
- [52] Dourado LFN, da Silva CN, Gonçalves RS, et al. Improvement of PnPP-19 peptide bioavailability for glaucoma therapy: Design and application of nanowafers based on PVA. *Journal of Drug Delivery Science and Technology*. 2022;**74**:103501
- [53] Kang SJ, Park SJ, Mishig-Ochir T, et al. Antimicrobial peptides: Therapeutic potentials. *Expert Review of Anti-Infective Therapy*. 2014. DOI: 10.1586/14787210.2014.976613
- [54] Pescina S, Ostacolo C, Gomez-Monterrey IM, et al. Cell penetrating peptides in ocular drug delivery: State of the art. *Journal of Controlled Release*. 2018. DOI: 10.1016/j.jconrel.2018.06.023
- [55] Hosoya K, Lee VHL, Kim K-J. Roles of the conjunctiva in ocular drug delivery: A review of conjunctival transport mechanisms and their regulation. *European Journal of Pharmaceutics and Biopharmaceutics*. 2005;**60**:227-240
- [56] Elsayed YY, Kühl T, Imhof D. Regulatory guidelines for the analysis of therapeutic peptides and proteins. *Journal of Peptide Science*. 2025;**31**:1-16. DOI: 10.1002/psc.70001
- [57] del Amo EM, Rimpelä AK, Heikkinen E, et al. Pharmacokinetic aspects of retinal drug delivery. *Progress in Retinal and Eye Research*. 2017;**57**:134-185

Chapter 2

Identifying Risk Factors for Glaucoma through Iris Images

Carolyn Aitken

Abstract

This study investigates the potential link between nutritional deficiencies and glaucoma. Building upon previous clinical research linking iris colour variations to certain ocular diseases, this study explores how specific nutritional deficiencies highlighted by iris analysis techniques could provide insight into the specific essential mineral deficiencies that contribute to optic nerve damage. Recent advancements in high-resolution iris imaging and digital display technologies have enhanced the feasibility of using iris features for diagnostic purposes. Notably, specific iris characteristics, such as localised fibre openings or loss of substance, pigmented collarette and the presence of a dark circumferential band around the pupillary border known as *shadow ring*, have been associated with individuals diagnosed with glaucoma. While iris recognition focuses on the overall structure, iris analysis studies the local variations within specific regions of the iris. This research compares certain colour differences in irises of participants with and without glaucoma, highlighting the rapid, non-invasive diagnostic potential of this approach.

Keywords: glaucoma, optic nerve, iris images, zinc deficiency, B3 deficiency, blood flow

1. Introduction

Glaucoma is a condition which can lead to sight loss and, in severe cases, blindness. Glaucoma is primarily characterised by progressive damage to the optic nerve. While elevated intraocular pressure (IOP) is a major risk factor, other underlying systemic and nutritional imbalances may also contribute to its progression. Recent research suggests that maintaining appropriate *zinc* levels [1]—a critical element for retinal and optic nerve function—is essential for retinal health. Imbalances, whether excess or deficiency, can negatively impact optic nerve function.

High-resolution iris images of individuals with glaucoma has revealed distinct patterns linked to zinc deficiency, impaired blood flow and iris shape irregularities linked to B3 deficiency, all of which may indicate metabolic disturbances affecting the optic nerve. Specific features—such as a darker band at the pupillary border, fibre rarefactions in key iris zones, lateral bulging of the iris, a green hue inside the pupil, and unusual vascular patterns—may provide insight into underlying dysfunctions impacting optic nerve health.

2. Understanding glaucoma

Glaucoma refers to a group of eye conditions that progressively damage the optic nerve leading to vision loss if left untreated. For a clear definition of glaucomatous optic nerve damage, see [2] and to better understand how these conditions affect sight, refer to [3]. There is a wealth of accessible, evidence-based information available through organisations such as Glaucoma UK and the Glaucoma Associates, where clinicians and patients alike can explore the latest research, treatment updates, and ongoing support to stay informed.

2.1 The role of the optic nerve

The optic nerve serves as the vital component between the retina and the brain, relaying visual signals that enable perception. Comprising around one million nerve fibres, it plays a critical role in maintaining a cohesive visual field. When intraocular pressure (IOP) rises beyond its functional threshold that will permit normal function of the optic nerve, its function can become compromised. Fortunately, optometrists can often detect early signs of optic nerve damage—before vision changes occur—through specialised tests during routine eye examinations.

Traditionally, glaucoma has been defined as a condition in which elevated IOP (typically above 21 mm Hg)—due to impaired aqueous fluid drainage—leads to damage of the optic nerve and retinal ganglion cells. However, current glaucoma management strategies, which focus primarily on lowering IOP, are not sufficient for all patients. In the UK Glaucoma Treatment Study (UKGTS), disease progression was observed in 20% of participants within just 24 months despite standard treatment [4]. These findings highlight the need for a broader, more integrative approach—one that not only manages IOP but also actively supports, protects, and potentially restores retinal ganglion cells (RGCs) and the optic nerve.

Glaucoma is classified into two main types: *primary* and *secondary* (**Figure 1**).

2.2 Glaucoma classification

2.2.1 Primary glaucoma

Develops without any identifiable external cause.

- Primary open-angle glaucoma (*POAG*): The most common type, occurring when the drainage system in the eye gradually becomes less efficient, leading to increased eye pressure over time.
- Normal-tension glaucoma (*NTG*): A form of POAG where optic nerve damage occurs despite normal eye pressure levels.
- Primary angle-closure glaucoma (*PACG*): A less common but more urgent type that happens when the eye's drainage angle becomes blocked, causing a rapid rise in eye pressure requiring urgent treatment.

2.2.2 Secondary glaucoma

Occurs as a result of another condition or external factor.

Types of Glaucoma

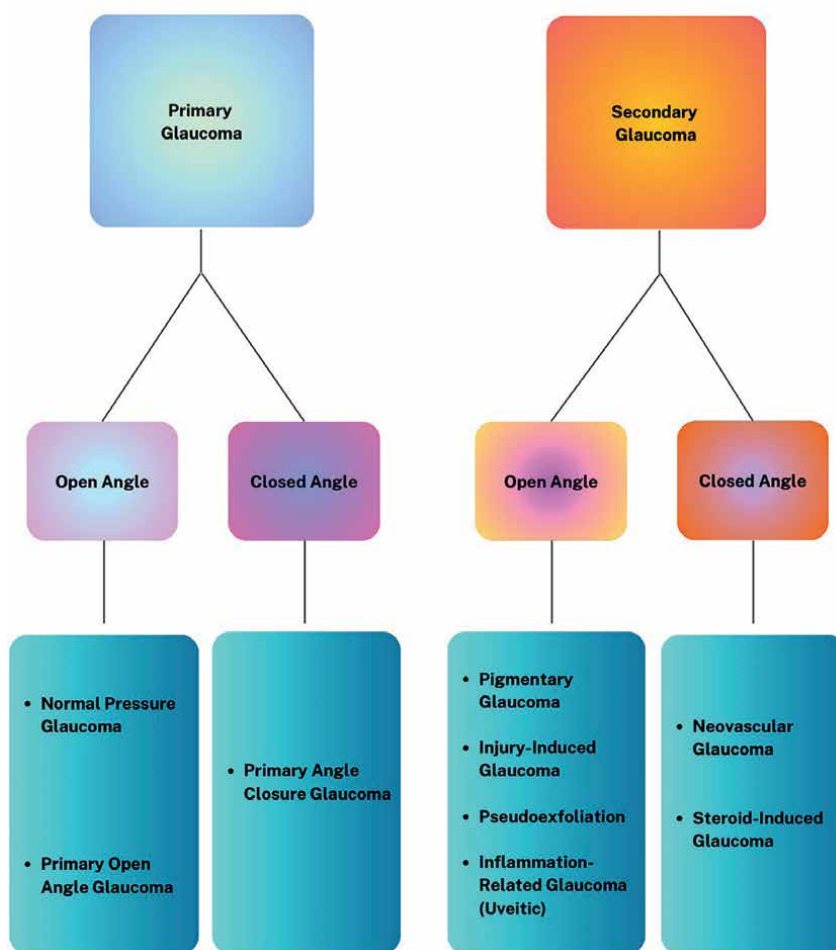


Figure 1.
 A visual classification of glaucoma subtypes for rapid reference.

- Pigmentary glaucoma: Caused by pigment particles blocking the drainage channels.
- Traumatic glaucoma: Injury-induced. Blood and debris from the injury can block the eye's drainage system.
- Pseudoexfoliation glaucoma: Linked to an abnormal accumulation of proteins that obstruct fluid drainage.
- Inflammation related glaucoma: Chronic Anterior Uveitis
- Advanced neovascular glaucoma: Associated with abnormal blood vessel growth, often due to diabetes or other vascular diseases.

- Steroid-induced glaucoma: Results from prolonged use of corticosteroid medications, leading to increased eye pressure.

2.3 Risk factors

Glaucoma risk factors encompass a range of demographic, genetic, and health-related variables. Age is a significant factor, with risk increasing notably after 40 years [5]. Family history plays a crucial role, with first-degree relatives of glaucoma patients having up to a 25% lifetime risk. Ethnicity also influences susceptibility, with African, Caribbean, and Asian populations at higher risk. Elevated intraocular pressure (IOP) remains a primary risk factor for many glaucoma types. Ocular conditions such as thin central corneas and high myopia (>6 diopters) contribute to increased risk. Systemic health issues, including diabetes, hypertension, and cardiovascular disease, may elevate glaucoma risk. Prolonged use of topical or systemic steroids can lead to steroid-induced glaucoma. Previous eye trauma or surgery may result in secondary glaucoma. Nutritional factors are also relevant, particularly for optic nerve health. B vitamins, especially vitamin B3 (nicotinamide), support mitochondrial function in retinal ganglion cells [6] and maintain nicotinamide adenine dinucleotide (NAD⁺) levels, a crucial coenzyme found in all living cells that plays a vital role in hundreds of metabolic processes, including energy production, DNA repair, and cellular health which are key for optic nerve health and function, which decrease with age, making cells more vulnerable to damage [7].

Vitamin B12 (Cobalamin): Essential for red blood cell formation and neurological function. Its deficiency can lead to optic neuropathy [8]. Vitamin B1 (Thiamine) and B6 (Pyridoxine): Support energy metabolism and are crucial for normal development and function of the visual pathways. Vitamin B9 (Folate): Important for DNA synthesis, repair, and cell growth, contributing to overall retina and optic nerve health [9]. Antioxidants protect the optic nerve from oxidative stress. Coenzyme Q10 (CoQ10): Acts as an antioxidant and plays a role in cellular energy production, potentially offering neuroprotective effects for the optic nerve [9].

Minerals are crucial for optic nerve function: zinc serves as a structural element in retinal enzymes and proteins. Zinc deficiency can make patients highly vulnerable to optic neuropathy [9]. Copper is essential for protecting the eyes from sunlight damage and supporting overall optic nerve health [9]. Other nutrients such as Arginine involved in nitric oxide production, which regulates blood flow to the eye, crucial for nourishing ocular tissues [9]. Omega-3 fatty acids support neural health and may indirectly benefit optic nerve function [9].

The optic nerve relies on key micronutrients to support critical functions such as energy production, DNA synthesis, protection against oxidative stress, and overall cellular maintenance. Ensuring sufficient intake—whether through diet or supplementation—is vital for maintaining its health and reducing the risk of glaucoma and other optic neuropathies.

2.4 Stress as a consequence and a cause

It can be both a consequence and a cause of vision loss, creating a potential vicious cycle. Here's an explanation of how stress affects the optic nerve:

Physiological stress/vascular effects: stress hormones influence vascular tone around the optic nerve, potentially impairing blood flow and autoregulation [10]. Elevated Cortisol: prolonged stress leads to increased cortisol levels, which can negatively impact the eye and brain through autonomic nervous system imbalance [11].

Intraocular pressure: stress-related factors like poor sleep patterns can increase intraocular pressure, a significant risk factor [12].

Psychological impact: anxiety and depression can exacerbate unhealthy behaviours and reduce adherence to treatment plans [12]. Stress may influence autoimmune responses, potentially contributing to conditions like optic neuritis [13].

Lifestyle factors: stress often leads to smoking, poor diet, and physical inactivity, all of which can affect optic nerve health. Some stress-related medications may have toxic effects on the optic nerve. Negative psychological states may alter immune system regulation and modulation of peripheral cytokines [14].

Pathophysiological mechanisms: recent research [15] from the Vanderbilt Eye Institute suggests that the earliest signs of injury in glaucoma occur in the brain. Similar to neurodegenerative diseases such as Parkinson's disease (PD), where neuronal damage begins in the distal projections through a process known as *dying back*, glaucoma appears to follow a comparable pattern. In dying back, neuronal axons progressively lose their ability to communicate with their target structures. In the case of glaucoma, researchers have demonstrated that axons in the optic nerve lose connectivity with their projection sites in the midbrain. Further research is necessary to determine whether glaucoma increases the risk of developing Parkinson's disease, if Parkinson's disease predisposes individuals to glaucoma, or if shared underlying factors contribute to the development of both conditions. Individuals diagnosed with either condition should undergo regular medical evaluations to monitor and manage potential comorbidities effectively.

2.5 Symptoms of glaucoma

Many people with glaucoma experience no early symptoms but as the disease progresses, signs may include: unfocused vision, with portions of the visual field seemingly absent. Gradual loss of peripheral vision. Blurred vision. Eye pain or pressure (in acute cases). Halos around lights. Sudden vision loss (in advanced or acute cases).

The symptoms of glaucoma vary depending on the type and stage of the disease: *Open-Angle Glaucoma*: Develops gradually and is often asymptomatic until significant vision loss occurs. Peripheral vision loss is usually the first noticeable sign. *Angle-Closure Glaucoma*: Can cause sudden symptoms such as severe eye pain, headache, nausea, blurred vision, and halos around lights. This is a medical emergency requiring immediate treatment.

2.6 Diagnosis and detection

Because glaucoma is often asymptomatic in its early stages, routine eye exams are crucial. Common diagnostic methods include:

- Tonometry: Measures the intraocular pressure (IOP), or the pressure inside the eye. It can help determine if there's a risk of developing glaucoma.
- Optical coherence tomography (OCT): Assesses the health of the optic nerve. The OCT 3D scan works like an ultrasound. However, rather than using sound waves, it uses light waves to see the detailed layers of the retina [16].
- Visual field test: This test detects blind spots (scotomas) and can reveal peripheral vision loss—one of the early signs of glaucoma.

- **Gonioscopy:** This procedure allows the optometrist to inspect the eye's drainage pathway—known as the anterior chamber angle—using a slit lamp and a specially designed lens. If the angle appears unusually narrow or blocked, it may indicate a risk of glaucoma.

2.7 Treatment and management

While glaucoma cannot be cured, its progression can be controlled with early treatment. The primary treatment options include: **Eye Drops:** medications that reduce eye pressure by either decreasing fluid production or improving fluid drainage. **Laser Therapy:** procedures like selective laser trabeculoplasty (SLT) help improve fluid outflow. **Surgery:** canaloplasty [17] and in severe cases, procedures like trabeculectomy or drainage implants may be necessary.

3. The optic nerve, a critical conduit

The optic nerve, or cranial nerve II, is a vital component of the visual system, responsible for transmitting visual information from the retina to the brain. Its intricate structure and function are essential for vision, and understanding its complexities offers insight into how we perceive the world. During embryonic development, the optic nerve originates from the optic stalks, outpouchings of the diencephalon, and its development commences during the seventh week.

The optic nerve is composed of over a million nerve fibres originating from retinal ganglion cells. It is divided into four segments: **Intraocular Part:** Located within the eyeball, this segment includes the optic disc, where nerve fibres converge. **Intraorbital Part:** Extending within the orbit, it allows for eye movement without stretching the nerve. **Intracranial Part:** This segment passes through the optic canal, a bony pathway connecting the orbit to the cranial cavity. **Intracranial Part:** Extending within the cranial cavity, it leads to the optic chiasm, where fibres partially cross to the opposite side. The optic nerve is ensheathed by layers of meninges—protective coverings also found surrounding the brain—which provide support and insulation.

3.1 Function

The primary role of the optic nerve is to convey visual impulses from the retina to the brain. When light enters the eye, it is focused onto the retina, where photoreceptor cells convert it into electrical signals [18]. These signals are then transmitted via the optic nerve to the visual cortex, where they are processed into images, enabling vision. Additionally, the optic nerve plays a role in controlling the size of the pupil, regulating the amount of light entering the eye.

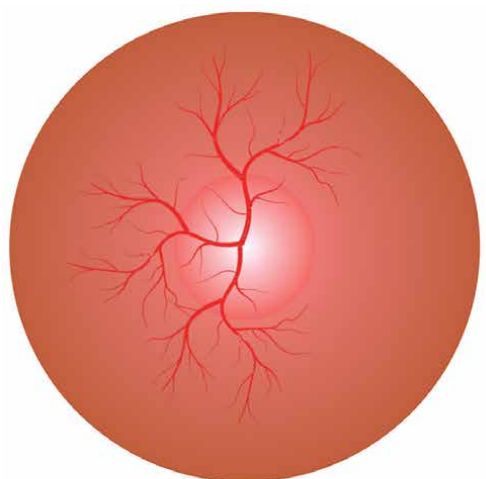
3.2 Blood supply

The optic nerve's health is heavily reliant on its blood supply. The intraocular segment, particularly the optic nerve head, receives blood from the short posterior ciliary arteries, branches of the ophthalmic artery. The central retinal artery, also a branch of the ophthalmic artery, penetrates the optic nerve posteriorly to supply the inner retinal layers. Disruptions in this blood supply can lead to conditions like

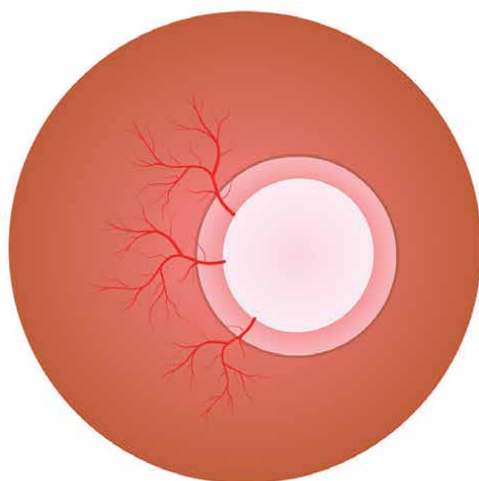
anterior ischemic optic neuropathy, characterised by sudden vision loss due to insufficient blood flow to the optic nerve [19].

3.3 Associated conditions

The optic nerve can be affected by various conditions. Optic Neuritis: Inflammation of the optic nerve, often associated with multiple sclerosis, leading to symptoms like eye pain and vision loss. Neuromyelitis Optica (NMO): An autoimmune disorder causing inflammation of the optic nerve and spinal cord, resulting in vision and neurological impairments. Optic Nerve Gliomas: Tumours that can form on the optic nerve, usually benign but can cause vision problems. Optic Nerve



Healthy Optic Nerve



Glaucomatous Cupping

Figure 2.
A comparison between a healthy disk and optic nerve cupping.

Coloboma: An inherited condition affecting optic nerve development, potentially leading to vision impairment.

4. Optic nerve changes in glaucoma

The primary site of damage in glaucoma is the optic nerve head, leading to characteristic changes [20]. For a visual depiction of these changes (see **Figure 2**).

4.1 Optic disc cupping

As retinal ganglion cells degenerate, their axons are lost, resulting in an increased cup-to-disc ratio. This manifests as an enlargement of the central depression (cup) of the optic nerve head.

4.2 Neuroretinal rim thinning

The neuroretinal rim, the area between the optic cup and the edge of the optic disc, becomes thinner, reflecting the loss of nerve fibres.

4.3 Retinal nerve fibre layer defects

Damage to the RNFL can be observed as localised or diffuse thinning, detectable through imaging modalities like optical coherence tomography (OCT).

4.4 Peripapillary atrophy

Atrophy around the optic disc may occur, indicating changes in the retinal pigment epithelium and choriocapillaris.

5. Zinc's role in ocular health

Zinc is an essential trace mineral that plays a significant role in ocular health, particularly concerning the optic nerve. It is involved in various cellular and metabolic processes within the visual pathway [21].

5.1 Zinc's interaction with the optic nerve

Research indicates that zinc (Zn) is crucial for the proper functioning of retinal ganglion cells (RGCs), which are neurons that transmit visual information from the retina to the brain via the optic nerve. Studies have shown that zinc is released from retinal cells shortly after optic nerve injury, suggesting its involvement in the response to neuronal damage. However, excessive zinc accumulation can be detrimental, leading to RGC death and hindering optic nerve regeneration. Conversely, chelating excess zinc has been found to promote RGC survival and enhance optic nerve regeneration, highlighting zinc's dual role in neurodegeneration and neuroprotection.

5.2 Source and transport of zinc to the optic nerve

Zinc is obtained through dietary intake and is transported via the bloodstream to various tissues, including ocular structures. Within the retina, zinc is predominantly localised in the inner plexiform layer and is stored in synaptic vesicles of amacrine cells, a type of interneuron. Upon optic nerve injury, zinc is mobilised from these amacrine cells and transferred to RGCs, where it can influence cell survival and axonal regeneration. This mobilisation underscores the importance of regulated zinc homeostasis in maintaining optic nerve health and function.

5.3 Zinc's contribution in ocular function

Zinc is found in high concentrations in the retina and choroid, the vascular layer of the eye. Zinc contributes to various ocular functions, including enzymatic function. Zinc is a component of numerous enzymes in the eye that are crucial for visual processing. These enzymes facilitate essential biochemical reactions within retinal cells, supporting overall visual function. Zinc also plays a role in the body's antioxidant defence system, helping to protect ocular tissues from oxidative stress. This protection is vital in reducing the risk of age-related macular degeneration (AMD) and other degenerative eye conditions. Zinc helps maintain the structural integrity of retinal cells and photoreceptors, which are essential for capturing light and initiating visual signals. Adequate zinc levels support the health and function of these cells, contributing to clear vision [22].

A study from October 2016 [21] highlights the role of disrupted zinc regulation in chronic neurodegenerative disorders such as Alzheimer's disease and amyotrophic lateral sclerosis. Zinc dysregulation was shown to contribute significantly to oxidative stress-related cell death in both neurons and oligodendrocytes. Building on this, the researchers explored zinc's involvement in retinal ganglion cell (RGC) degeneration following optic nerve injury. Their findings revealed that zinc ions (Zn^{2+}) rapidly accumulate in amacrine cell processes soon after injury and are subsequently transferred to RGCs. Notably, the use of zinc chelators not only enhanced RGC survival for extended periods but also strongly promoted axonal regeneration.

Patients with Parkinson's disease often exhibit reduced circulating zinc levels. Research published in October 2022 [23] suggests that zinc ions enhance the function of human serum albumin (HSA)—a major transport protein in the bloodstream—by improving its capacity to inhibit the aggregation of α -synuclein, a key process associated with the development of Parkinson's disease.

5.4 Zinc deficiency worldwide

Zinc deficiency is a global health concern, affecting various populations to differing extents. In the United Kingdom, zinc deficiency affects specific segments of the population. A study by the International Zinc Nutrition Consultative Group (IZiNCG) reported that approximately 10% of women in the UK have low serum zinc levels. Additionally, data from the World Health Organisation (WHO) indicate that about 8.6% of the UK population is at risk of inadequate zinc intake [24].

Globally, the prevalence of zinc deficiency varies significantly. In many high-income countries, under 10% of the population is affected. In contrast, regions

such as sub-Saharan Africa and South Asia experience much higher rates, with a sizeable share of the population being deficient. Assessing zinc deficiency often involves measuring serum zinc concentrations and evaluating dietary intake. However, data on zinc status are limited in many countries, underscoring the need for more comprehensive nutritional surveillance [25]. Addressing zinc deficiency requires targeted public health interventions, including dietary diversification, food fortification, and supplementation programs, especially in regions with high prevalence rates. The National Institutes of Health (NIH) recommends [26] a tolerable upper intake level of 8 mg per day for adult women—including those aged 45 to 65. Consuming zinc significantly above this limit may cause gastrointestinal symptoms such as nausea, vomiting, and diarrhoea, and can interfere with copper absorption, potentially leading to copper deficiency. This can lead to anaemia and to weakening of the bones. Chronic over-supplementation might also impair immune function and disrupt the balance of other essential minerals. According to Food Standard Scotland [26], adults should avoid consuming more than 25 mg of zinc per day through supplements, unless advised otherwise by a healthcare professional. In cases where higher doses are medically necessary, supplementation may continue under supervision.

Top dietary sources of zinc include oysters, red meat, poultry, dairy, pumpkin seeds, cashews, pine nuts, legumes, and whole grains. Among the most common [27].

6. Zinc and B3 compounds homeostasis

Recent glaucoma research is exploring the use of nicotinamide supplements as a means to support mitochondrial function and protect the optic nerve. Interestingly, there is some evidence suggesting that forms of vitamin B3, such as nicotinic acid, can enhance zinc absorption and utilisation [28] implying that B3 compounds might positively influence zinc homeostasis. Nicotinamide is one of the three forms of vitamin B3, along with nicotinic acid (niacin) and nicotinamide riboside.

Zinc is critical for numerous cellular processes, including antioxidant defence and the health of retinal ganglion cells, which are vital for vision. Therefore, any intervention that could improve zinc status might indirectly benefit ocular health and potentially contribute to glaucoma management. However, it is important to note that while these findings suggest a mechanistic link between vitamin B3 and zinc metabolism, direct clinical evidence linking B3 supplementation to the correction of zinc deficiency specifically in glaucoma patients is still limited. Further research is needed to determine whether nicotinamide can effectively address zinc deficiency and if this interaction plays a significant role in managing glaucoma.

Nicotinamide plays crucial roles in the body [29]. It is a component of the coenzymes nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP⁺). It helps convert nutrients into energy and is involved in creating and repairing DNA. It is required for the function of fats and sugars in the body and to maintain healthy cells. Nicotinamide can be found naturally in foods, including: meat, fish, and poultry, nuts and legumes, green vegetables, mushrooms, milk and eggs. Unlike nicotinic acid, nicotinamide does not cause skin flushing and is often preferred for treating niacin deficiency [30]. It is also being researched for potential benefits in treating skin conditions, such as acne and ageing skin, as well as for its possible role in cancer prevention and treatment of HIV [31].

6.1 Biomarker for glaucoma progression

A recent study in 2024 by Professor Garway-Heath [32] identified a new biomarker for glaucoma progression. “Mitochondrial function has emerged as a potential susceptibility factor,” he said. They were able to measure the function of these mitochondria in white blood cells and found that it was lower in people with glaucoma and lowest in those who developed glaucoma with high pressure in the normal range and the rate of vision loss in people with glaucoma was correlated to that mitochondrial function. Zinc plays an important role in mitochondrial function, with neurons being notably reliant on this organelle to fulfil the high energy demands of the central nervous system [33].

7. Developmental origins of the iris and its inner pupillary border

The formation of the inner pupillary border (IPB) in the iris of the eye is rooted in the organogenesis phase of ocular development, which occurs between the 4th and 8th weeks of gestation [34]. During this critical period, pigmented cells emerge in the superotemporal wall of the optic vesicle—specifically in regions that do not undergo invagination. These cells give rise to the pigmented retinal epithelium (RPE), which subsequently contributes to the development of the IPB. By week 4, this early pigmented layer begins forming, and if proper contact between the surface ectoderm and the optic vesicle fails, the region may instead form a pigmented epithelium akin to the RPE, potentially leading to rare instances of epithelial-neural transdifferentiation. Around week 5, melanosomes begin to appear in both the retina and iris, indicating the onset of pigmentation processes. The IPB continues its differentiation in week 6, forming a single cuboidal epithelial layer as the embryonic fissure closes. In week 7, key structural changes occur: anterior epithelial fibres attach to primary lens fibres, while neural crest-derived mesenchymal cells migrate in three distinct waves. The third wave is traditionally credited with forming the iris stroma, although some evidence suggests that the second wave plays a more primary role. The IPB plays an inductive role in this process, also contributing to scleral development through signalling mechanisms linked to the RPE. By week 8, the pigmented retinal epithelium is largely mature, although melanosome production and migration persist into the second trimester. Notably, vitamin C is thought to influence the viscosity and structural dynamics of developing ocular tissues, including the IPB.

At this embryonic stage, the optic nerve already contains approximately 2.67 million axons and 34,000 growth cones, which have reached the brain and initiated the formation of the optic chiasm. Macrophages also begin populating the meningeal layers, marking early immune activity in ocular structures. Together, these events underscore the neuroectodermal origin, pigment-linked differentiation, and structural interdependence of the inner pupillary border with surrounding tissues. The IPB’s developmental timeline also highlights its potential diagnostic value when assessed in relation to early neural development and pigment deposition patterns.

8. From observation to investigation

The iris offers a unique insight into an individual’s health, yet its potential remains largely underutilised. Each person’s iris is unique; even the right and left iris of the same person differ.

Not dissimilar to retinal imaging serving as a valuable, non-invasive tool to detect systemic diseases by revealing changes in retinal blood vessels that correspond to broader vascular and organ health issues, the iris provides valuable details about local variations in iris patterns, brightness or darkness, placement and shape of pigments. These characteristics can offer insights into various health conditions.

8.1 Iris patterns as potential indicators of glaucoma

This observational study was initiated in Scotland, following repeated clinical observations of distinctive iris markings in patients diagnosed with glaucoma. The idea emerged from the hypothesis that specific structural or pigment-related iris features may reflect early or ongoing glaucomatous changes in the optic nerve.



Figure 3.
Recruiting participants poster.

The aim of the study was to investigate whether these iris patterns could offer additional insight into glaucoma risk, complementing conventional diagnostic methods.

8.2 Study design and method

The study employed a cross-sectional observational design and recruited participants through a community-based clinic in the Scottish town of Helensburgh. Inclusion criteria included individuals over the age of 40 who volunteered to take part in meaningful research. The study group consisted of participants with a confirmed diagnosis of primary open-angle glaucoma, alongside an age-matched control group without known ocular pathology (see recruitment poster, **Figure 3**). Each participant underwent high-resolution iris photography using a Nikon D5300 camera with flash, under standardised lighting conditions in a controlled setting at The Lomond Clinic. The images were examined for characteristic iris features, including orange pigment deposits, fibre separation within the iris stroma, variations in the collarette (that remnant of the embryonic persistent pupillary membrane that separates the pupillary zone from the ciliary zone near the outer edge of the iris) patterns and overall iris shape, indicators of impaired blood flow, signs of possible cholesterol and the structural integrity of the pupillary border. These features were then analysed for their frequency and distribution across both the glaucoma and control groups. In addition to image capture, permission to observe their irises and photographs was obtained in writing. The study also recorded each participant's current intraocular pressure, the presence and extent of visual field defects, whether they were still driving, details of ongoing treatment including prescribed eye drops, and relevant family history—specifically glaucoma, Parkinson's disease, or shingles. Participants were also asked to report their overall quality of life and any significant personal traumas around the time of glaucoma diagnosis. These data points allowed potential correlations to be explored between iris features and structural optic nerve damage.

8.3 Strengths of the study

- Novel observational insight: This study represents one of the first structured investigations into the potential role of iridology in glaucoma risk stratification, adding to the discourse on integrative diagnostic approaches.
- Community-based setting: The real-world setting allows for the inclusion of diverse participants representative of the local population.
- Non-invasive imaging: Iris photography is a simple, non-invasive procedure that could be easily adopted into routine screenings if clinically validated.
- Early detection potential: If associations between iris features and optic nerve changes are confirmed, this method could support earlier identification of individuals at risk of developing glaucoma. Specially in populations at higher risk.

8.4 Limitations

- Sample size: As a preliminary local study, the participant pool was limited, which may affect the generalisability of findings.

- Subjectivity of pattern recognition: Although a structured observation protocol was used, interpretation of iris markings retains an element of subjectivity, potentially introducing observer bias.
- Lack of longitudinal data: The cross-sectional design does not allow conclusions regarding causality or the progression of iris changes over time.
- Potential confounding variables: Factors such as ocular comorbidities may influence iris features independently of glaucoma, and controlling for these variables could be challenging.

9. Specific iris characteristics in participants with glaucoma

9.1 Shadow ring

Through observation of participants undergoing treatment for primary open-angle glaucoma (POAG), a set of characteristic iris features has been identified. Among these, one of the most prevalent findings is the shadow ring, a dark circumferential band surrounding the pupillary border (also known as pupillary ruff). This ring appears in the nutritive zone of the iris, an area traditionally associated with nutrient assimilation, and has been linked to impaired zinc absorption with an 84.12% correlation from 5121 cases (4308 out of 5121). Confirmed via blood or urine analysis, or documented history of zinc deficiency. This dark band varies in shade from dark grey to black and remains unchanged regardless of illumination angle. Histological examination of affected tissue reveals signs of spindle cell atrophy, suggesting compromised cellular regeneration in this region. Atrophy in this context may arise from various causes, including malnutrition, nerve damage, disuse, or underlying disease. Optimal visualisation requires a combination of front and side illumination alongside high-resolution digital imaging to ensure accurate detection of this feature. Interestingly, pigment-related zinc uptake in ocular tissues has been previously reported, with fundus pigmentation shown to influence zinc storage [35].

9.2 Iris bulge

Another notable characteristic observed in individuals with glaucoma is an irregular iris shape, where the iris deviates from its typical circular disk shape and appears to bulge laterally (almond shape). The ratio of the iris disk is larger on the inferior part of the iris while appearing noticeably flatter in the superior region (see **Figure 4**). This morphological irregularity has been considered a potential sign of vitamin B3 (niacin) deficiency according to Aliyeva, Shulpina, Velchover [36], further reinforcing the potential role of nutritional factors in glaucoma pathophysiology. On the sclera, at the site of the bulge, a lanula—a light blue / white arc—is observed, which may indicate heart rhythm disturbances. In the left eye, it corresponds to sinus tachycardia, while in the right eye, it is associated with sinus bradycardia [37]. This presentation may support a potential link between vitamin B3 deficiency and impaired blood flow.

On the bulbar conjunctiva, typically translucent and allowing visibility of the sclera, an unusual vascular pattern was observed. Tiny blood vessels extended toward

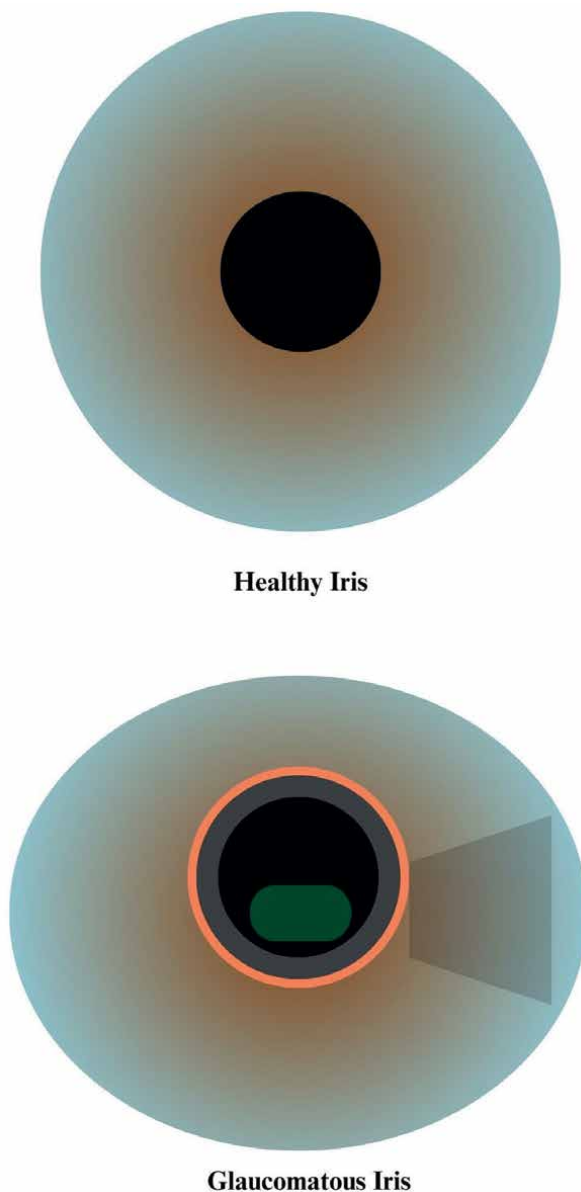


Figure 4.
Visual depiction of the iris features comparison.

the superior part of the iris (corneal limbus) before looping back, forming a distinctive arc-like configuration. This pattern may indicate underlying blood flow irregularities. Given that glaucoma is associated with both systemic hypotension and vascular dysregulation, these findings could be significant in assessing ocular perfusion and microcirculatory changes in affected individuals. The looping vascular pattern may represent a compensatory response to reduced ocular blood flow, warranting further investigation.

MODERN IRIIDOLOGY CHART

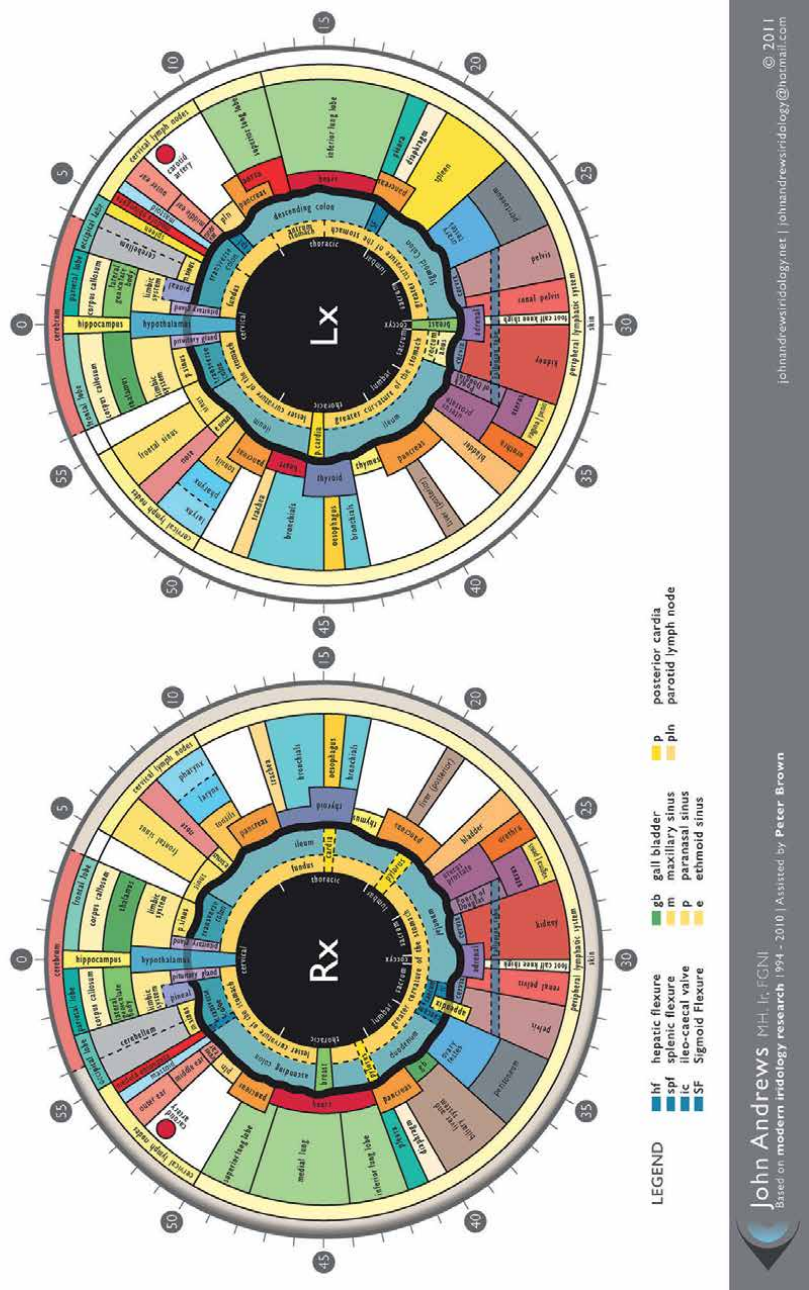


Figure 5.
Courtesy of Andrews, John. *Modern Iridology Chart*, UK, 2011.

9.3 Pigmented constricted collarette

The collarette, a remnant of the embryonic pupillary membrane, serves as a key indicator of autonomic nervous system function. A very tight (constricted) collarette is associated with: Sympathetic dominance indicating the body is in a prolonged state of “fight or flight.” Nervous system tension especially in the digestive tract (e.g. irritable bowel, spastic colon). Control-oriented personality traits, these individuals may internalise stress or have difficulty relaxing. Possible tendency toward constipation, cold extremities, or tension headaches. Orange pigmentation in the collarette is traditionally associated with pancreatic stress or dysfunction. According to John Andrews [38], a constricted endocrine-type collarette has been linked to hyperadrenal syndromes, which may contribute to elevated IOP which is a major risk factor for glaucoma.

9.4 Sectoral shading

All participants exhibited distinct cardiovascular markers within the iris, suggesting a possible link between irregularities in blood flow and glaucoma. A consistent feature among individuals with glaucoma was sectoral shading—a region of lower fibre density with sparse, thinning fibres, or containing rarefactions or lacunae (gaps or holes) appearing as a darker zone. This pattern was found in the left iris at 3 o'clock, indicating a loss of fibre integrity, exposing the underlying dark epithelium, particularly in the heart and lung zones of the iris according to iridology charts. See current Iridology Chart by John Andrews (**Figure 5**), suggesting compromised circulation. A study has identified differences in melanin content in the irises of individuals with glaucoma, potentially influencing these sectoral variations [39]. Unlike iridoschisis, which involves detachment and fragmentation of iris fibres, this shading did not exhibit structural fibre separation. Instead, it may reflect venous circulatory insufficiency, weakened cardiovascular walls, and inadequate nutrient and nerve supply to these areas. If this pattern correlates with systemic vascular insufficiency, it could support the hypothesis that circulatory dysfunction plays a role in glaucoma progression.

9.5 Green hue inside the pupil

A distinct green hue was observed inside the pupil when photographing some glaucomatous eyes. While normally, the pupil appears black due to light absorption by the retina, elevated intraocular pressure (IOP) may alter how light interacts with intraocular structures. This phenomenon could be due to changes in the refractive properties of the lens (those who had recent cataract operations did not display a green hue), alterations in corneal transparency, or differences in retinal reflectivity in those with glaucoma due to structural changes. Additionally, this greenish reflection might indicate increased light scatter from the optic nerve head, where glaucomatous damage is known to occur. Further investigation using optical coherence tomography (OCT) and fundus imaging could help determine whether this hue correlates with optic nerve alterations, retinal nerve fibre layer thinning, or other intraocular changes associated with glaucoma.

10. Iris morphology comparison

Participants of the same mean age were compared. **Figure 6**, shows a female participant with primary open-angle glaucoma (POAG), where a distinct shadow ring, iris



Figure 6.
Characteristic features of glaucoma: bulging sideways, shadow ring, endocrine orange constricted collarette.

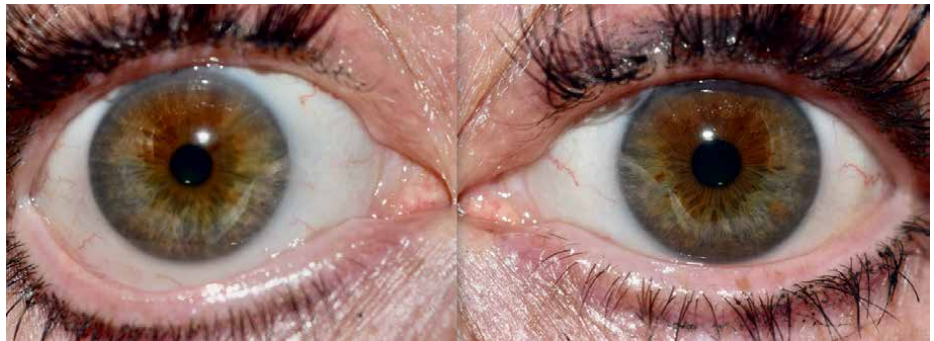


Figure 7.
Circular shaped iris without the open fibres at 3 o'clock on the left iris, no shadow ring.

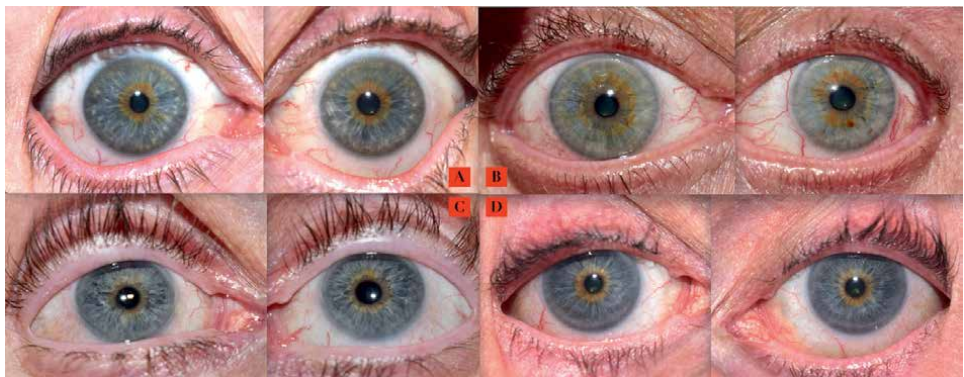


Figure 8.
A. Female 66 years old recently diagnosed with nasal step defect, IOP within range, started eye drops treatment. B. Male 69, diagnosed with POAG 20 years ago, IOP under control, family history of glaucoma. C. Female 79, with POAG for the last 15 years, still driving, family history of glaucoma. D. Male 65, diagnosed with POAG 12 years ago, severely sight impaired, eye drops treatment 3 times a day and family history of glaucoma.



Figure 9.
Control group age 60 to 79.

shape irregularities and all previously mentioned features were observed. In contrast (**Figure 7**) depicts a female without glaucoma, showing a circular uniformly black pupil, a circular iris shape, no sectoral shading, and no shadow ring around the pupil.

10.1 Comprehensive description

Between 2019 and 2025, iris image analysis was conducted on 192 participants, revealing that only 6.77% had a confirmed diagnosis of primary open-angle glaucoma (POAG). Between March and June 2025, thirteen individuals diagnosed with POAG were invited for further assessment. Notably, 100% of these participants exhibited all the key iris features identified in this study (see **Figure 8**).

When POAG participants were asked during brief consultations about potential triggers or how they were feeling around the time of their glaucoma diagnosis, many reported experiencing heightened stress, urgency, feelings of being overwhelmed, and in some cases, a sense of personal obsolescence. Remarkably, the feature known as shadow ring—interpreted by behavioural iridologist [40] Andrew Mason as a pronounced form of the Accomplishment ring associated with mental tension, fear of failure, and deep subconscious pressure. It tends to manifest through heightened sensitivity, compulsive behaviours, and persistent worry, often linked to concerns about not completing tasks or living up to expectations. Such emotional states may lead to feelings of unease or powerlessness, as though life is moving forward uncontrollably. Despite this emotional burden, many participants demonstrated a strong sense of intuition and an ability to adapt and recover—suggesting that psychological stress and individual coping mechanisms could influence how glaucoma is perceived, managed, and potentially even triggered.

Interestingly, all participants with POAG who displayed the full set of iris features also appeared to share a strikingly similar iris presentation and a similar light blue eye colour, suggesting a possible genetic or phenotypic correlation worthy of further investigation.

An age-matched control group without glaucoma, was also evaluated (see **Figure 9**). Within this group, 50% showed minor irregularities in iris shape, though not all the characteristic features appeared simultaneously. Half showed signs of impaired blood flow known as corneal arcus on the superior part of the cornea. Half exhibited a green pupil in at least one eye, while 20% displayed sectoral shading in the lung and heart zones. None of the control group participants presented with a shadow ring, orange pigmented constricted collarette. Most reported no known nutritional deficiencies, although some disclosed a history of liver-related issues.

11. Conclusions

This study investigates the potential of high-resolution iris images to detect subtle ocular biomarkers associated with primary open-angle glaucoma (POAG), particularly in the context of micronutrient deficiencies and optic nerve health. The shadow ring emerged as the most consistently observed iris feature among participants with POAG, followed by lateral iris bulging. Additional features included a pigmented, constricted collarette, fibre rarefactions at the key location, vascular markings, and in some cases, a greenish hue within the pupil.

Remarkably, these characteristics were absent in the control group, with the exception of minor iris shape irregularities, which lacked the full pattern observed in POAG cases. Moreover, all individuals exhibiting the full spectrum of these features

also shared a similar shade of light blue iris, suggesting a possible phenotypic or genetic association.

These findings suggest that by correlating iris patterns with clinical findings, may highlight its potential application in complementing traditional diagnostic methods. Future studies integrating high-resolution imaging, biochemical analysis, and clinical trials will be essential to validate these observations and refine the role of iris analysis in understanding glaucoma pathophysiology.

Furthermore, growing research supports the role of zinc homeostasis in maintaining retinal and optic nerve function, with both excess and deficiency potentially exacerbating neurodegenerative changes. Given the prevalence of dietary zinc insufficiency in many populations, investigating its link to glaucoma could lead to new strategies for early detection, risk assessment, and nutritional intervention.

Finally, this research highlights the potential of iris imaging as a supplementary tool in glaucoma screening and underscores the need for further interdisciplinary studies combining ophthalmology, nutrition, and iridology.

Acknowledgements

The author expresses her gratitude to The Lomond Clinic in Helensburgh for the lovely approach to the meaningful research conducted in the premises: 55-56 West Clyde Street, Helensburgh G84 8AX, Scotland, U.K.

Conflict of interest

The author declares no conflict of interest.

Thanks

The author would like to thank John Andrews, The Guild of Naturopathic Iridologists International Vice-President www.gni-international.org for his infinite knowledge, encouragement and support with this study.

The author would also like to thank Andrew Mason, Behavioural Iridologist www.behaviouraliridology.com and friend, for his invaluable time and thoughtful conversations, which greatly enriched the behavioural interpretation of iris patterns in glaucoma participants.

Author details

Carolyn Aitken
The Lomond Clinic, Helensburgh, Scotland, UK

*Address all correspondence to: carolyn@iridologyscotland.com

IntechOpen

© 2025 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. 

References

- [1] Glaucoma Research Foundation. Zinc in the retina may indicate a new way to protect and regenerate the optic nerve in glaucoma patients. 2024. Available from: <https://glaucoma.org/articles/zinc-in-the-retina-may-indicate-a-new-way-to-protect-and-regenerate-the-optic-nerve-in-glaucoma-patients>
- [2] Glaucoma Associates. What Is Glaucoma? 2024. Available from: <https://www.glaucomaassociates.com/glaucoma/what-is-glaucoma/>
- [3] Glaucoma UK. What Is Glaucoma? 2024. Available from: <https://glaucoma.uk/about-glaucoma/what-is-glaucoma/>
- [4] Kerr NM. Neuroprotection: The future of glaucoma treatment. *The Ophthalmologist*. 2024. Available from: <https://theophthalmologist.com/issues/2024/articles/jul/neuroprotection-the-future-of-glaucoma-treatment>
- [5] Glaucoma UK. Who Is Most at Risk of Glaucoma? 2024. Available from: <https://glaucoma.uk/who-is-most-at-risk-of-glaucoma/>
- [6] Xiao Y, Prokup J, Peterson JM, et al. Zinc homeostasis and neurodegenerative diseases: Implications for glaucomatous retinal ganglion cell death. *International Journal of Molecular Sciences*. 2017;**18**(5):1081. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC5408298/>
- [7] Nutravision. The game-changing benefits of vitamin B3 (nicotinamide) for eye health. 2024. Available from: <https://nutravision.com.au/blogs/journal/the-game-changing-benefits-of-vitamin-b3-nicotinamide-for-eye-health>
- [8] Chavala SH, Kosmorsky GS, Lee MK, Lee MS. Optic neuropathy in vitamin B₁₂ deficiency. *European Journal of Internal Medicine*. 2005;**16**(6):447-448. DOI: 10.1016/j.ejim.2005.01.021. Available from: <https://pubmed.ncbi.nlm.nih.gov/33204422/>
- [9] EyeWiki. Nutrients for eye health and disease management. 2024. Available from: https://eyewiki.org/Nutrients_for_Eye_Health_and_Disease_Management
- [10] Demmig-Adams B, Adams WW III. The role of micronutrients in plant and human biology: Lessons from photosynthesis. *Journal of Agricultural and Food Chemistry*. 2018;**66**(10):2535-2544. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC5972137/>
- [11] Lee J, Kim JH. Role of nicotinamide adenine dinucleotide in glaucoma. *Frontiers in Neuroscience*. 2018;**12**:275. Available from: <https://pubmed.ncbi.nlm.nih.gov/29896314/>
- [12] Glaucoma Research Foundation. The role of stress and anxiety in glaucoma: Understanding and management. 2024. Available from: <https://glaucoma.org/articles/the-role-of-stress-and-anxiety-in-glaucoma-understanding-and-management>
- [13] Mayo Clinic. Optic Neuritis: Symptoms and Causes. 2024. Available from: <https://www.mayoclinic.org/diseases-conditions/optic-neuritis/symptoms-causes/syc-20354953>
- [14] Osborne NN et al. Role of oxidative stress in retinal diseases and glaucoma. *Eye (London)*. 2009;**23**(1):1-12. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC2723676/>
- [15] Ophthalmology Times Europe. Research set to change how we think

about glaucoma in the future. 2016. Available from: <https://europeophthalmologytimes.com/view/research-set-change-how-we-think-about-glaucoma-future>

[16] The College of Optometrists. Optical coherence tomography (OCT) . 2024. Available from: <https://www.college-optometrists.org/bycategory/oct>

[17] Chandler M. Restoring the anatomy with canaloplasty. Cataract & Refractive Surgery Today. 2024. Available from: <https://crstoday.com/articles/restoring-the-anatomy-with-canaloplasty/restoring-the-anatomy-with-canaloplasty#:~:text=Canaloplasty,describes a procedure in,trabecular meshwork and collector channels>

[18] Sharon A, Subin PS, Arun G, Jayaraj MK, Antony A. Surface-modified TiO₂ nanorods using oxygen plasma for optical synaptic performance and neuromorphic computing applications. Surfaces Interfaces. 2025;**64**:106357. DOI: 10.1016/j.surfin.2025.106357

[19] Biousse V, Newman NJ. Retinal and optic nerve ischemia. Continuum (Minneapolis, Minn). Neuro-Ophthalmology. Aug 2014;**20**(4):838-856

[20] COA Vision. Optic Nerve Head Blood Supply and Ischemia. 2024. Available from: <https://www.coavision.org/i4a/pages/index.cfm?pageID=4323>

[21] Kidambi S, Wang J, Peters K, et al. Role of zinc in neurodegeneration. Proceedings of the National Academy of Sciences of the United States of America. 2016;**113**(47):13509-13514. DOI: 10.1073/pnas.1616811114

[22] Eye Surgery Guide. Zinc dosage for macular degeneration: What you need to know. 2024. Available from: <https://eyesurgeryguide.org/>

zinc-dosage-for-macular-degeneration-what-you-need-to-know/

[23] KAUST study reveals unexpected role for zinc in prevention of Parkinson's disease. News Medical. 2022. Available from: <https://www.news-medical.net/news/20221017/KAUST-study-reveals-unexpected-role-for-zinc-in-the-prevention-of-Parkinsons-disease.aspx#:~:text=It%20turns%20out%20that%20zinc,Al-Harthi,%20a%20Ph>

[24] Nowak G, Ratajczak MZ. Zinc and neurodegenerative diseases: Experimental and clinical perspectives. Pharmacological Reports. 2007;**59**(5):598-610. Available from: <https://pubmed.ncbi.nlm.nih.gov/18046856/>

[25] Lowe NM, Fekete K, Decsi T. Indicators of zinc status at the population level: A review of the evidence. The British Journal of Nutrition. 2009;**101**(5):759-773. Available from: <https://www.cambridge.org/core/journals/british-journal-of-nutrition/article/indicators-of-zinc-status-at-the-population-level-a-review-of-the-evidence/2646F6C5CD169BD7D26851F23B01ADDE>

[26] Food Standards Scotland. Vitamins and minerals: Zinc [Internet]. 2024 [cited 2025 Jun 19]. Available from: <https://www.foodstandards.gov.scot/consumers/healthy-eating/nutrition/vitamins-minerals>

[27] Health.com. Foods high in zinc. 2024. Available from: <https://www.health.com/foods-high-in-zinc-7546254>

[28] King JC, Shames DM, Woodhouse LR. Zinc homeostasis in humans. Journal of Nutrition. May 2000;**130**(5S Suppl):1360S-1366S

[29] Harvard TH. Chan School of Public Health. Niacin (Vitamin B3). The Nutrition Source; 2024 [cited

2025 Jun 19]. Available from: <https://nutritionsource.hsph.harvard.edu/niacin-vitamin-b3/>

[30] Wikipedia Contributors. Nicotinamide. Wikipedia. 2025. Available from: <https://en.wikipedia.org/wiki/Nicotinamide>

[31] WebMD. Niacinamide. 2024. Available from: <https://www.webmd.com/vitamins/ai/ingredientmono-1534/niacinamide>

[32] Nature. New research on glaucoma. 2025. Available from: <https://www.nature.com/articles/s41591-024-03068-6>

[33] Liu HY, Gale JR, Reynolds IJ, Weiss JH, Aizenman E. The multifaceted roles of zinc in neuronal mitochondrial dysfunction. *Biomedicine*. 2021;**9**(5):489. DOI: 10.3390/biomedicines9050489

[34] Lo Rito D, Andrews J. Embryology & Iridology: New Topographical Research. Abano Terme (Italy): Seminar Materials; 2004. Published as e-book, c. 2009. Available from: <https://www.iridologyclinic.co.uk>

[35] Kokkinou D, Kasper HU, Schwarz T, Schraermeyer U. Zinc uptake and storage: The role of fundus pigmentation. *Graefe's Archive for Clinical and Experimental Ophthalmology*. 2005;**243**(10):1050-1055. DOI: 10.1007/s00417-005-1197-7. Available from: <https://pubmed.ncbi.nlm.nih.gov/15357838/>

[36] Shulpina NB, Aliyeva ZA. Fundamentals of Iridodiagnosics. Baku: Azerneshr; 1982. Also see: Shulpina NB. Propaedeutics of Iridodiagnosics: Manual for Doctors. Moscow; 1990

[37] ScienceDirect. Oculocardiac reflex. 2024. Available from: <https://www.sciencedirect.com/>

topics/medicine-and-dentistry/oculocardiac-reflex

[38] Andrews J. Endocrinology & Iridology. 1st ed. ISBN 1-903358-069

[39] Shakhmardanov OG et al. Estimation of melanin content in iris of human eye: Prognosis for glaucoma diagnostics. *Journal of Ophthalmology Research*. 2013;**15**(4):240-247. Available from: https://www.researchgate.net/publication/241586606_Estimation_of_melanin_content_in_iris_of_human_eye_Prognosis_for_glaucoma_diagnostics

[40] Mason A. Behavioural Iridology. London: Aeon Books; 2022. ISBN: 978-1-80152-151-2. Available from: <https://health.aeonbooks.co.uk/product/behavioural-iridology/95292>

Living with Glaucoma: Challenges in Daily Activities

Fatma Merve Bektaş

Abstract

Glaucoma is the leading cause of irreversible blindness. Although it appears to be an asymptomatic disease in its early stages, glaucoma patients have reported declines in vision-dependent mobility, reading ability, and driving skills, even during these initial phases. These patients have also reported a higher risk of motor vehicle collisions and falls, as well as suffering from mental health disorders and experiencing social isolation. The severity, location, and rate of progression of glaucomatous damage, along with visual acuity (VA) loss, reduced contrast sensitivity (CS), and adaptation problems to sudden light changes, all influence the impact on quality of life (QoL). Furthermore, high-level visual deficits such as eye-hand coordination impairment, face recognition issues, and visual search difficulties also affect daily activities. A comprehensive understanding of the impact of visual function loss on quality of life is essential for guiding patient-centered therapeutic decisions. Furthermore, this knowledge will help ophthalmologists communicate more effectively with patients, which could improve compliance and outcomes.

Keywords: daily activities, glaucoma, quality of life, visual field defect, visual functions

1. Introduction

Glaucoma is an optic neuropathy characterized by the progressive degeneration of retinal ganglion cells. Due to its potential to cause blindness, glaucoma poses a significant health challenge globally. It is expected that by 2040, 111.8 million people will be affected by glaucoma worldwide [1].

While glaucoma may appear asymptomatic in its early stages, patients often report challenges unrelated to peripheral visual field (VF) loss. A large percentage of glaucoma patients experience difficulties with their visual functioning under extreme luminance (low, high, or changing) conditions, especially in the dark [2]. Contrast sensitivity (CS) loss, which begins even in the early stages of glaucoma and worsens over the course of the disease, also creates challenges for patients. Visual acuity (VA) loss typically occurs later in the disease's progression, along with a gradual decline in VF sensitivity, primarily assessed by the mean deviation (MD), from early to advanced stages of the disease. Each can influence daily visual function and quality of life (QoL) [3].

In ophthalmology, good visual function, as determined by examination, does not adequately reflect the effects of diseases on daily life. The visual tests may not reflect

real-world visual functions [3]. It is known that individuals with similar levels of disease severity report very different QoL experiences due to changing environmental factors and adaptive behaviors [3, 4]. The ability to perform daily tasks, mobility function, emotional well-being, and participation in social activities should be investigated [3].

The various effects of impaired vision often raise the question, “How can we best assess the impact of glaucoma on a patient’s life?” Assessing glaucoma-related disability involves various methods, each with its strengths and limitations. QoL questionnaires enable an understanding of the impact of visual functions on QoL at different stages of ophthalmic disease [5]. They are reports obtained directly from the patient, without interference from the clinician or anyone else regarding the patient’s feedback about their health status. In other words, these are validated questions that evaluate the person’s views on health status, disability, and QoL. However, the implementation of questionnaires has certain limitations. Psychological factors, personality, and recall bias may influence patients’ responses [3].

Even if QoL questionnaires can serve as valuable tools for assessing patients’ functional ability, more objective methods are necessary [4]. Another method for assessing visual impairment caused by glaucoma involves evaluating performance on daily tasks or surrogate tasks relevant to independent living [6, 7]. Performance tests provide objective data that is generally more easily understood than questionnaire results, supporting subjective information obtained from QoL scales. Moreover, these methods can also indicate specific underlying causes of functional impairment [7]. Performance-based methods identify early functional impairments before patients are aware of them. These assessments also raise awareness among patients, their families, clinicians, and health policymakers about the potential impact of glaucoma on daily visual functioning [6].

Understanding the impact of ophthalmic diseases on an individual’s daily functional capacity continues to pose challenges for the clinician. Recently, there has been growing recognition of the importance of improving understanding of the impact of glaucoma on QoL and the ability to perform vision-related tasks of daily living, such as driving, shopping for groceries, and reading [1].

2. Challenges related to the decline of visual functions

2.1 Reading

Written communication remains a prominent method for sharing messages globally. The prevalent use of smartphones underscores the importance of assessing written content, even in communities with low literacy levels [1]. Reading is crucial for many daily activities and for achieving various societal goals [8]. Consequently, difficulties in reading can lead to significant impairments [1].

Patients suffering from glaucoma may face reading difficulties and limitations owing to several factors. Glaucoma is commonly associated with peripheral vision loss; however, studies show that central vision, which is vital for reading, can also be impaired in those with glaucoma [9]. Moreover, glaucoma can severely disrupt reading skills even in patients with preserved central VA [1, 10]. While the relationship between VA and reading performance is well-established, the extent to which VF loss affects reading remains unclear [11]. As expected, individuals with pronounced bilateral VF defects show slower reading speeds. Regardless of VA, reading speed

aloud diminishes as VF loss becomes more significant [9]. The inferior left section of the binocular VF may notably influence reading speed in glaucoma patients. This region may assist in identifying new lines of text during reading [11]. Reduced contrast sensitivity (CS) may also affect reading outcomes in glaucoma, even when VA is largely unaffected. Compared to individuals with normal vision, patients with glaucoma struggle more with decreased letter contrast [8].

Reading necessitates complex coordination of eye movements and visual processing in the brain. Evaluating reading abilities based solely on VA or VF examinations is insufficient [10]. During reading, attention is split between the current word and its neighboring words, which slows reading speed because of limited attentional resources [1]. A person's capacity to divide attention plays a critical role in linking glaucoma-related vision loss and reading speeds [12]. Research indicates a connection between increased VF loss and difficulties in finding the next line of text. Patients with VF impairments show fewer saccades during various tasks, implying that abnormal eye movements may contribute to reading challenges in glaucoma. Thus, glaucoma complicates reading, making it more arduous and fatiguing. People with glaucoma often avoid reading and find it increasingly difficult to engage in tasks that require extended reading [8].

2.2 Driving

Driving plays a crucial role in helping older adults maintain their independence, especially those with glaucoma [13]. Individuals suffering from glaucoma often struggle with nighttime driving and navigating in rain, fog, and unfamiliar areas [14]. Compared to those without the condition, glaucoma patients face significantly more challenges with observation, lane maintenance, and approach planning, leading to more frequent driving errors, particularly at traffic-controlled or give-way intersections [13].

Visual field defects can lead to inconsistencies in driving performance and reduced hazard perception [15]. The relationship between driving difficulties and the severity of glaucoma or specific VF defect patterns remains unclear [13]. Although patients with mild to moderate VF loss experience relevant functional issues, their driving performance is notably impaired when compared to age-matched peers. Research indicates a clear link between unsafe driving behaviors and glaucoma, especially among individuals with advanced stages of the disease [16]. Hazardous situations are often first detected in the superior sections of the VF through the vehicle's windshield, whereas the inferior VF focuses on the vehicle's interior (steering wheel, speedometer, and controls). A decline in superior integrated visual field (IVF) loss severely affects the ability to identify driving hazards more than corresponding inferior field loss. Consequently, it is not surprising that a deterioration in superior IVF correlates with driving difficulties and avoidance [14]. VF impairments, especially in the left upper and lower fields (with the left field posing the highest risk), are closely linked to an increased chance of motor vehicle accidents [16].

Driving self-regulation is the process by which drivers adjust their habits, either by reducing their driving frequency or actively avoiding challenging driving scenarios. Hence, glaucoma patients who steer clear of high-risk situations tend to drive less to mitigate the likelihood of accidents arising from their VF loss. Advanced age contributes to a greater preference for avoiding lane changes as well as nighttime, rainy, foggy, and freeway driving. Older adults face a higher risk of traffic incidents due to factors such as sensory and motor function deficiencies. This increased difficulty level from VF loss suggests that not only those with glaucoma but also older individuals

generally tend to restrict their driving to safer circumstances or may cease driving altogether. Therefore, older drivers are less inclined to engage in high-risk driving than younger drivers [14].

Recent studies utilizing on-road driving evaluations and simulation technology have provided more insights [16]. Not all drivers with glaucomatous field loss demonstrate driving errors, indicating that some can adapt to their impairment [13]. Certain drivers showed differences in visual scanning and eye movement behavior, such as larger saccades and increased head and gaze movements toward their field defect. Conversely, other drivers might adopt a slower, more cautious driving approach to mitigate their impairment [13, 16].

The multifaceted nature of driving, influenced by both vision and non-vision factors, underscores the necessity for thorough and personalized evaluations for drivers with glaucoma. Self-reported difficulties in driving may manifest even in the early stages of glaucoma, and slowing disease progression could potentially extend the period that glaucoma patients are able to drive [16].

2.3 Physical activities and mobility

Physical activity plays a crucial role in health and well-being. Research indicates that being physically active has a positive impact on the quality of life (QoL) for patients with chronic illnesses and advanced cancer [17].

Peripheral vision is essential for daily activities, especially when navigating uneven ground or walking up and down stairs, as it helps assess the distance between the foot and the step. Additionally, when considering outdoor mobility, it is important to recognize the influence of other factors, such as adjusting to glare in bright conditions or adapting to darkness at night [18]. Consequently, patients with glaucoma report challenges when walking. Difficulties in walking can lead to a fear of falling (FoF), prompting patients to reduce their physical activity, which can negatively affect their QoL and potentially result in increased morbidity and mortality [17].

Visual impairment caused by glaucoma significantly impacts patients' mental health and social functioning, which further restricts their physical activity [17]. The average daily step count is lower among patients with glaucoma compared to those without the condition. In the glaucoma group, daily step counts show a correlation with worsened VA loss, social functioning, and mental health, aside from VF deficits. Additionally, increasing deterioration in binocular VF mean deviation and advancing age serve as independent predictors of poorer performance on the Cambridge Glaucoma Visual Function Test [3], indicating that patients with advanced glaucoma tend to be less active [17].

2.4 Falls and balance

Patients with glaucoma face a greater risk of falling and suffering injuries from falls than those without the condition [19]. Factors that elevate the risk of future falls in glaucoma patients include a history of falls or fractures, FoF, best-corrected vision in the poorer eye, older age, and the presence of diabetes mellitus or systemic hypertension [20, 21]. While substantial VF loss is acknowledged as a risk factor for falls, the severity of glaucoma at the point this risk arises remains unclear. Even individuals with mild glaucoma may face an increased risk of falls in comparison to those who do not have ocular diseases. Moreover, the likelihood of falling increases with the severity of glaucoma [19]. The adjusted risk of experiencing a fall or fracture is 1.34 times

greater in patients with severe open-angle glaucoma at baseline than in those with ocular hypertension [21].

Falls among older adults present a major public health concern, impacting morbidity and mortality and generating both individual and societal costs [19]. Additionally, falls or fractures add to the existing economic burden of managing diseases [21]. Besides implications for morbidity and mortality, falls also have psychological consequences. Factors that contribute to FoF in glaucoma patients include older age, female gender, damage to the inferior peripheral VF, previous falls within the past year, severe visual impairment, a high risk of falling, dependence on assistance with daily living activities, and an abnormal psychological state [22, 23]. Yet, the frequency of past falls and serious falls did not correlate with FoF [23, 24]. Other possible influences on FoF may include psychological factors (such as the fall experiences of friends or family) [24].

A fear of falling typically leads to reduced confidence in daily tasks, prompting activity restrictions [24]. There is a connection between worsening glaucoma severity and FoF, along with the avoidance of activities deemed high-risk for falls. This relationship may not be entirely linear, as FoF levels were similar in the control and mild glaucoma groups, showing a rise only when glaucoma progressed to a moderate stage. A notable rise in the FoF was seen among individuals with moderate to advanced glaucoma. Injurious falls, in contrast to non-injurious ones, were linked to decreases in physical activity [19].

Patients with advanced-stage glaucoma exhibit the highest incidence of falls, FoF, and avoidance of activities that pose a risk. Therefore, an individual's FoF and their tendency to avoid risky activities greatly impact their overall well-being [19]. It is crucial for clinicians to identify vulnerable patients so they can develop and implement educational and intervention programs aimed at reducing the risk of falls, preventing injuries from falls, and minimizing the related morbidity and mortality. Additionally, these programs should emphasize enhancing the quality of life for glaucoma patients and improving rehabilitation efforts to mitigate the negative effects of falls, especially concerning the safe return to and increase in physical activities [19, 24].

2.5 Social functions

Glaucoma, as a leading cause of irreversible blindness, poses substantial difficulties that greatly affect overall well-being. Engaging actively in various social roles is crucial for maintaining and restoring health [25].

In the case of glaucoma, even if individuals have good central vision, those with severe VF loss face challenges participating in social activities such as community, religious, and cultural events, as well as sports, travel, family interactions, and maintaining relationships [25, 26]. These challenges are partly attributed to findings that people with glaucoma tend to walk more slowly, are more prone to colliding with objects, experience heightened fear of falling, have a higher incidence of falls, and face disruptions in gaze-foot coordination [26]. Beyond the challenges posed by diminished visual function, treatment requirements (due to medication regimens) limit long-distance travel and increase home dependency, making individuals more homebound and less likely to travel away from their residences [27]. As a result, greater severity of glaucoma correlates with lower QoL, increased dissatisfaction with vision, and more significant disability related to the disease in the community [28].

The roles affected by glaucoma are not only challenging but also crucial, contributing to reduced satisfaction [25]. While glaucoma significantly diminishes

participation in various social activities [29]. Loneliness and social isolation are associated with an increased risk of developing glaucoma. Therefore, it is essential to implement positive mental health and social network interventions for individuals at high risk for glaucoma [26]. Furthermore, enhancing social engagement serves as a changeable element. It is important to promote the creation of policies and programs that encourage increased social involvement among those with glaucoma, particularly seniors, to ultimately prevent social isolation and support successful aging despite vision disorders [29]. Hence, acknowledging the significance of participation in social activities is vital for patient-centered care and should be a key aspect of vision rehabilitation services [25].

2.6 Mental health

Glaucoma is a chronic condition that necessitates ongoing management; its effects reach beyond visual impairment, significantly impacting mental health and QoL [30]. The literature review presents strong evidence of a significant association between glaucoma and heightened levels of anxiety and depression [30–33]. Glaucoma acts as a psychological disruptor, independent of demographic factors. The psychological burden of glaucoma is shaped by several elements [30, 31]. Gradual vision loss directly affects physical capabilities in carrying out daily activities [30]. The fear of potential blindness, the necessity for lifelong treatment, financial constraints, possible neurobiological connections, and the chronic character of the disease may contribute to heightened anxiety and depression [30, 31, 34]. Glaucoma can also provoke anxiety and depression due to issues like social isolation, loss of relationships, guilt, and uncertainties regarding the future [31].

Factors such as the length of treatment, coexisting visual impairment, stress, and biological, psychological, and sociodemographic factors such as female gender, socioeconomic status, and, in some cases, older age were recognized as important influences on the prevalence and intensity of psychiatric issues [31, 32, 35]. Advanced age is associated with depression, while younger age is related to anxiety [34, 36]. The effect of glaucoma severity on emotional well-being is controversial. As the disease progresses, patients may experience greater challenges in daily tasks, further worsening anxiety and depression, which can lower life satisfaction. Conversely, anxiety during early stages arises from the diagnosis itself, uncertain prognosis, and the need for lifelong treatment, rather than merely the level of VF loss [30]. Additionally, anxiety is a risk factor for developing glaucoma, not just a result of it [34].

Anxiety and depression can lead to reluctance in adhering to medications and attending follow-up appointments, undermining essential efforts to slow disease progression. Undoubtedly, disease progression reduces the overall QoL for patients. Those facing mental health difficulties often resort to maladaptive coping strategies [31].

Acute stress might lead to increased intraocular pressure (IOP) through activation of the sympathetic nervous system. This temporary increase in IOP may be associated with potential VF defects. Chronic stress, indicated by markers like allostatic load, long-term stresses from comorbidities, and stress related to personality traits, seems to affect the risk of developing glaucoma [33]. Moreover, sleep disturbances are significantly more prevalent among glaucoma patients, showing a notable relationship between the severity of glaucoma and the degree of sleep disruptions [32].

Numerous antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs), are generally not recommended for individuals with glaucoma, especially those susceptible to angle-closure glaucoma, as these drugs have the potential to

elevate IOP. Addressing sleep issues through non-pharmacological methods, such as sleep hygiene practices, mindfulness, biomedicines, cognitive-behavioral therapy, lifestyle modifications, and newer medications with lower IOP risk, could be vital in enhancing both physical and mental health outcomes for glaucoma patients. Implementing strategies can help reduce the risks associated with SSRI use while ensuring effective depression management [32].

Patients who lack adequate information regarding their medical condition often report elevated levels of anxiety and depression. This observation underscores the critical significance of patient education in alleviating psychological distress. Education that empowers patients to manage their condition better may have a positive effect on mental health and QoL. Ophthalmologists can significantly help in identifying at-risk individuals by incorporating brief mental health evaluations during routine glaucoma check-ups to identify anxiety and depression symptoms [30]. It is advised that mental health assessments be conducted for advanced-stage glaucoma patients, younger individuals diagnosed with glaucoma, those experiencing sleep issues, and during treatment adjustments or disease progression [32, 34].

3. Additional complex visual deficits associated with glaucoma

3.1 Eye-hand coordination impairment

Eye-hand coordination is essential for many everyday tasks, including reaching for and grasping objects, preparing meals, writing, using a phone, eating, and working. Effective eye-hand coordination relies on several sensorimotor systems, such as the visual system, central processing, and effector components, working together harmoniously [37]. Visual information about the object's spatial location is critical to achieving quick and accurate reaching [4]. During goal-directed hand movements toward a target, both monocular (including accommodation, CS, and perspective) and binocular (like retinal disparity and convergence) information come into play [37].

Reaching and grasping involve planning and initiating movement, as well as using the fingertips for reaching and grasping. Regarding reach-to-grasp behavior, individuals diagnosed with glaucoma exhibit delays in planning and initiating movements, leading to slower and more cautious reaches toward objects on a tabletop, especially at greater distances. Moreover, they display negligible differences in grasp-posture programming or grip execution when compared to normal control subjects. Under both monocular and binocular viewing conditions, the patients demonstrated prolonged movement times when compared to the control group, suggesting a deficiency in initial movement planning. Patients with reaching and grasping impairments may experience significant asymmetries in VF, causing extended neural processing times [4].

Deficits in eye-hand coordination are also noted in patients with glaucoma compared to age-matched sighted controls. In tasks requiring precise and accurate movements, patients suffering from glaucoma demonstrated slower performance on the aiming test and exhibited a greater incidence of longer-duration errors during the linear tracking test compared to normal subjects. Scores on tremor and tapping tests indicate a decrease in steadiness (the ability to maintain a specific eye-arm/hand position with minimal positional change) and maximum frequency of movements [37].

Visual field defects do not entirely account for these findings. A single significant correlation was identified between VF defects and eye-hand coordination movements; specifically, MD scores in the worse eye showed a significant relationship with the

duration of error in the linear tracking task. Research based on self-reported functional capabilities for daily tasks reveals a weak correlation between task difficulty and the severity of VF defects in glaucoma patients. Eye-hand coordination scores were negatively affected by the presence of asymmetrical VF defects but were not influenced by binocular deficits. Additionally, eye-hand coordination declines with aging and reduced VA in glaucoma patients. Glaucoma, a group of progressive optic neuropathies, can result in impaired neural conductivity, leading to longer neural processing times [37].

3.2 Face recognition

Facial recognition is fundamental to our social behaviors, and the ability to identify faces is integral to numerous social judgments and relationships [6]. It is plausible that diminished facial recognition skills adversely impact patients' QoL [38].

Central VF loss appears to be significant in terms of the impairment of facial recognition [6]. Nevertheless, patients with glaucoma exhibit a compromised ability to recognize faces, despite possessing adequate central VA [38]. The advanced visual impairment in glaucomatous patients results in diminished facial recognition capabilities compared to patients with milder defects and control groups [6]. Patients exhibiting central deficits demonstrate deficiencies in both the detection and categorization of low-contrast scenes and facial stimuli. In contrast, patients without such deficits exhibit performance that is comparable to that of age-matched controls concerning the detection and categorization of face stimuli. Regarding scene recognition, the performance of both central deficit and noncentral deficit patients did not significantly differ from that of controls in detection tasks; however, they exhibited a marked deficiency in categorization tasks [39]. CS is pivotal in successful facial recognition and various everyday tasks. A reduction in CS contributes to the facial recognition difficulties experienced by some patients [6]. Facial recognition may be hindered by diminished CS and paracentral VF loss, both of which stem from macular damage captured by the 10–2 VF test [38]. The significance of vigilance regarding VF points in proximity to fixation and CS in clinical practice is emphasized, in conjunction with the customary 24–2 VF test [6].

Indeed, a high-level visual deficit is not solely determined by basic retinal sensitivity in the central VF of patients. Loss of peripheral vision can subtly impact high-level visual function in central sight. Although it has lower resolution, peripheral vision in individuals with normal eyesight is quite capable, allowing them to recognize scenes and objects even at significant eccentricities (over 70 degrees). Additionally, peripheral information can play a role in the recognition process occurring in central vision. The progressive degeneration of retinal ganglion cells in glaucoma may induce trans-synaptic degeneration in the lateral geniculate nucleus and visual cortex. This can result in both structural and functional changes in higher-level cerebral areas, thereby affecting overall visual function [39].

3.3 Visual search

Numerous daily living activities depend significantly on effective visual search processes. This may include tasks such as locating an object in a visually cluttered environment, such as finding a specific book on a bookshelf, an item on a supermarket shelf, or a place name on a map. Furthermore, individuals engage in activities such as finding the next word in a body of text, navigating an unfamiliar environment, and identifying traffic hazards while driving [40, 41].

Visual field defects can adversely affect the efficacy of visual search. Peripheral vision plays a pivotal role in the behavior of saccadic eye movements [40]. Patients exhibiting glaucomatous VF defects in both eyes demonstrate distinct saccadic behaviors when engaging with images of everyday scenes, in comparison to visually healthy individuals of similar age [41]. A gradual decline in visual quality at the periphery is likely to decrease the number of saccades executed, thus affecting search behavior performance. Additionally, glaucoma patients tend to exhibit smaller saccades (reduced saccade amplitude) within intact regions of their vision. The eye movements of these patients were correlated with visual search durations: a higher frequency of saccades executed per second by a patient corresponds to a reduced time taken to locate the target. The rate of saccades made by glaucoma patients, unlike those of the control group, is associated with search duration, suggesting that eye movement behavior underlies some of the challenges with visual search observed in certain patients [40]. Moreover, subjects with glaucoma tend to engage in more focal searches rather than global search patterns during active gaze scanning [42].

Contrast sensitivity was found to have a significant correlation with the frequency of saccades executed during the search task. Stimulus contrast plays a vital role in determining eye movement behavior, as evidenced by the fact that stimuli characterized by higher contrast are more likely to be selected for fixation. The performance of visual search and executive function, as assessed using a novel computer-based Trail Making Test B (TMT-B), was found to be diminished in individuals with mild to moderate glaucomatous visual impairment among older adults. The mechanisms leading to the reduced executive function and visual search capabilities in older adults with glaucoma may stem from the decline in their visual functionality [41].

4. Other associations

4.1 Economics of glaucoma

Glaucoma is a chronic condition that necessitates lifelong monitoring, even among individuals at low risk for blindness. However, we have limited information regarding which diagnostic and therapeutic strategies can effectively preserve vision over extended periods while ensuring cost sustainability. Frequent follow-up appointments do not explicitly indicate improved disease management; they undoubtedly escalate treatment costs [43].

The economic impact of glaucoma on individuals, healthcare systems, and society can be categorized into three types: direct medical costs, direct nonmedical costs, and indirect costs [43]. Direct medical costs encompass expenses related to treatments aimed at reducing IOP, consultations with healthcare providers and hospitals, and procedures associated with glaucoma management. Direct nonmedical costs refer to expenses related to transportation, visual aid devices, insurance assistance, social assistance, guide dogs, and home care adaptations that are not directly related to medical treatments [44, 45]. Indirect costs include caregiver expenses and lost productivity, encompassing missed workdays [44].

Glaucoma places a substantial economic burden on healthcare resources worldwide. The effects of glaucoma on overall direct and indirect costs at the population level remain poorly understood. A major portion of the costs is attributed to non-eye-related health service use and loss of productivity [46]. In Finland, while direct expenditures associated with glaucoma represented 0.86% (EUR 202,094,791) of the total healthcare

costs, productivity losses caused by glaucoma accounted for 0.03% (EUR 71,233,046) of the product in 2019 [46]. In Italy, annual costs per patient ranged from approximately €788.7 (direct costs for early-stage glaucoma) to €3973.30 (direct and indirect costs for more advanced stages) from 2000 to 2010 [45]. In India, the estimated annual direct medical cost and indirect cost were ₹8028 and 2436, respectively [47].

When evaluating the cost-effectiveness of diagnosing and treating glaucoma and ocular hypertension, treating glaucoma is deemed highly cost-effective, assuming that expenses related to diagnostic assessments are not included [44]. The financial burden associated with glaucoma escalates in correlation with the severity of the disease [21, 45, 48]. In advanced-stage disease, frequent hospitalizations and the need for complex treatments are prevalent, resulting in heightened direct and indirect costs [44, 45]. Additionally, patients with severe glaucoma typically show increased reliance on caregivers and necessitate more specialized rehabilitation, which significantly drives up overall expenses [28, 44]. Various treatment strategies demonstrate significant variations in both costs and resource utilization [46]. Implementing selective laser trabeculoplasty could reduce total treatment costs by decreasing the use of eye drops [49]. Laser therapy and consequent IOP-lowering medications are the most cost-effective strategies in patients with mild glaucoma. Minimally invasive glaucoma surgery is also a cost-effective option for managing mild to moderate glaucoma. However, surgical procedures, particularly trabeculectomy and filtration surgery, are identified as major cost drivers [45]. Surgical intervention is considered more cost-effective than topical treatment for moderate to advanced cases of glaucoma [48]. The economic significance of adhering to glaucoma medication suggests that early surgical intervention should be prioritized for patients who are noncompliant with topical treatment [47, 50]. Consequently, the cost-effectiveness comparison between medical and surgical glaucoma treatments is still unclear [46].

Glaucoma, being a chronic condition, requires continuous treatment, resulting in significant overall care costs [45]. The global prevalence of glaucoma is on the rise, largely due to the aging adult population [46]. This underscores the need for health-care systems to take into account individual patient factors, such as comorbidities and the possibility of enhanced outpatient monitoring, as these can increase resource utilization and elevate costs [45].

4.2 Rehabilitation

Rehabilitation enhances functionality by maximizing residual vision and providing practical adaptations to address the social, psychological, emotional, and economic challenges associated with visual impairment. Numerous eye diseases, such as glaucoma and age-related macular degeneration, lead to visual impairment and blindness, which cannot be cured and necessitate rehabilitation. Understanding the impact of glaucoma on daily living activities is essential for determining the most suitable approach for both glaucoma treatment and rehabilitation.

It is crucial to educate patients about hazardous situations, such as engaging in daily activities under optimal ambient lighting conditions, operating motor vehicles at reduced speeds, and avoiding environments characterized by abrupt changes in lighting [51]. Furthermore, training patients to adjust the frequency of their fixations has been shown to improve their task performance, which may be beneficial for rehabilitation [40]. Achieving an 84% rehabilitation success rate can be accomplished through the utilization of optical typoscopes for both near and distant vision, a basic electronic typoscope, a magnifying glass, and a monocular telescope [51].

5. Conclusions

Glaucoma constitutes a debilitating and chronic ocular condition that has the potential to result in blindness. Recent clinical and epidemiological studies indicate that glaucoma substantially affects individuals' ability to participate in critical vision-related activities, thereby diminishing the quality of life for individuals affected, even during the early stages. Proper prevention and management of glaucoma patients are essential in minimizing impairments to vision-related quality of life while also reducing individual and economic burdens.

Acknowledgements

No grants and/or support have been received from any organization and/or institution.

Conflict of interest

The author declares no conflict of interest.

Author details

Fatma Merve Bektaş
Mersin City Training and Research Hospital, Mersin, Turkey

*Address all correspondence to: fmerveb@gmail.com

IntechOpen

© 2025 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. 

References

- [1] Ikeda MC, Bando AH, Hamada KU, et al. Is reading performance impaired in glaucoma patients with preserved central vision? *Journal of Glaucoma*. 2021;**30**(4):e153-e158. DOI: 10.1097/IJG.0000000000001806
- [2] Bierings RAJM, van Sonderen FLP, Jansonius NM. Visual complaints of patients with glaucoma and controls under optimal and extreme luminance conditions. *Acta Ophthalmologica*. 2018;**96**(3):288-294. DOI: 10.1111/aos.13695
- [3] Skalicky SE, McAlinden C, Khatib T, et al. Activity limitation in glaucoma: Objective assessment by the Cambridge Glaucoma Visual Function Test. *Investigative Ophthalmology & Visual Science*. 2016;**57**(14):6158-6166. DOI: 10.1167/iovs.16-19458
- [4] Kotecha A, O’Leary N, Melmoth D, Grant S, Crabb DP. The functional consequences of glaucoma for eye-hand coordination. *Investigative Ophthalmology & Visual Science*. 2009;**50**(1):203-213. DOI: 10.1167/iovs.08-2496
- [5] Gazzard G, Kolko M, Iester M, Crabb DP. Educational Club of Ocular Surface and Glaucoma (ECOS-G) members. A scoping review of quality of life questionnaires in glaucoma patients. *Journal of Glaucoma*. 2021;**30**(8):732-743. DOI: 10.1097/IJG.0000000000001889
- [6] Glen FC, Crabb DP, Smith ND, Burton R, Garway-Heath DF. Do patients with glaucoma have difficulty recognizing faces? *Investigative Ophthalmology & Visual Science*. 2012;**53**(7):3629-3637. DOI: 10.1167/iovs.11-8538
- [7] Sotimehin AE, Ramulu PY. Measuring disability in glaucoma. *Journal of Glaucoma*. 2018;**27**(11):939-949. DOI: 10.1097/IJG.0000000000001068
- [8] Nguyen AM, van Landingham SW, Massof RW, Rubin GS, Ramulu PY. Reading ability and reading engagement in older adults with glaucoma. *Investigative Ophthalmology & Visual Science*. 2014;**55**(8):5284-5290. DOI: 10.1167/iovs.14-14138
- [9] Ramulu PY, Swenor BK, Jefferys JL, Friedman DS, Rubin GS. Difficulty with out-loud and silent reading in glaucoma. *Investigative Ophthalmology & Visual Science*. 2013;**54**(1):666-672. DOI: 10.1167/iovs.12-10618
- [10] Ishii M, Seki M, Harigai R, Abe H, Fukuchi T. Reading performance in patients with glaucoma evaluated using the MNREAD charts. *Japanese Journal of Ophthalmology*. 2013;**57**(5):471-474. DOI: 10.1007/s10384-013-0259-3
- [11] Burton R, Saunders LJ, Crabb DP. Areas of the visual field important during reading in patients with glaucoma. *Japanese Journal of Ophthalmology*. 2015;**59**(2):94-102. DOI: 10.1007/s10384-014-0359-8
- [12] Swenor BK, Varadaraj V, Dave P, West SK, Rubin GS, Ramulu PY. Impact of the ability to divide attention on reading performance in glaucoma. *Investigative Ophthalmology & Visual Science*. 2017;**58**(5):2456-2462. DOI: 10.1167/iovs.17-21520
- [13] Wood JM, Black AA, Mallon K, Thomas R, Owsley C. Glaucoma and driving: On-road driving characteristics. *PLoS One*. 2016;**11**(7):e0158318. DOI: 10.1371/journal.pone.0158318
- [14] Yamasaki T, Yuki K, Awano-Tanabe S, et al. Binocular superior visual field areas

associated with driving self-regulation in patients with primary open-angle glaucoma. *The British Journal of Ophthalmology*. 2021;**105**(1):135-140. DOI: 10.1136/bjophthalmol-2019-315187

[15] Blane A. Through the looking glass: A review of the literature investigating the impact of glaucoma on crash risk, driving performance, and driver self-regulation in older drivers. *Journal of Glaucoma*. 2016;**25**(1):113-121. DOI: 10.1097/IJG.0000000000000193

[16] Montana CL, Bhorade AM. Glaucoma and quality of life: Fall and driving risk. *Current Opinion in Ophthalmology*. 2018;**29**(2):135-140. DOI: 10.1097/ICU.0000000000000455

[17] Huang W, Gao K, Liu Y, Liang M, Zhang X. The adverse impact of glaucoma on psychological function and daily physical activity. *Journal of Ophthalmology*. 2020;**2020**:9606420. DOI: 10.1155/2020/9606420

[18] Nayyar S, Kumar S, Rehman O, Ichhpujani P, Singla E. Impact of moderate and severe primary open-angle glaucoma on quality of life due to activity limitation. *Indian Journal of Ophthalmology*. 2022;**70**(2):552-557. DOI: 10.4103/ijo.IJO_1687_21

[19] Bhorade AM, Perlmutter MS, Sabapathypillai SL, Goel M, Wilson B, Gordon MO. Rate of falls, fear of falling, and avoidance of activities at-risk for falls in older adults with glaucoma. *American Journal of Ophthalmology*. 2021;**227**:275-283. DOI: 10.1016/j.ajo.2021.02.017

[20] Adachi S, Yuki K, Awano-Tanabe S, et al. Factors associated with the occurrence of a fall in subjects with primary open-angle glaucoma. *BMC Ophthalmology*. 2017;**17**(1):213. DOI: 10.1186/s12886-017-0613-1

[21] Shih V, Parekh M, Multani JK, et al. Clinical and economic burden of glaucoma by disease severity: A United States claims-based analysis. *Ophthalmology Glaucoma*. 2021;**4**(5):490-503. DOI: 10.1016/j.ogla.2020.12.007

[22] Ren J, Zhang X, Lin H, Zeng JH. Influencing factors of fear of falling among glaucoma patients in West China: A cross-sectional study. *International Journal of Ophthalmology*. 2023;**16**(4):563-570. DOI: 10.18240/ijo.2023.04.10

[23] Yuki K, Asaoka R, Ono T, Awano-Tanabe S, Murata H, Tsubota K. Evaluation of fear of falling in patients with primary open-angle glaucoma and the importance of inferior visual field damage. *Investigative Ophthalmology & Visual Science*. 2020;**61**(3):52. DOI: 10.1167/iovs.61.3.52

[24] Jian-Yu E, Mihailovic A, Schrack JA, et al. Characterizing longitudinal changes in physical activity and fear of falling after falls in glaucoma. *Journal of the American Geriatrics Society*. 2021;**69**(5):1249-1256. DOI: 10.1111/jgs.17014

[25] Yang Y, Trope GE, Buys YM, et al. Glaucoma severity and participation in diverse social roles: Does visual field loss matter? *Journal of Glaucoma*. 2016;**25**(7):e697-e703. DOI: 10.1097/IJG.0000000000000353

[26] Zhu X, Li B, Zhang X, et al. Loneliness and social isolation are associated with an increased risk of glaucoma: A UK biobank cohort study. *BMC Public Health*. 2024;**24**(1):2109. DOI: 10.1186/s12889-024-19649-6

[27] van Landingham SW, Willis JR, Vitale S, Ramulu PY. Visual field loss and accelerometer-measured physical activity

- in the United States. *Ophthalmology*. 2012;**119**(12):2486-2492. DOI: 10.1016/j.opthta.2012.06.034
- [28] Dubey S, Bedi H, Bedi M, et al. Impact of visual impairment on the wellbeing and functional disability of patients with glaucoma in India. *Journal of Current Ophthalmology*. 2020;**32**(1):14-18. DOI: 10.1016/j.joco.2019.09.006
- [29] Jin S, Trope GE, Buys YM, et al. Reduced social participation among seniors with self-reported visual impairment and glaucoma. *PLoS One*. 2019;**14**(7):e0218540. DOI: 10.1371/journal.pone.0218540
- [30] Alves Ambrósio J, Pestana Aguiar C, Cardoso Teixeira P, Chibante Pedro J, Jesus J. Mental health and quality of life in glaucoma patients: Insights from a comparative study. *Cureus*. 2025;**17**(2):e79241. DOI: 10.7759/cureus.79241
- [31] Ramesh PV, Morya AK, Azad A, et al. Navigating the intersection of psychiatry and ophthalmology: A comprehensive review of depression and anxiety management in glaucoma patients. *World Journal of Psychiatry*. 2024;**14**(3):362-369. DOI: 10.5498/wjp.v14.i3.362
- [32] Jesus J, Ambrósio J, Meira D, Rodriguez-Uña I, Beirão JM. Blinded by the mind: Exploring the hidden psychiatric burden in glaucoma patients. *Biomedicine*. 2025;**13**(1):116. DOI: 10.3390/biomedicines13010116
- [33] Isserow LJ, Harris D, Schanzer N, et al. Impact of physiological and psychological stress on glaucoma development and progression: A narrative review. *Medicina (Kaunas, Lithuania)*. 2025;**61**(3):418. DOI: 10.3390/medicina61030418
- [34] Berchuck S, Jammal A, Mukherjee S, Somers T, Medeiros FA. Impact of anxiety and depression on progression to glaucoma among glaucoma suspects. *The British Journal of Ophthalmology*. 2021;**105**(9):1244-1249. DOI: 10.1136/bjophthalmol-2020-316617
- [35] Stamatiou ME, Kazantzis D, Theodossiadi P, Chatziralli I. Depression in glaucoma patients: A review of the literature. *Seminars in Ophthalmology*. 2022;**37**(1):29-35. DOI: 10.1080/08820538.2021.1903945
- [36] Wu N, Kong X, Sun X. Anxiety and depression in Chinese patients with glaucoma and its correlations with vision-related quality of life and visual function indices: A cross-sectional study. *BMJ Open*. 2022;**12**(2):e046194. DOI: 10.1136/bmjopen-2020-046194
- [37] Zwierko T, Jedziniak W, Lesiakowski P, Śliwiak M, Kirkiewicz M, Lubiński W. Eye-hand coordination impairment in glaucoma patients. *International Journal of Environmental Research and Public Health*. 2019;**16**(22):4332. DOI: 10.3390/ijerph16224332
- [38] Hirji SH, Liebmann JM, Hood DC, Cioffi GA, Blumberg DM. Macular damage in glaucoma is associated with deficits in facial recognition. *American Journal of Ophthalmology*. 2020;**217**:1-9. DOI: 10.1016/j.ajo.2020.04.032
- [39] Roux-Sibilon A, Rutgé F, Aptel F, et al. Scene and human face recognition in the central vision of patients with glaucoma. *PLoS One*. 2018;**13**(2):e0193465. DOI: 10.1371/journal.pone.0193465
- [40] Smith ND, Glen FC, Crabb DP. Eye movements during visual search in patients with glaucoma. *BMC Ophthalmology*. 2012;**12**:45. DOI: 10.1186/1471-2415-12-45

- [41] Lee SS, Wood JM, Black AA. Impact of glaucoma on executive function and visual search. *Ophthalmic & Physiological Optics*. 2020;**40**(3):333-342. DOI: 10.1111/opo.12679
- [42] Nagarajan S, Meethal NSK, Pel JJM, Asokan R, Negiloni K, George R. Characterization of gaze metrics and visual search pattern among glaucoma patients while viewing real-world images. *Journal of Glaucoma*. 2024;**33**(12):987-996. DOI: 10.1097/IJG.0000000000002493
- [43] Park I, Gale J, Skalicky SE. Health economic analysis in glaucoma. *Journal of Glaucoma*. 2020;**29**(4):304-311. DOI: 10.1097/IJG.0000000000001462
- [44] Varma R, Lee PP, Goldberg I, Kotak S. An assessment of the health and economic burdens of glaucoma. *American Journal of Ophthalmology*. 2011;**152**(4):515-522. DOI: 10.1016/j.ajo.2011.06.004
- [45] Pennisi F, Gentile L, Borlini S, Gianfredi V, Signorelli C. Direct and indirect healthcare costs of ocular diseases in Italy: A literature review on glaucoma, diabetic retinopathy, and macular degeneration. *Annali di Igiene*. 2025;**37**(4):532-555. DOI: 10.7416/ai.2025.2676
- [46] Purola PKM, Taipale J, Väättäinen S, Harju M, Koskinen SVP, Uusitalo HMT. Price tag of glaucoma care is minor compared with the total direct and indirect costs of glaucoma: Results from nationwide survey and register data [published correction appears in *PLoS One*. 2025 Jan 30;**20**(1):e0318723. DOI: 10.1371/journal.pone.0318723.]. *PLoS One*. 2023;**18**(12):e0295523. DOI: 10.1371/journal.pone.0295523
- [47] Usgaonkar UPS, Naik R, Shetty A. The economic burden of glaucoma on patients. *Indian Journal of Ophthalmology*. 2023;**71**(2):560-566. DOI: 10.4103/ijo.IJO_1676_22
- [48] Cantor L, Lindfield D, Ghinelli F, 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. *Clinical Ophthalmology*. 2023;**17**:85-101. DOI: 10.2147/OPTH.S389406
- [49] Barbosa LEO, Barboza WL, Guedes RAP, Chaoubah A, Hatanaka M. Cost-effectiveness of selective laser trabeculoplasty as a replacement for hypotensive eye drops in the Brazilian public health system. *Clinics (São Paulo, Brazil)*. 2025;**80**:100650. DOI: 10.1016/j.clinsp.2025.100650
- [50] Aptel F, Toren A. Societal and economic impact of poor glaucoma medication adherence. *Ophthalmology*. 2020;**127**(5):599-600. DOI: 10.1016/j.opthta.2020.02.015
- [51] Luo RJ, Liu SR, Tian Z, Zhu WH, Zhuo YH, Liao RD. Rehabilitation of vision disorder and improved quality of life in patients with primary open angle glaucoma. *Chinese Medical Journal*. 2011;**124**(17):2687-2691

Techniques in Trabecular Meshwork and Canal Surgery

Francesco Stringa, Karl Mercieca and Paolo Brusini

Abstract

Trabecular meshwork (TM) and canal surgery have become an increasingly popular surgical option amongst anterior segment surgeons. Depending on the severity and type of glaucoma, anatomical features of the irido-corneal angle, and individual considerations, TM and canal surgery offer a number of advantages over traditional filtering surgery including a higher safety profile, better preservation of the ocular anatomy, faster postoperative recovery time, while still providing intra-ocular pressure (IOP) reduction and potentially minimizing the burden of IOP-lowering medications. This chapter explores the evolution in techniques, materials and indications of angle surgery, with particular emphasis on minimal invasive glaucoma surgery (MIGS) and the latest advancements in ab-interno devices and implant free surgical techniques. Additionally, the authors provide a review of current practice and evidence-based indications.

Keywords: trabecular meshwork, canaloplasty, minimally invasive glaucoma surgery, viscodilation, schlemm's canal

1. Introduction and background

Glaucoma is characterized by a progressive structural damage of the optic nerve and corresponding visual field loss [1]. While multiple factors are involved in its development, high intra-ocular pressure (IOP), caused by a dysregulation in the aqueous humor (AH) outflow, remains the most significant and only modifiable risk factor recognized to date. Landmark studies, such as the Ocular Hypertension Treatment Study (OHTS) and the Early Manifest Glaucoma Trial (EMGT), have shown that lowering the IOP can significantly slow the rate of visual field damage in subjects with ocular hypertension and open-angle glaucoma [2, 3].

The aqueous humor (AH) exits the eye through two pathways – the trabecular meshwork (TM) and the uveoscleral pathway. The TM pathway (also called “conventional” route) represents the 70% to 90% of the AH outflow. The AH follows a pressure gradient directed from the TM into Schlemm’s canal (SC) and from the SC into the aqueous veins. This seems to be determined by both a passive (or pressure-dependent) and active (transcellular) mechanism [4]. In the human eye, the TM represents the main site of outflow resistance, accounting for the 75% of the resistance; the remaining 25% occurs beyond the SC. Glycosaminoglycan and protein

deposition in the extracellular matrix of the TM have been postulated to be the cause for the increased outflow obstruction [5, 6]. From a pathophysiological point of view the interior wall of SC and the TM adjacent the collector channels (CC) represent the primary sources of resistance to AH outflow. A marginal role in AH resistance outflow is played by the exterior wall of the SC and surrounding tissues [7]. This anatomical area is known as the juxtacanalicular space which is presumed to be the principal location of IOP regulation [8]. Ocular hypertension in glaucoma derives from an increased resistance in AH outflow and not by an increased AH production. Interestingly, such resistance in aqueous drainage is not constant in time, but rather a function of IOP (increases as IOP rises) [9].

Because the damage to the optic nerve derived from glaucoma and consequential visual field loss are irreversible, early and sustained IOP control is paramount in preserving visual function and preventing vision loss. Treatment strategies, including medications, laser therapy, and surgical interventions aim to improve AH outflow and/or reduce its production to achieve a target IOP that minimizes further optic nerve damage. Surgical approaches targeting the TM and Schlemm's canal have been gaining prominence amongst anterior segment specialists for their ability to restore physiological outflow pathways with potentially fewer complications and faster postoperative recovery than traditional filtering surgeries. Canaloplasty provides an increased physiological drainage of TM by opening or expanding the SC without functional filtering bleb formation [10]. This technique, therefore avoids postoperative complications related to the presence of a subconjunctival or sub-Tenon bleb such as blebitis, conjunctival damage and toxicity related to the use of antimetabolite drugs, bleb scarring and the need for bleb needling. Furthermore, since the pressure in the collector channels has been estimated to be 9–10 mmHg, canal surgery can reduce the occurrence of hypotony and related clinical sight-threatening complications such as choroidal effusion and hypotony maculopathy [9].

2. Surgical techniques and materials: Evolution and current approaches

Following the description of the SC in 1830 by the German anatomist and physicist Friedrich Schlemm, the first documented intervention on the irido-corneal angle was carried out by Otto Barkan in 1936, who performed an ab-interno goniotomy under visualization with a direct gonioscope lens to enhance the AH outflow and reduce the IOP in a patient with congenital glaucoma. Despite this technique being developed specifically for treating congenital glaucoma, it laid the groundwork for modern TM and canal surgery and subsequently minimally invasive glaucoma surgery (MIGS) with a wider range of indications.

There are two main approaches in canal surgery: ab-interno and ab-externo techniques. Although the initial approach described by Barkan was ab-interno (i.e. through a corneal incision and direct visualization with a gonio-prism), ab-externo techniques were subsequently developed, following the introduction of non – penetrating canalostomy procedures as a safer alternative to trabeculectomy in the late 1990's – early 2000's; these techniques involved dilation of the Schlemm's canal with viscoelastic substance [10]. Further developments and variations from the original technique described by Stegman in 1995 were then introduced. These procedures involve conjunctival peritomy

superiorly, dissection of the superficial and deep scleral flap, unroofing and circumferential cannulation of the Schlemm's canal. Cannulation is performed with microcatheters (like the iTrack™ 250A Canaloplasty Microcatheter, Ellex/ Nova Eye Medical), which have an atraumatic luminous tip equipped with an optical fiber, providing transscleral illumination. This feature enables real-time visualization during the catheterization over 360-degree of the SC, enhancing surgical precision. The catheter is attached to a 10-0 polypropylene suture (canaloplasty); after removal of the microcatheter, the polypropylene is then tightened and left in place maintaining a centripetal tension on the inner wall of the SC (**Figure 1**). Such tension, along with the cannulation and unroofing of the SC, is thought to be responsible for reducing the IOP [11, 12].

Nevertheless, tying the 10-0 polypropylene suture is often arduous and represents the least controlled step in canaloplasty [13]. Furthermore, the appropriate amount of tension to the suture, which is essential for the success of the procedure, is not completely known, and suture protrusion into the anterior chamber is a lifelong risk due to the thin diameter of the 10-0 suture. Therefore, microdevices that could be implanted into the SC, (such as the Stegmann Canal Expander®) were engineered with the purpose of reducing the complexity this step, improving controllability and reproducibility [14].

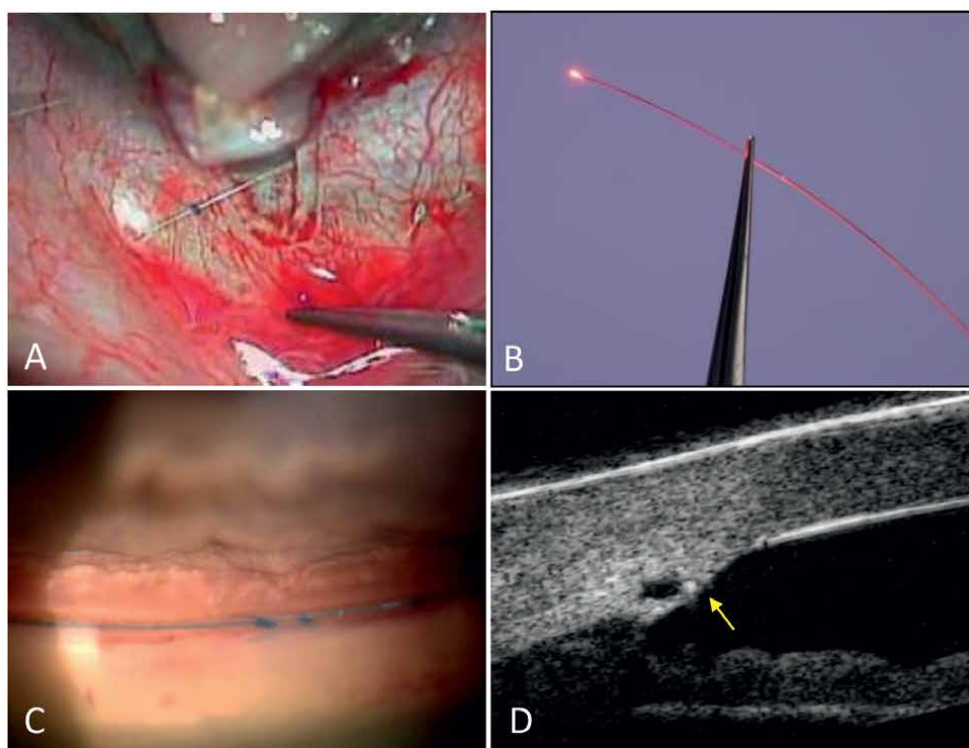


Figure 1.
(a) Ligation of 10-0 polypropylene suture to the catheter. (b) Optical fibre catheter with luminous tip. (c) Intraoperative gonioscopic view of the irido-corneal angle, showing the 10-0 polypropylene suture placed in the SC. (D) Anterior segment OCT b-scan image showing dilation of the SC under the tension of polypropylene suture (hyperreflective dot pointed by yellow arrow).

While the ab-externo canal surgery approach has been deemed to be an effective and less invasive (compared to trabeculectomy) way to reduce the IOP, it presents some disadvantages, such as:

- Significant tissue manipulation: conjunctival peritomy, superficial and deep scleral flap formation, which could promote scarring and compromising the surgical site for potentially future penetrating procedures required
- Time consuming and steep learning curve, particularly in locating and unroofing Schlemm's canal
- Risk of perforation of the TM/SC complex that can compromise the outcome of the procedure, potentially requiring intraoperative conversion into penetrating surgery.

This has brought to the development and improvement of ab-interno TM and canal surgery techniques (with and without permanent implant), which offer the following advantages over their ab-externo counterpart:

- Avoiding conjunctival and scleral manipulation, offering less scarring and better preservation of the tissues.
- Technically less complex to perform, requiring overall less surgical steps
- Faster postoperative recovery and fewer external tissue-related complications
- Practical and efficient intraoperative combination with cataract surgery, offering the opportunity of decreasing patients' access and time spent in the hospital, without compromising surgical outcomes.

Modern ab-interno techniques fall under the umbrella of Minimally Invasive Glaucoma Surgery (MIGS), which has been referred specifically to ab-interno non-bleb-forming procedures targeting the TM and the SC (along with the suprachoroidal space) [15]. These procedures can be further classified depending on the use of permanent implants/devices to the TM into “implant-free” and “with-implant” (**Table 1**). Further classification aims to distinguish procedures based on their mechanism of action (**Table 2**).

In ab-interno procedures gonioscopy lenses are needed in order to visualize the TM and surrounding structures intraoperatively. The lenses most commonly used are “direct lenses”, allowing direct visualization of the TM, by placing them on the cornea, with a viscoelastic medium between lens and cornea, in order to optimize coupling. Indirect lenses are less commonly used in MIGS, and more frequently for diagnostic or in pediatric exams. Some examples of direct lenses include the Volk Vold Gonio – MIGS lens, with a handle, stabilization ring, and magnification of 1.20x; the Katena® Surgical Gonio Prism Lens; and the OCULUS GONIO ready®, which is a hands-free, microscope-integrated system. Performing ab-interno TM or SC procedures requires the view of the surgeon to be perpendicular to the surgical target (the TM), and so both the patient's head and the microscope have to be tilted to

Ab-Interno TM & Canal Surgery		
With-Implant		
Device	Year/FDA-Approval	Mechanism
iStent [®] (I generation)	2012	Snorkel-shaped titanium device implanted into the TM to create a bypass directly into Schlemm's canal, facilitating AH outflow.
iStent inject [®] (II generation)	2018	Delivery of two preloaded stents through a single-entry point, each with four 50-micron outlets, to enhance AH outflow via the TM into Schlemm's canal.
iStent inject W [®] (III generation)	2018	It is similar to the II generation, has a wider base, to enhance stability
iStent infinite [®]	2022	It offers the possibility to implant up to 3 stents, with the same design as the iStent inject W [®] . It is the only TM stent approved as standalone
Hydrus [®]	2018	Crescent-shaped nitinol device, 8 mm long, (90 degrees of Schlemm's canal). It dilates and scaffolds the canal, creating a bypass through the TM.

Table 1.
Trabecular bypass devices and their mechanism of action.

align the appropriate angulation of the anatomical structures and to allow clear visualization.

The first FDA-approved MIGS device targeting the TM, was the iStent[®] (Glaukos, Laguna Hills, CA) in 2012. The first iStent[®] generation was a L-shaped 1 mm long device, made of heparin-coated, surgical titanium which is nonferromagnetic and therefore MRI-safe. The ridged, “snorkel-type” design, aimed for inserting into SC through the TM, thus bypassing the point of main AH resistance [16]. Following the first generation iStent[®] other designs of the same device, and new devices, such as the Hydrus[®] Microstent (Alcon, Geneva, Switzerland) were introduced (see **Table 1**).

A number of “implant-free” procedures have also been developed based on the concept of “removing” (excising or ripping) the point of main resistance of AH with the theoretical advantage of avoiding a foreign body being left in the eye. **Table 2** summarizes such procedures, distinguishing the techniques that “excise” the TM, “rip” the TM and/or visco-dilate/cannulate the SC, and their corresponding mechanisms of action.

3. Clinical evidence and outcomes

3.1 Ab-externo procedures

Evidence for the effectiveness of ab-externo viscocanalostomy dates back to the late 1990s-early 2000s, with the first data analysis of this technique by Dr Robert Stegman [17]. The evolution of viscocanalostomy, called canaloplasty, involved the use of a microcatheter (iTrack[®]) with viscoelastic and a 10–0 polypropylene suture inserted in the SC; based on the available literature this

Ab-Interno TM & Canal Surgery		
Implant-free “rippers” & canaloplasty		
Procedure/Device	Year/FDA-Approval	Mechanism
GATT (Gonioscopy-Assisted Transluminal Trabeculotomy)	2014	A suture or microcatheter is threaded through a goniotomy over 360° and ran through Schlemm’s canal. The thread is then pulled through, tearing the trabecular meshwork circumferentially, which removes resistance to AH outflow.
OMNI® Surgical System (Sight Sciences)	2018	It combines canaloplasty, viscodilation of the and trabeculotomy. Retraction of the micro-catheter is combined to injection of viscoelastic. The OMNI® Ergo-Series is the latest version, with an improved cannula tip profile and a removable viscoelastic connector (Figure 2).
iTrack™ Advance (Nova Eye Medical)	2022/23	A microcatheter with a fiber-optic light providing visualization during canaloplasty. It provides pressurized viscodilation and the option of trabeculotomy
Implant-free “exciser”		
Trabectome® (NeoMedix Corp)	2006	It uses electrocautery to ablate the trabecular meshwork and the inner wall of Schlemm’s canal. It is combined with in-built simultaneous irrigation-aspiration system
Kahook Dual Blade (New World Medical)	2015	The ramp under the blades lifts and stretches the TM before the two blades slice both sides simultaneously. Surgeon pulls smoothly along the angle (90–120 degrees)
TrabEx (MicroSurgical Technology MST)	2017	It directly engages and slice the TM (without a ramp to lift); the instrument is moved along the angle to excise a strip of TM.
Bent Angle Needle Goniotomy (BANG)	1962	It uses a 26-gauge needle. It is a cost-effective MIGS procedure designed to remove a strip of TM.

Table 2.
Implant-free Ab-interno techniques targeting the TM and/or the schlemm’s canal.

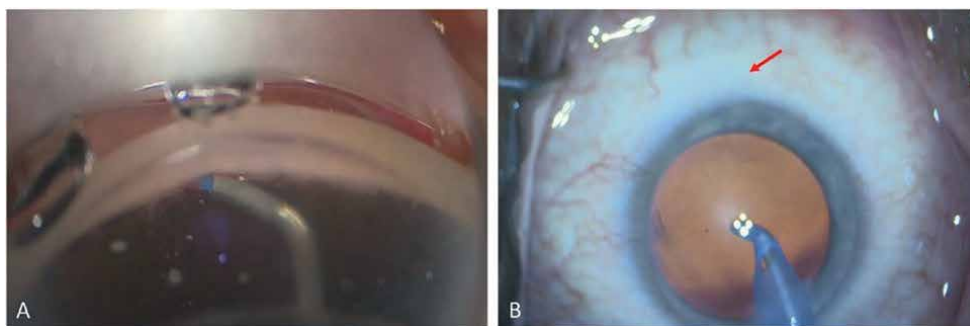


Figure 2.
(a) Intraoperative gonioscopic view of the catheter insertion into SC with the OMNI® surgical system. (b) “The blanching sign” of episcleral vessels in the nasal quadrant, during irrigation-aspiration, following viscocanalostomy and trabeculotomy with OMNI® surgical system. This represents a potential sign of improved outflow facility observed following TM and canal surgery.

technique has shown an IOP reduction ranging between 25 and 56%, with a medication reduction of 53–88% [18–21]. There is significant variability in the outcomes of this technique, which is potentially linked to the timing of follow-up, cohort sizes, surgeon experience, and variability between patients such as ocular pathology and comorbidities. There is a scarcity of studies comparing the efficacy of ab-externo canaloplasty as a standalone procedure versus combined with phacoemulsification. In a report by Arthur et al, the combined procedure showed more favorable results compared to canaloplasty standalone [22]. The percentage of postoperative complications is very low. The most frequently reported side effects being early hyphema (1.6–6.1%), IOP spikes (defined as IOP >30 mmHg) (1.6–8.7%), detachment of the Descemet’s membrane (1.6–6.1%), all of them mainly resolving without intervention [11]. More sight-threatening complications have also been reported, such as hypotony and choroidal effusion, though with a significantly lower incidence compared to trabeculectomy [23].

3.2 Ab-interno procedures

In more recent years, ab-interno canaloplasty (ABiC) procedures, such as Gonioscopy-Assisted Transluminal Trabeculotomy (GATT) with iTrack, VISCO360[®] ViscoSurgical System (Sight Sciences), or the OMNI[®] Surgical System (Sight Sciences), have become favoured over ab-externo canaloplasty due their comparable safety profile, shorter surgical time and with a more minimally invasive, conjunctiva-sparing approach. Evidence on the efficacy of iTrack[®] and OMNI[®] regarding IOP and reduction of glaucoma medication is summarised in **Table 3**.

iTrack’s efficacy as a solo procedure and in combination with phacoemulsification was investigated by Köerber and Ondrejka over a 4-year follow up period. A reduction in IOP of 5.2 mm Hg (–26.2%) at 48 months, and a decrease in glaucoma drugs from 1.9 at baseline to 0.9 medications (–52.6%), amongst all analysed eyes was observed. Additionally, there was no significant difference between the two groups when observed separately [24]. The ROMEO and GEMINI are well-known multicentre studies on OMNI, often cited as a supporting evidence in favour of the use of the device. The ROMEO is a retrospective study analysing 72 patients, diagnosed with mild to moderate OAG

iTrack	IOP Reduction	Medication Reduction
• Combined with phaco [24–27]	1–40%	48–80%
• Standalone [24–27]	1–37%	30–62%
• All eyes (combined and not) [24–28]	30–35%	53%–97%
OMNI		
• Combined with phaco [29–35]	15–40%	24–80%
• Standalone [30, 33, 34]	4–40%	15–74%
• All eyes (combined and not) [34, 35]	29–36%	34–75%

Table 3.
Evidence of efficacy in terms of IOP and reduction of two main abic devices.

and with baseline IOP of >18 mm Hg (group I) or <18 mm Hg (group II). After 12 months, phacoemulsification combined with OMNI was observed to decrease the mean IOP from 21.9 ± 3.7 mmHg to 15.1 ± 3.7 mmHg (-31.1%) in group I, and from 14.1 ± 2.5 mmHg to 13.4 ± 3.1 mmHg (-5.0%) in group II. Only 5% of eyes had IOP spikes in the early postoperative follow up period. The use of glaucoma medication decreased by 23.5 in group I and by 35.0% in group II. A high safety profile with minimal adverse events rate was observed in all patients. Mild postoperative inflammation occurred in 11% of eyes. At 24 months, the mean IOP was 15.6 mmHg (representing a reduction of 28% from baseline) in group I and 13.7 mmHg (4.2% from baseline) in group II, with glaucoma medications reduction of 15.0 and 14.7%, respectively in group I and II. No complications specifically related to the device were reported; nevertheless 8.3% of eyes required a subsequent surgical reintervention to improve the IOP control.

There is a significant wealth of evidence showing the effectiveness of trabecular bypass (i.e. iStent® and Hydrus®). As of May 2025, there were over 385 peer-reviewed publications on iStent (including all the generations of the device), encompassing more than 20,000 eyes studied over nearly two decades. A 7-year prospective study published in 2023 provides long-term data on safety and efficacy of the iStent inject®, both as a standalone procedure and in combination with phacoemulsification, producing a reduction in IOP of 34 and 44%, respectively and a reduction in glaucoma medications of 58 and 76%, respectively [36]. The HORIZON study, is currently one of the largest prospective, randomized, controlled trials to date evaluating a MIGS device. It was conducted to assess the efficacy and safety profile of the Hydrus® when implanted during phacoemulsification in subjects with mild and moderate primary open-angle glaucoma (POAG). Conducted across 38 hospitals in nine countries, the trial enrolled 556 patients who were randomized to undergo either cataract surgery alone (control group), or cataract surgery combined with Hydrus®. After 24 months, 77.3% of patients in the Hydrus group achieved a reduction in IOP (with no glaucoma medications) of equal or more than 20%, compared to 57.8% in the control group. The mean IOP reduction was greater in the Hydrus group (-7.6 mmHg) compared to the control group (-5.3 mmHg). Also, at 24 months, 78% of patients with the Hydrus® were off glaucoma medications, versus 48% in the control group. Long term results show that at 5 years, 66% of Hydrus patients remained on the target IOP and free from medications, compared to 46% in the control group. Furthermore, the Hydrus group had a lower cumulative risk of requiring further glaucoma surgery (2.4% vs. 6.2%). Regarding the safety profile in the Hydrus® group, it was comparable to cataract surgery alone. Nevertheless, the Hydrus group presented a higher incidence of postoperative peripheral anterior synechiae (PAS), though most cases were non-obstructive and did not impact the IOP [37].

A further ab-interno “implant free technique” is the STREAMLINE® Surgical System (New World Medical, Rancho Cucamonga, CA, USA), which was approved by the FDA in 2021 for use in mild-to-moderate open angle glaucoma. This MIGS procedure involves creating micro-goniotomy incisions in the TM, normally in number of 8 to 12 with focal canaloplasty of the SC by conveying small volumes of ophthalmic viscoelastic device (OVD) [38]. The VENICE study, a multi-centre, randomized, controlled trial (RCT), compared the STREAMLINE® Surgical System canaloplasty with implantation of iStent inject W in subjects with mild and moderate primary open-angle glaucoma (POAG) undergoing cataract surgery. The interim

results at 6 months show comparable IOP and medication reduction between the two techniques, when combined with phacoemulsification [39].

Finally, the use of laser in ophthalmology has also been applied to TM/canal surgery, with Excimer Laser Trabeculostomy (ELT), which is an ab-interno, implant-free, MIGS technique, using a 308-nm xenon chloride excimer laser delivered via a fiberoptic probe to create small channels (typically 6–10) in the TM under gonioscopic visualization. ELT was first introduced in the late 1990s-early 2000s, pioneered by Dr Michale Berlin, in Germany [40]. Evidence on effectiveness shows an average IOP reduction of approximately 30% [41, 42]. More recently, an evolution of ELT has been introduced into practice, named Excimer Laser Intraocular Trabeculostomy (ELIOS), which also applies a 308-nm xenon chloride excimer laser, but with refinements in delivery, technique, and device design [43].

A systematic review on MIGS techniques for open angle glaucoma, such as Trabectome, iStent, and Hydrus was published in 2017, concluding that MIGS techniques appear overall similarly effective in lowering IOP, reducing the need for glaucoma medications and with a favorable safety profile. However, the authors noted that such evidence mainly derived from non-comparative studies, highlighting the need for more high-quality Randomized Clinical Trials (RCTs) [44]. In 2021, a meta-analysis analyzing six eligible Cochrane reviews discussing iStent, Hydrus, trabeculotomy with Trabectome, endoscopic cyclophotocoagulation, supraciliary and subconjunctival drainage devices, concluded that, among the products available, data from available RCTs suggest that the Hydrus is associated with less postoperative glaucoma drops and lower IOP than iStent; however, the extent of such difference was small [45].

4. Indications, patient selection, and comparison of surgical approaches

Traditionally, the ideal candidates for angle surgery are patients with a good view of the irido-corneal angle and surgical access to its structures. Patients with chronic angle closure, peripheral anterior synechiae, neovascular glaucoma, angle recession and eyes that have been exposed to previous surgery that impede cannulation of the SC are generally not suitable for canaloplasty, trabeculotomy or trabecular bypass surgery [46]. Nevertheless, reports have shown favorable outcomes regarding IOP reduction and safety in patients with angle closure glaucoma treated with ABiC, comparable to those in patients with POAG [47].

Canaloplasty and TM surgery are generally designated to patients with early and/or moderate OAG, particularly those eyes requiring moderate pressure reduction to a level of mid-teens, as canaloplasty obviates potential serious side effects, frequent follow ups in the early postoperative period (often weekly) and protracted use of steroid eye drops (usually for months) seen following bleb-based procedures [48]. However, reports in the literature have suggested that canaloplasty can be offered as a treatment option across a wider range of glaucoma severities and etiopathogenesis, such as pigmentary glaucoma and corticosteroid-induced glaucoma [49, 50]. For example, positive results have been reported in the treatment of patients with severe/advanced glaucoma [27, 51, 52] and in eyes with previous multiple surgical procedures [53, 54]. Additionally, a comparative study has reported that ab-externo canaloplasty can significantly reduce the IOP, approaching values obtained with trabeculectomy [55].

A 24-month retrospective analysis of ABiC with OMNI in eyes with advanced glaucoma of various etiopathogenesis reported IOP and glaucoma medications reductions of 26.9 and 7.5%, respectively [52]. Gallardo et al. conducted a comparison of ABiC with iTrack between eyes with mild-to-moderate glaucoma and eyes with severe glaucoma. They reported a comparable reduction in IOP (mild-to-moderate: 32.7%; severe: 33%) over a 24-month follow up period [27]. In accordance with the aforementioned studies, it appears that both patients with mild-to-moderate and advanced stages of glaucoma achieved similar target IOP levels postoperatively, but subjects with advanced glaucoma requires a higher glaucoma drops regime compared to those with a mild-to-moderate stage [52].

Since surgeons and patients nowadays have the option of ab externo and ab interno approaches in canaloplasty and TM surgery, a discussion on pros and cons for each approach should be considered. Gallardo et al. conducted a retrospective analysis comparing ab-externo with ab-interno (iTrack) canaloplasty in 12 subjects over 12 months. They did not observe any significant differences in terms of IOP reduction (ab-externo: -25.4%, ab-interno: -25.4%; $p > 0.05$) nor in glaucoma medications reduction (ab-externo: -62.5%, ab-interno: -66.7%; $p > 0.05$) between the two groups, indicating that both techniques could have a similar efficacy profile [21]. On the other hand, Toneatto et al, using the World Glaucoma Associations (WGA) guidelines, carried out a study comparing their surgical success outcomes with OMNI, to those with ab-externo canaloplasty reported by Lewis et al, and they found their results to be inferior to those achieved with ab-externo canaloplasty (Standalone group: 40 vs 68.1%; combined group: 67.9 vs 77.8%). The authors speculated that this could be linked to the fact that the tensioning suture in ab-externo canaloplasty, would provide a more clinically significant (and protracted in time) distension of the Schlemm's canal compared to OMNI [33]. Additionally, most ab-externo canaloplasty surgeons would now admit that a subclinical degree of sub-conjunctival/sub-scleral flow from the scleral window could help with lowering the IOP further. However, ab-externo canaloplasty carries some disadvantages over ABiC such as the fact that is more time consuming, has a steeper learning curve for the surgeon, conjunctival manipulation and suturing, placement of tensioning suture with possible laceration of the TM and migration into the AC, intrascleral lake formation and possible perforation of the canal; These disadvantages could potentially counteract its slight increase in efficacy when compared to ABiC.

5. Conclusion

Canaloplasty and TM surgery represent a significant advancement in the surgical management of open-angle glaucoma, expanding the arsenal of procedures available to surgeon and patients. These techniques offer an effective IOP reduction with a favorable safety profile and postoperative care, placing themselves as an attractive option between medical/laser treatments and filtering surgery within the glaucoma management paradigm.

While ab-externo techniques have shown a consistent and solid efficacy/safety profile as reported in literature, ab-interno approaches offer some potential advantages, such as preservation of conjunctival tissue, allowing for potentially needed future bleb-forming procedures, and the possibility of combining them with cataract surgery without compromising the surgical outcome.

As our understanding of aqueous outflow dynamics continues to evolve, so too does the refinement of surgical approaches aimed to restore the physiological drainage. Nevertheless, despite a growing evidence in the efficacy and safety of TM and SC surgery, there is still the need for a biomarker of success; a test which predicts outcomes or potentially helps selecting patients at higher chance of success. The continue innovation in surgical devices and techniques combined with more long-term outcomes data in angle surgery will further clarify its role in comprehensive glaucoma care.

Author details

Francesco Stringa^{1,2*}, Karl Mercieca³ and Paolo Brusini²

1 Department of Ophthalmology, University Hospital Southampton NHS Foundation Trust, Southampton, Hampshire, UK

2 Department of Ophthalmology, Health Center City of Udine, Udine, Italy

3 Department of Ophthalmology, University Hospital of Bonn, Bonn, Germany

*Address all correspondence to: fs.eyesurgery@gmail.com

IntechOpen

© 2025 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. 

References

- [1] Tham Y-C, et al. Global prevalence of glaucoma and projections of glaucoma burden through 2040: A systematic review and meta-analysis. *Ophthalmology* 2014;**121**:2081–2090
- [2] Kass MA, et al. The Ocular Hypertension Treatment Study (OHTS). *Archives of Ophthalmology* 2002;**120**:701–713
- [3] Heijl A, Leske MC, Bengtsson B, et al. The Early Manifest Glaucoma Trial (EMGT). *Archives of Ophthalmology* 2002;**120**:1268–1279
- [4] Bill A, Svedbergh B. Scanning electron microscopic studies of the trabecular meshwork and the canal of schlemm - An attempt to localize the main resistance to outflow of aqueous humor in man. *Acta Ophthalmologica*. 1972;**50**(3): 295–320
- [5] Berggren L, Vrabec F. Demonstration of a coating substance in the trabecular meshwork of the eye and its decrease after perfusion experiments with different kinds of hyaluronidase. *American Journal of Ophthalmology*. 1957;**44**(2):200–208
- [6] Bhattacharya SK, Annangudi SP, Salomon RG, Kuchtey RW, Peachey NS, Crabb JW. Cochlin deposits in the trabecular meshwork of the glaucomatous DBA/2J mouse. *Experimental Eye Research*. 2005;**80**(5):741–744
- [7] Gabelt BT, Kaufman PL, Rasmussen CA. Effect of nitric oxide compounds on monkey ciliary muscle in vitro. *Experimental Eye Research*. 2011;**93**:321–327
- [8] Goel M, Picciani RG, Lee RK, Bhattacharya SK. Aqueous humor dynamics: A review. *The Open Ophthalmology Journal*. 2010;**4**:52–59
- [9] Phelps CD, Armaly MF. Measurement of episcleral venous pressure. *American Journal of Ophthalmology*. 1978;**85**(1):35–42
- [10] Stegman RC. Visco-canalostomy: A new surgical technique for open angle glaucoma. *Anales Del Instituto Barraquer*. 1995;**25**:229–232
- [11] Lewis RA, von Wolff K, Tetz M, Koerber N, Kearney JR, Shingleton BJ, Samuelson TW. Canaloplasty: Circumferential viscodilation and tensioning of Schlemm canal using a flexible microcatheter for the treatment of open-angle glaucoma in adults: Two-year interim clinical study results. *Journal of Cataract and Refractive Surgery*. 2009;**35**:814–824
- [12] Brusini P, Caramello G, Benedetti S, Tosoni C. Canaloplasty in open-angle glaucoma: Mid-term results from a multicenter study. *Journal of Glaucoma*. 2016;**25**:403–407
- [13] Grieshaber MC. Canaloplasty: A step- by-step approach. *Techniques in Ophthalmology*. 2011;**9**:76–83
- [14] Grieshaber MC, Schoetza A, Grieshaber HR, Stegmann R. Canaloplasty with Stegmann Canal Expander for primary open-angle glaucoma: Two-year clinical results. *Acta Ophthalmologica*. 2017;**95**:503–508
- [15] Pinto LA, Mègevand GS, Stalmans I. European Glaucoma Society - A guide on surgical

innovation for glaucoma. *British Journal of Ophthalmology*. 2023;**107** (Suppl 1):15–20

[16] Spiegel D, Wetzel W, Haffner DS, Hill RA. Initial clinical experience with the trabecular micro-bypass stent in patients with glaucoma. *Advances in Therapy*. 2007;**24**(1):161–170

[17] Stegmann R, Pienaar A, Miller D. Viscocanalostomy for open-angle glaucoma in black African patients. *Journal of Cataract and Refractive Surgery*. 1999;**25**(3):316–322

[18] Mansouri K, Shaarawy T. Update on Schlemm's canal based procedures. *Middle East African Journal of Ophthalmology*. 2015;**22**(1):38–44. DOI: 10.4103/0974-9233.148347

[19] Ayyala RS, Chaudhry AL, Okogbaa CB, et al. Comparison of surgical outcomes between canaloplasty and trabeculectomy at 12 months' follow-up. *Ophthalmology* 2011;**118**:2427–2433

[20] Fujita K, Kitagawa K, Ueta Y, et al. Short-term results of canaloplasty surgery for primary open-angle glaucoma in Japanese patients. *Case Reports in Ophthalmology* 2011;**2**:65–68

[21] Gallardo MJ, Supnet RA, Ahmed IIK. Circumferential viscodilation of Schlemm's canal for open-angle glaucoma: Ab-interno vs ab-externo canaloplasty with tensioning suture. *Clinical Ophthalmology*. 2018;**12**:2493–2498

[22] Arthur SN, Cantor LB, WuDunn D, et al. Efficacy, safety, and survival rates of IOP-lowering effect of phacoemulsification alone or combined with canaloplasty in

glaucoma patients. *Journal of Glaucoma* 2014;**23**:316–320

[23] Garriss WJ, Le C, Zurakowski D, et al. Comparison of surgical outcomes between canaloplasty and trabeculectomy with mitomycin C at 2-year follow-up: A longitudinal cohort study. *Indian Journal of Ophthalmology* 2018;**66**:66–70

[24] Koerber N, Ondrejka S. Four-year efficacy and safety of iTrack ab-interno canaloplasty as a standalone procedure and combined with cataract surgery in open-angle glaucoma. *Klinische Monatsblätter Für Augenheilkunde*. 2023;**240**(12):1394–1404

[25] Khaimi MA. Long-term medication reduction in controlled glaucoma with iTrack ab-interno canaloplasty as a standalone procedure and combined with cataract surgery. *Therapeutic Advances in Ophthalmology*. 2021;**13**:1–9

[26] Gallardo MJ, Supnet RA, Ahmed IIK. Viscodilation of Schlemm's canal for the reduction of IOP via an ab-interno approach. *Clinical Ophthalmology*. 2018;**12**:2149–2155

[27] Gallardo MJ. 24-month efficacy of viscodilation of Schlemm's canal and the distal outflow system with iTrack ab-interno canaloplasty for the treatment of primary open-angle glaucoma. *Clinical Ophthalmology*. 2021;**Volume 12**:1591–1599

[28] Gallardo MJ. 36-month effectiveness of ab-interno canaloplasty standalone versus combined with cataract surgery for the treatment of open-angle glaucoma. *Ophthalmology Glaucoma*. 2022;**5**(5):476–482

[29] Hirsch L, Cotliar J, Vold S, et al. Canaloplasty and trabeculectomy ab

interno with the OMNI system combined with cataract surgery in open-angle glaucoma: 12-month outcomes from the ROMEO study. *Journal of Cataract and Refractive Surgery* 2021;**47**:907–915

[30] Williamson BK, Vold SD, Campbell A, et al. Canaloplasty and trabeculotomy with the OMNI system in patients with open-angle glaucoma: Two-year results from the ROMEO study. *Clinical Ophthalmology*. 2023;**17**:1057–1066

[31] Vold SD, Williamson BK, Hirsch L, et al. Canaloplasty and trabeculotomy with the OMNI system in pseudophakic patients with open-angle glaucoma: The ROMEO study. *Ophthalmology Glaucoma* 2021;**4**:173–181

[32] Gallardo MJ, Pyfer MF, Vold SD, et al. Canaloplasty and trabeculotomy combined with phacoemulsification for glaucoma: 12-month results of the GEMINI study. *Clinical Ophthalmology*. 2022;**16**:1225–1234

[33] Toneatto G, Zeppieri M, Papa V, et al. 360° ab-interno schlemm’s canal viscodilation with OMNI viscosurgical systems for open-angle glaucoma-midterm results. *Journal of Clinical Medicine* 2022;**11**:259

[34] Grabska-Liberek I, Duda P, Rogowska M, et al. 12-month interim results of a prospective study of patients with mild to moderate open-angle glaucoma undergoing combined viscodilation of Schlemm’s canal and collector channels and 360° trabeculotomy as a standalone procedure or combined with cataract surgery. *European Journal of Ophthalmology* 2022;**32**:309–315

[35] Murphy Iii JT, Terveen DC, Aminlari AE, et al. ROMEO study group. a multicenter 12-month retrospective evaluation of canaloplasty and trabeculotomy in patients with open-angle glaucoma: The ROMEO 2 study. *Clinical Ophthalmology*. 2022;**16**:3043–3052

[36] Hengerer FH, Auffarth G, Conrad-Hengerer I. 7-year efficacy and safety of iStent inject trabecular micro-bypass in combined and standalone usage. *Advances in Therapy*. 2024;**41**(4): 1481–1495

[37] Ahmed IK, De Francesco T, Rhee D, et al. Long-term outcomes from the HORIZON randomized trial for a schlemm’s canal microstent in combination cataract and glaucoma surgery. *Ophthalmology* 2022;**129**: 742–751

[38] Lazcano-Gomez G, Antzoulatos GL, Kahook MY. Combined phacoemulsification and STREAMLINE surgical system canal of schlemm transluminal dilation in eyes of hispanic patients with mild to moderate glaucoma. *Clinical Ophthalmology*. 2023;**17**:1911–1918

[39] Goldberg DF, Orlich C, Flowers BE, et al A randomized controlled trial comparing STREAMLINE canaloplasty to trabecular micro-bypass stent implantation in primary open-angle glaucoma. *Clinical Ophthalmology*. 2024;**18**:2917–2928

[40] Berlin M, et al Excimer laser trabeculotomy: A new surgical approach to reduce intraocular pressure in glaucoma. *Graefe’s Archive for Clinical and Experimental Ophthalmology*. 2001;**239**:126–131

- [41] Babighian S, Rapizzi E, Galan A. Efficacy and safety of ab interno excimer laser trabeculotomy in primary open-angle glaucoma: Two years of follow-up. *Ophthalmologica*. 2006;**220**(5):285–290
- [42] Babighian S, Caretti L, Tavolato M, et al. Excimer laser trabeculotomy vs 180° selective laser trabeculoplasty in primary open-angle glaucoma. A 2-year randomized, controlled trial. *Eye*. 2010;**24**:632–638
- [43] Durr GM, Töteberg-Harms M, Lewia R, et al. Current review of Excimer laser Trabeculostomy. *Eye and Vision*. 2020;**7**:24
- [44] Lavia C, Dallorto L, Maule M, et al. Minimally-invasive glaucoma surgeries (MIGS) for open angle glaucoma: A systematic review and meta-analysis. *PLoS One*. 2017;**12**(8):1–33
- [45] Bicket AK, Jimmy TL, Azura-Blanco A, et al. Minimally invasive glaucoma surgical techniques for open-angle glaucoma. *JAMA Ophthalmology* 2021;**139**:1–7
- [46] Godfrey DG, Fellman RL, Neelakantan A. Canal surgery in adult glaucomas. *Current Opinion in Ophthalmology*. 2009;**20**:116–121
- [47] Khaimi MA, Harvey BJ, Hsueh J, et al. Canaloplasty via an ab-interno surgical technique in patients with primary angle closure glaucoma. *International Ophthalmology* 2024;**44**:401
- [48] Matlach J, Dhillon C, Hain J, et al. Trabeculectomy versus canaloplasty (TVC study) in the treatment of patients with open-angle glaucoma: A prospective randomized clinical trial. *Acta Ophthalmologica* 2015;**93**:753–761
- [49] Brusini P, Papa V. Canaloplasty in pigmentary glaucoma: Long-term outcomes and proposal of a new hypothesis on its intraocular pressure lowering mechanism. *Journal of Clinical Medicine*. 2020;**9**:4024
- [50] Brusini P, Tosoni C, Zeppieri M. Canaloplasty in corticosteroid-induced glaucoma. Preliminary results. *Journal of Clinical Medicine*. 2018;**7**(2):31
- [51] Patel S, Reiss G. Long-term clinical and safety outcomes of canaloplasty performed across all grades of glaucoma severity. *Journal of Ophthalmology*. 2023;**2023**:5625990
- [52] Yadgarov A, Dentice K, Aljabi Q. Real-world outcomes of canaloplasty and trabeculotomy combined with cataract surgery in eyes with all stages of open-angle glaucoma. *Clinical Ophthalmology*. 2023;**139**:2609–2617
- [53] Riaz KM, Gill MS, Murphy DA, et al. Surgical management of intraocular pressure with ab interno canaloplasty in postkeratoplasty patients: 12-month results. *Cornea* 2023;**42**:52–59
- [54] Terveen DC, Sarkisian Jr SR, Vold SD, et al. Canaloplasty and trabeculotomy with the OMNI® surgical system in OAG with prior trabecular microbypass stenting. *International Ophthalmology* 2022;**43**:1647–1656
- [55] Mercieca K, Azzopardi M, Vallabh NA, et al. Comparison of outcomes of deep sclerectomy, canaloplasty, and viscocanaloplasty: A multicenter study. *Journal of Glaucoma* 2025;**34**:349–357

Objective Evaluation of Anterior Chamber Characteristics in Angle Closure Disease Diagnosis and Treatment

*Debdas Mukhopadhyay, Tamal Roy
and Amitendu Saha*

Abstract

A gonioscope is the only tool to diagnose angle closure diseases. It is indispensable, but unfortunately underperformed and completely subjective. The angle of the anterior chamber is not the only structure that contributes to closure. Other factors, like axial length, lens thickness, lens vault, corneal diameters, and pupil dark-light dynamics, also contribute to the development of an acute attack. A single-time gonioscopy cannot assess the other elements contributing to angle closure. Gonioscopy-dependent classification of drainage angles as “open” or “not-open” is another source of confusion and fails to predict where primary angle closure glaucoma (PACG) is possible in the future. Gonioscopy-dependent angle closure disease management might result in losing many eyes. Attempts were made to remove these subjectivities. Definite advantages can be extracted from anterior segment (spectral domain/swept source) ocular coherence tomography (OCT) for the assessment of anterior chamber configuration and iris-pupil dynamics. AS-OCT can measure and document most of the required parameters contributing to angle closure. Some alternative readily available methods that are quick, easy to perform, and patient-friendly are very much needed for general ophthalmologists, as well as objective and reproducible. AS-OCT could prove to be the best companion. The only limitation of AS-SD-OCT is that it cannot identify the contents of angles.

Keywords: iris-pupil dynamics, lens thickness, lens vault, anterior segment OCT, gonioscopy, occludable angle, primary angle closure diseases

1. Introduction

If we consider the different causes of irreversible loss of vision, globally, glaucoma tops the list. Though it was believed that open-angle glaucoma is far more common than angle closure glaucoma, it is now recognized that this is not true. Angle closure glaucoma may be more widespread, especially in some parts of the world. Population-based studies reveal that, on average, PACG carries a threefold increased risk of severe

bilateral visual impairment when compared to the rates of blindness in POAG [1]. Angle closure glaucoma is a major cause of blindness in some populations [2], with 16 million people affected and nearly 4 million of them bilaterally blind [3, 4]. In the developing world, over 90% of glaucoma patients go undiagnosed and untreated [5]. Only half of glaucoma patients are now diagnosed by doctors, even in industrialized nations [5]. Less than 5% of the world's ophthalmologists are available to about 17% of the world's population in 132 countries. The world's population can only be served by 29 ophthalmologists per million [5]. Due to this paucity of treating ophthalmologists, objective evaluation of anterior chamber characteristics in Angle Closure Disease Diagnosis and Treatment should be emphasized and allowed.

2. Pathophysiology

As of the present, the gonioscopic angle evaluation serves only as a diagnostic standard to determine whether or not a person has angle closure. However, a single gonioscopic measurement made by a single person under arbitrary illumination conditions could lead to significant errors down the road [6]. A number of interrelated ocular anatomical and physiological characteristics, including axial length/refractive state, iris parameters, fluid retention/shadowing capacity of the iris, choroid swelling, lens thickness, and lens vault, contribute to gonioscopic appearance. In the treatment of angle closure diseases, especially in the suspect group, these measurable, objective, and documentable criteria are still not included in standard protocol.

The main underlying cause of PACG is pupillary obstruction. In secondary forms, various other mechanisms come into play, either driving the iris toward the trabecular meshwork or pushing it forward from behind. Patients with angle closure glaucoma, both primary and secondary, may have a sudden, sharp increase in intraocular pressure (IOP) along with the usual symptoms and indicators. Or they can develop without any symptomatic condition.

Angle closure glaucoma (ACG) is caused by the forward-bowing peripheral iris closing the anterior chamber angle either synechially (when there is a permanent adhesion because of recurrent inflammation) or appositionally (when closure can be relieved by indentation). Pupillary block, whether functional or total, is the main disease-causing mechanism in primary angle closure. In order to diagnose glaucoma, the International Society of Geographic and Epidemiologic Ophthalmology (ISGEO) created a scheme in 2002 [7]. Since then, it has progressively evolved into a common definition of PACG in population-based epidemiological research.

Disk cupping and field abnormalities run parallel to one another in open-angle glaucoma, whether or not the eye seems normal. However, a fully formed primary angle closure glaucoma in angle closure illnesses progresses through four different stages:

1. Primary angle closure suspect (PACS): Here, the sole anomaly is the shallow anterior chamber angle (without increased IOP, cupping, or field abnormalities).
2. Primary angle closure (PAC): IOP is observed to be high, in addition to the anterior chamber being shallow (no cupping, no field abnormalities).
3. Primary angle closure glaucoma (PACG): Here, the anterior chamber is shallow, and all the signs of glaucoma are present (Elevated IOP, disk cupping, and field flaws).

4. Acute angle closures: During any phase, there might be sporadic, very high-rise IOP along with specific clinical symptoms and indicators (acute angle closures).

In clinical practice, shallowness of the eye is the only anomaly of the eye that may indicate angle closure illness. The depth of the limbal anterior chamber can be suspected by the well-accepted Van Herick method (**Figure 1a–c**) [8]. Failing to detect the shallowness of the AC angle results in subsequent evaluations being off course. Within 5 years, 20% of PACS patients advance to the next stage [9].

Gonioscopy is the next stage of assessment. That is still the only acceptable method of diagnosing angle closure. The doctor can determine whether the anterior chamber is shallow appositionally or synechially with the use of this gonioscopy technique. Gonioscopy is challenging to perfect because it requires rigorous procedural requirements. It is challenging for general ophthalmologists to reach a decision, especially in cases that are borderline questionable.

In contrast to glaucoma specialists, general ophthalmologists see a wide variety of patients in their day-to-day clinical practice. They struggle to find the time to perform

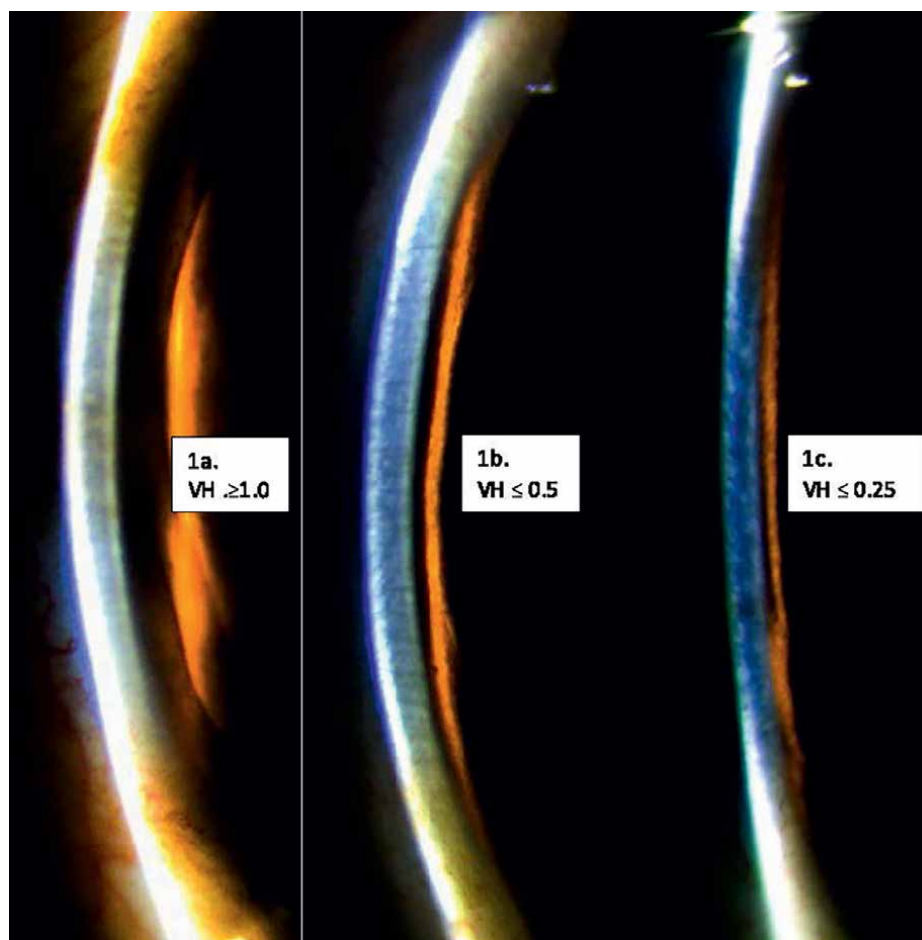


Figure 1.
(a, b, c) VH images (the distance between the anterior iris surface and the peripheral posterior corneal surface is less than one-fourth the corneal thickness).

gonioscopy in every suspect instance, make a firm determination regarding the shallowness of AC, and take the appropriate action. To lessen the uncertainty, they require some kind of technical assistance to supplement their gonioscopic findings.

Angle closure diseases are more likely to occur in the eye due to some unique characteristics. Hyperopia due to shorter axial length, a relatively large lens, a plateau iris, shallowness of AC, and anteriorly placed ciliary processes are recognized characteristics. Other factors, such as age (ACG is more frequent in older people), ethnicity (Asian and Inuit groups are at higher risk), and family history, can potentially raise the chance of having ACG in addition to these physical characteristics.

3. Various structures affecting angle closure in the eye

3.1 Iris

Quigley, in his attempt to explain the “Understanding the Problem of Angle-Closure Glaucoma” [6], claimed that the condition is a dynamic one rather than static. He emphasized that a single anterior chamber angle measurement is insufficient in determining the time and illumination conditions to distinguish between those who want angle closure and those who do not.

The development of primary angle closure diseases (PACD) is also becoming more and more dependent on iris parameters, such as iris thickness, area, and curve [10]. Tiedeman [11] viewed the iris as a thin sail that is securely fastened at the iris root. It is subject to four forces. These include the hydrostatic pressures in both chambers of the eye, the force holding the iris root, the centrally located sphincter, and the radially directed dilator fibers [11]. The aqueous passes through the pupil to reach the anterior chamber. For this, the iris must be raised out of contact with the anterior lens surface [11]. This force is equal to the area of the pupil times the pressure in the anterior chamber minus the pressure in the posterior chamber [11]. The iris is thought to float over the lens surface like a sluice gate and apply force to generate a resistance to aqueous passage through the pupil; hence, the lens is believed to be out of contact with the iris in this research. The shape of the iris-lens contour is determined by the fluid that accumulates in the posterior chamber. If the resistance is greater than the net aqueous pressure difference, the peripheral iris that is thinner will bow forward and may touch the anterior chamber angle initially by temporary contact (appositional closure) and a permanent adhesion (synechial closure).

Although a thicker iris stroma would raise the pressure differential between the chambers, it would not change the shape of the iris. The more anteriorly placed lens in relation to the iris root, the iris in the model becomes a convex form and bows forward more [11].

The iris stores extracellular fluid in its stroma, much like a sponge. When the pupil dilates, this fluid is forced out of its stroma, and when the pupil contracts, it is taken up again. Cross-sections obtained during OCT allow us to quantify a true reduction of iris area (**Figure 2**). Acute attacks are more likely to occur in those whose irises retain fluid even when they dilate, though iris “sponginess” differs from person to person (**Figure 2**). As the iris reacts to nerve stimuli, fluid is continuously exchanged through its pores. Understanding its biomechanical activity could aid in our comprehension of its function in the development of ACG, specifically in the eyes [13]. The iris’s architecture and physiology combine to pose a concern. As provocative tests (the dark room test or the mydriatic test), the absence of iris area loss on pupillary expansion is now

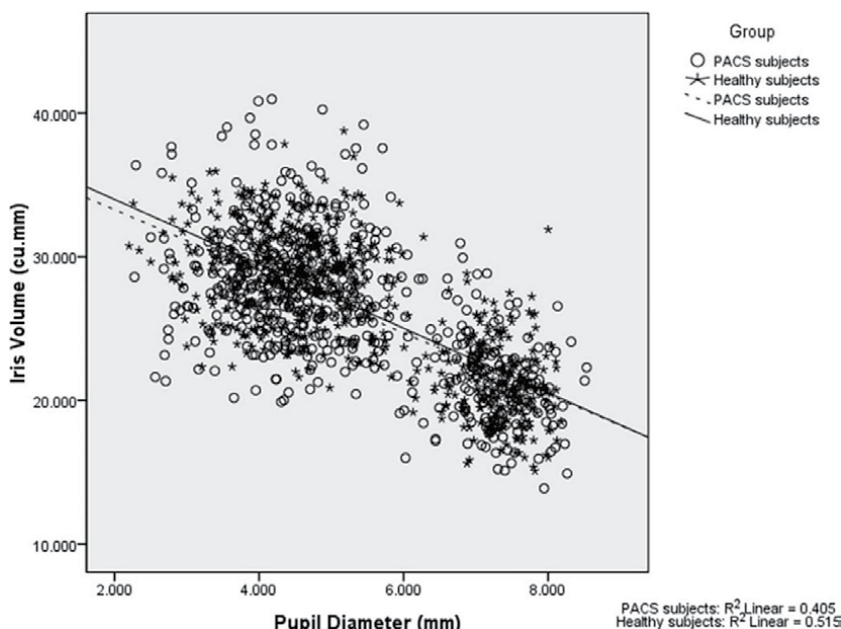


Figure 2.
 Pupillary diameter versus iris volume. Iris “sponginess” [12].

being assessed. In recent years, the significance of iris morphological and biomechanical parameters in affecting angle closure has increased [14]. Because completing this task in a real-world environment is extremely challenging, they used a hypothetical finite element (FE) analysis in their investigation. In their investigation into the significance of iris stiffness, Pant et al. discovered that there is a mechanical link between increased iris stiffness and angle closure glaucoma as well as an omnipresent PACG risk factor [15].

3.2 Choroid

Another physiological stimulus implicated in angle closure is choroidal enlargement. The choroid expands after ingesting fluid for reasons that are still unknown, increasing its total volume. The peripheral iris bows forward to narrow the angle, the lens advances, increasing pupillary block with increased iris-lens contact, and the intraocular pressure (IOP) rises instantly as the choroid’s volume increases in the globe’s small space. Significant evidence has been published by Sakai et al. showing that eyes with angle closure have greater choroidal expansion [16], that angle closure eyes have greater changes in choroidal thickness following water consumption [17], and that topiramate-induced angle closure glaucoma is an example of choroidal swelling and ACG [18].

3.3 The crystalline lens’s function

Angle closure is thought to be determined by lens parameters as well (Figure 3), such as lens thickness and lens vault [19]. Nongpiur et al. studied the role of lens thickness and lens vault and other lens parameters in development of ACG and established the importance of various lens characteristics [19]. The development of ACG is significantly influenced by a combination of factors such as short axial length (AL), increasing lens thickness (LT), and shallow anterior chamber depth (ACD). However,

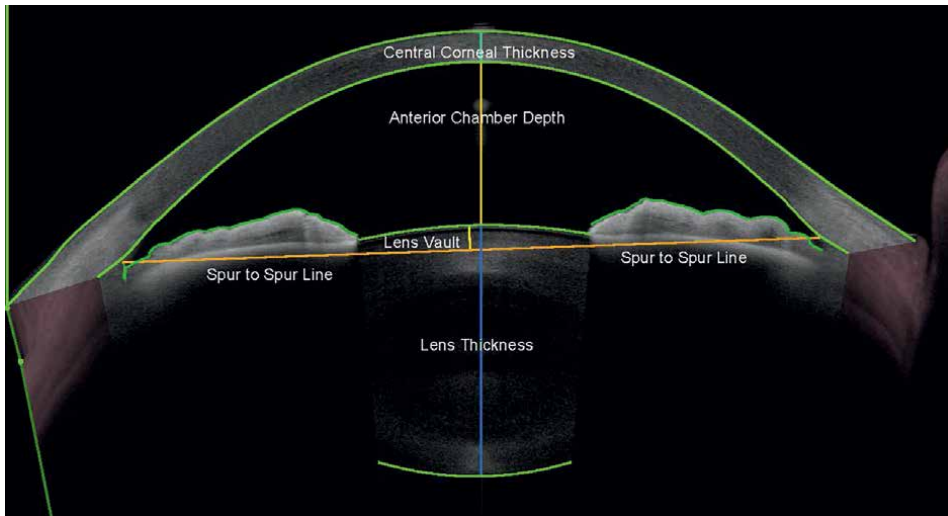


Figure 3.
Lens parameters.

there have been conflicting reports regarding the significance of lens position (LP) and relative lens position (RLP) with angle closure [19], and the association of different lens parameters, such as lens position (LP; defined as $ACD + 1/2 LT$), relative lens position (RLP; defined as $LP/axial\ length$), and LT-to-AL (LT/AL) ratio, has been evaluated inconclusively [19]. The ratio of lens volume to globe volume increases with decreasing eyeball size. It also occurs when an intumescent cataract causes lens-induced glaucoma.

LV, or lens vault, is one of the factors. Lens vault (LV) is defined as the distance between the crystalline lens's anterior pole and the horizontal line connecting the two scleral spurs on AS-OCT scans. Narrow angles were independently linked to lens vault, which could be helpful in screening for narrow-angle eyes [19, 20]. In the effectiveness in angle-closure glaucoma of lens extraction (EAGLE) Study, the lens's contribution to angle closure glaucoma is fairly balanced [21]. According to this study, clear-lens extraction should be taken into consideration as a first-line therapy option because it demonstrated higher efficacy. Compared to laser peripheral iridotomy (LPI), it was more economical.

4. Prevalence and progression

In primary angle closures and suspicious cases, gonioscopy is the sole method used to determine occludable angles and the indication for peripheral iridotomy. Only 23% of Indians are served by ophthalmologists, 70% of whom work in cities and suburbs [22]. In individuals aged 40 and older from Tajimi, Japan, the prevalence of PACG, SG, and total glaucoma was 0.6%, 0.5%, and 5.0%, respectively [23].

In Kumejima, the prevalence of PACG was 2.2%, which was 3.7 times higher than in the Tajimi study and among the highest reported in population-based research [24]. In one eastern Indian study, the prevalence of PACD is 1.5% to 1.9% [25]. Although the 5-year incidence of PACS progression to PAC was 22% in this population-based study of PACS by Thomas et al., none of the PACS patients experienced functional damage [9]. Twenty-two percent of PACS suspects progress to primary

angle closure (PAC)/primary angle closure glaucoma (PACG) in 5 years [9]. One clinical risk factor for advancement was bilateral PACS. The key to preventing irreparable blindness is early detection. It is important not to overlook this opportunistic assessment. Two (2.5%) of the other eyes had definite or probable glaucoma at the time of diagnosis after acute primary angle closure in one eye, and five (6.5%) developed it throughout a mean follow-up of 6 years. Compared to the eye that experienced acute primary angle closure (APAC), almost 80% of this group maintained good vision in the contralateral eye [26]. The majority of this group's visual impairment was caused by unoperated cataracts [26]. Even with a patent LPI, the majority of eyes with established PACG need additional therapy to manage intraocular pressure [26]. Most of the time, medical treatment is ineffective, and filtration surgery is required. If this trend is not identified, patients run the danger of developing more glaucomatous visual damage [27]. Twenty-eight percent of PACS participants who underwent LPI went on to PAC, according to a hospital-based study. The development of PACS to PAC was predicted by a decreasing anterior chamber angle (ACA) [28]. However, in another study, the study participants' IOP, history, or symptoms of an acute glaucoma episode did not rise following LPI [29]. No eye with PACS advanced to PAC or PACG following LPI, according to another hospital-based study [30]. The natural course of PACS, PAC, and PACG seems to be positively altered by LPI [30].

5. Screening

Rapid, low-cost screening techniques that do not require highly qualified operators are needed for clinical practice because angle closure glaucoma is quite common and morbid in many nations.

5.1 The oblique flashlight test

The oblique flashlight test makes use of a penlight beam that shines over the anterior chamber and parallel to the iris. However, this test has a relatively low specificity and is rarely used as a screening tool due to subjectivity in evaluating the test result and variations in flashlight illumination [8].

5.2 The van Herick approach

The van Herick approach (**Figure 1a–c**) is far more weighted and assessed [8]. It assesses the anterior chamber depth by shining a narrow slit beam at a 60-degree angle onto the cornea directly in front of the limbus. The distance between the anterior iris surface and the posterior corneal surface is taken into account. If the distance is less than one-fourth the corneal thickness, a narrow angle is suspected, and gonioscopy should be performed if the distance between the anterior iris surface and the posterior corneal surface is less than one-fourth the corneal thickness. The limbal chamber depth test is a modification of this technique that adds more grades.

Van Herick believed that gonioscopy was necessary for the categorization of glaucoma in the original publication. But gonioscopy would be impossible for routine examinations of non-glaucomatous patients. Only if the angles were believed to be narrowed should it be done [31]. With a high detection rate, numerous studies suggested this approach for primary screening [8, 32]. This approach was unquestionably rejected by several investigations [33, 34].

6. Diagnosis

The gold standard technique for evaluating angles is gonioscopy, which is essential for diagnosing the two types of glaucoma (open and closed angle). It is also crucial for grading the pigmentations at angles, their contents, and the anatomic narrowness of angles or angle closure. Should gonioscopies be performed on every patient in the General Eye Outpatients Department (OPD)? It would be impracticable to do gonioscopy on every patient, according to van Herick [31]. The question now is, who requires or qualifies for gonioscopy? Therefore, a procedure for choosing gonioscopy candidates is required.

An attentive assessment of the possibility of any type of glaucoma, whether angle closure disease (by Limbal Anterior Chamber Depth (LACD) by the van herick (VH) method) or open-angle glaucoma (by suspicious disks), during a routine clinical examination of a patient for whatever reason they are attending the OPD/ER, may lead to additional evaluation with gonioscopy and/or other supportive investigations. To put it another way, “unless proven otherwise, all patients are glaucoma patients.” A single examiner using gonioscopy on a primary angle closure suspect (PACS) cannot categorically classify the situation as occludible or non-occludible; instead, one or more objective investigations are required to evaluate the risk of future angle closure or an acute attack and to supplement gonioscopy. Research indicated a 22% probability of advancement within 5 years [9].

We can develop a very basic algorithm that could potentially decrease the number of glaucoma cases that go unnoticed in our offices.

6.1 Glaucoma suspicions in the general clinic

Is the VH Method's LACD less than 0.5?

Corneal abnormality.

Iris's abnormality:

Untrustworthy Disks: The ratio of cups to disks.

IOP if it exceeds 21 mm Hg (although there is not a practical cut-off limit).

Because light causes miosis and opens an appositionally closed angle in roughly one-third of cases, gonioscopy is best performed in a low-light room with a small rectangle of slit-lamp light that is only bright enough to view the angle structures. Since dynamic or compression or indentation gonioscopy is necessary to distinguish between appositional closure or narrowness and synechial closure, glaucoma evaluation should be performed using “small foot-plate gonioscopes,” such as Posner four-mirror lenses, Zeiss four-mirror lenses, and Sussman four-mirror lenses. Gently pressing the cornea with the goniolens foot plate pushes back the iris, thus pushing fluid into the periphery that creates spaces in appositional closure. If the angle cannot be widened anymore, synechial closure is evident. This maneuver can also aid in breaking acute episodes.

7. Limitations of gonioscopy

In primary angle closures and suspicious cases, gonioscopy is currently the sole method available for defining occludable angles and identifying candidates for peripheral iridotomy.

Even though gonioscopy is essential for assessing angle structures, it is sadly underutilized for a variety of reasons, including lack of knowledge about gonioscopy and time restrictions [35, 36].

A sizable portion of rural residents also declines gonioscopy due to anxiety and worry. The percentage and prognosis of patients for whom gonioscopy was not possible were not mentioned. During clinic evaluations, 24% of the patients in their study declined gonioscopy [37]. Although the causes were not thoroughly examined, fear of the large gonio contact lens was one of the most frequent ones. The current gonioscopy-dependent care regimen would leave these patients' futures unknown [37].

Many borderline cases are excluded due to the strict binary designation of drainage angle width as "occludable" or "not occludable," which further complicates evaluation [7, 38]. Subjectivity and varied agreement are further characteristics of gonioscopy [39]. In her discussion of the risk factor in evaluation and glaucoma screening, Coleman noted that while gonioscopy is the gold standard, it is challenging to perform in a screening setting due to the need for highly skilled observers and a costly diagnostic lens [40]. Subjectivity and fluctuating agreement are other well-known characteristics. In their investigation on the agreement between glaucoma experts and seasoned optometrists in gonioscopy grading, Kumar et al. [41] found that there was good agreement between glaucoma specialists and trained optometrists. However, despite their findings, the three glaucoma specialists could not be evaluated for agreement, and significant agreement could not be officially confirmed.

Numerous studies described gonioscopy in detail, including its technique, protocols, grading system, angle closure status, and required management. In addition to being subjective due to inter-observer variability, they frequently remain ambiguous over whether to perform YAG iridotomy right away or to observe with uncertain follow-up or stamp as never-occludible. Real-time and one-time grading is a dichotomous process that can lead to irreversible blindness that was formerly preventable if an incorrect diagnosis is made and the likelihood of future closure is not evaluated. "Creeping angle closure" was not emphasized by them. Those on whom gonioscopy is not possible are likewise unknown to fate. Once more, that requires consistent follow-up, which is challenging in third-world nations.

8. Other imaging techniques

Other imaging techniques are required to help gonioscopy quantify and objectify angle features. Glaucoma specialists and general ophthalmologists are likely

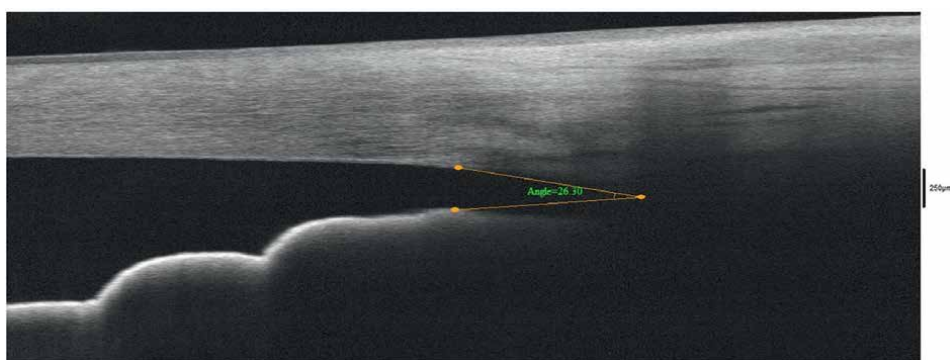


Figure 4.
Optiview only provides one angle scan at a time among the many equipment.

interested in finding ways to overcome the limits of gonioscopy, especially with regard to subjectivity and the need for a high level of competence.

These factors led to the evaluation of alternative imaging techniques to help quantify and objectify angle characteristics, even if gonioscopy remains the gold standard for assessing the anterior chamber angle. When used alone, these more recent tools were unable to replace traditional slit-lamp gonioscopy. They could supplement to the fullest extent possible, especially in cases where gonioscopy was challenging [42]. These methods will be more crucial in the age of telemedicine and virtual ophthalmology, particularly in light of the so-called coronavirus disease (COVID-19) period [43]. With promising outcomes, gonio-photographs and AS-OCT imaging (**Figure 4**) have already been utilized for remote angle closure screening and evaluation [44].

9. Modalities of imaging

A number of anterior segment imaging technologies that offer quantitative measures and comprehensive images of structures are available to complement the information gleaned *via* gonioscopy. In addition to being helpful in detecting angle closure, they can also be used to identify other cases of angle closure due to anterior rotation or ciliary body masses. There are currently no commonly accepted quantitative measurement cut-offs that differentiate between an open and a narrow angle derived from these instruments. There have been efforts to lessen the gonioscopy's subjectivity. "Biometric Gonioscopy" was created by Congdon et al. [45], but it was controversial [46]. Non-gonioscopic techniques were assessed, including optical biometers, scanning peripheral anterior chamber depth analyzer (SPAC), eye-cam, Scheimpflug photography, and ultrasonic biomicroscopy (UBM) anterior segment optical coherence tomography (AS-OCT) [47]. On their own, these new tools could not replace traditional slit-lamp gonioscopy. They could supplement to the fullest extent possible, especially in cases where gonioscopy was challenging. These methods will be more crucial in the age of telemedicine and virtual ophthalmology, particularly in light of the so-called coronavirus disease (COVID-19) pandemic [43].

Where and when to do laser peripheral iridotomy (LPI) in PACS are not clearly defined. Regarding the scheduling of LPI in PACS, the International Society of Geographic and Epidemiologic Ophthalmology (ISGEO) does not offer any precise guidelines. They give PACS with questionable follow-up as an indicator.

10. OCT of the anterior segment (AS-OCT)

Over the past 15 years, OCT has proliferated in ophthalmology imaging. OCT was first used in 1988 [48] to measure the axial length of the eye *in vivo*. This modality creates detailed images of the anterior segment from the cornea to the anterior part of the ciliary body that are comparable to those obtained with UBM by using a diode light source in place of sound. Due to scleral light scattering and posterior pigmented iris shadowing, AS-OCT performs worse than UBM in imaging structures posterior to the iris plane. Being non-contact, AS-OCT can scan simultaneously without patients' discomfort, and can be photographed with the patient sitting upright to prevent positional lens alterations.

Compared to ultrasonic biomicroscopy (UBM), anterior segment OCT (AS-OCT) offers a significant benefit in terms of ease of image acquisition. Being non-contact,

unaltered structural details of the cornea and anterior chamber are available. Although AS-OCT lacks the ability to photograph deep structures like the ciliary body, it does have a higher axial resolution (5–10 μm for AS-OCT versus 25 μm for UBM). Spectral-domain and swept-source OCTs have essentially superseded time-domain anterior segment OCTs in terms of scan speed and resolution. For sufficient visualization of the anterior chamber angle, a shorter wavelength laser is needed. That is provided by a super-luminescent diode; the absence of that can compromise the visibility of the scleral spur, a crucial landmark for measuring the angle width. The introduction of swept-source anterior segment OCT has greatly enhanced the ability to see angle structures and made it easier to perform a thorough 360-degree angle assessment.

With AS-OCT imaging at longer wavelengths, high-resolution pictures of the iris, angle, and sclera can be obtained. 850-nm systems may also produce high-resolution images of the anterior chamber angle, which has made Schlemm's canal and the trabecular meshwork visible. The scleral spur and Schlemm's canal must be identified in order to image the anterior chamber angle [49]. In 2008, Tomey (Nagoya, Japan) unveiled the first generation of anterior segment swept-source OCT (Casia SS-1000 OCT) [50]. Because of previous, less advanced equipment, the first success rate for identifying scleral spurs was poor [51]. As machine technology advances and various methods for identifying scleral spurs and related structures are studied, identification rates are now very high [52]. A recent study using deep learning algorithms with Anterion System (Heidelberg Engineering) showed promise of improving the clinical utility of AS-OCT imaging, particularly for evaluating patients with angle closure. Scleral spur-based biometric parameters are measured at an expert level using deep learning algorithms on the Anterion (Heidelberg Engineering) in a separate patient group [52]. Anterior segment OCT (AS-OCT) imaging was initially used in 1994 [53], and in 2001 [54], AS-OCT was made commercially available.

Due to the significant advancements in imaging of ocular structures by OCT, it is now utilized globally for the investigation of anterior segment structures. Over the past few years, OCT technology has advanced quickly from time-domain to spectral-domain to swept-source OCT. OCT is emerging as a crucial instrument for determining the anterior chamber angle and identifying angle closure suspects. A more thorough in-depth examination of the anterior chamber angle is now possible by increasing the OCT scan speed and image resolution. Now, the scleral spur, Schlemm's canal, and Schwalbe's line are easily recognized [55]. 360-degree angle examination is possible with high-speed imagery. The iris profiles and angle configurations are better visualized with three-dimensional reconstruction [55]. A large number of commercially available OCTs are capable of doing anterior region imaging well. It goes without saying that one machine will perform better than the other in terms of a certain anterior segment imaging characteristic. Overall, the agreement between gonioscopy and AS-OCT (Zeiss Visante) in identifying a closed ACA quadrant was fair, with a K of 0.4, according to a study by Sakata et al. [56]. Compared to gonioscopy, AS-OCT tended to find more closed ACAs. The technical challenges of executing each procedure could be the cause of the different results between AS-OCT and gonioscopy in the different quadrants [56]. A comparison of OCT Visante (Zeiss) and CASIA (Tomey) revealed that both AS-OCTs showed remarkable repeatability [57]. They have good agreement in angle measurements, with the exception of the ACD and SSA [57]. A study conducted by Rania Medhat Fahmy found that the mean central corneal thickness (CCT) and AD of Pentacam and Visante OCT differed statistically significantly [58]. In their study, Pentacam is more reliable than Visante OCT when assessing CCT and AD in myopic individuals. However, when measuring ACD, there was

considerable agreement between these two devices [58]. Optiview only provides one angle scan at a time among the many equipment (**Figure 4**). Two scans that are diagonally opposing are provided simultaneously by Zeiss Cirrus or Visante (**Figure 5**). Both Casia (**Figure 6**) and Anterior (**Figure 7**) provide many scans at once.

Using AS-OCT, dynamic variations of the anterior chamber angle in dark and light were examined by Leung, Cheung et al. [59]. When comparing anterior chamber metrics in a dark and light environment, Lin, Wang et al. discovered an increase in angle opening distance (AOD) and trabecular-iris space area (TISA), more pronounced in

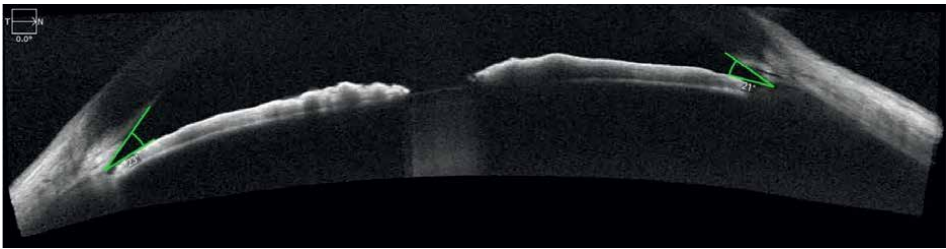


Figure 5.
Zeiss Cirrus or Visante.

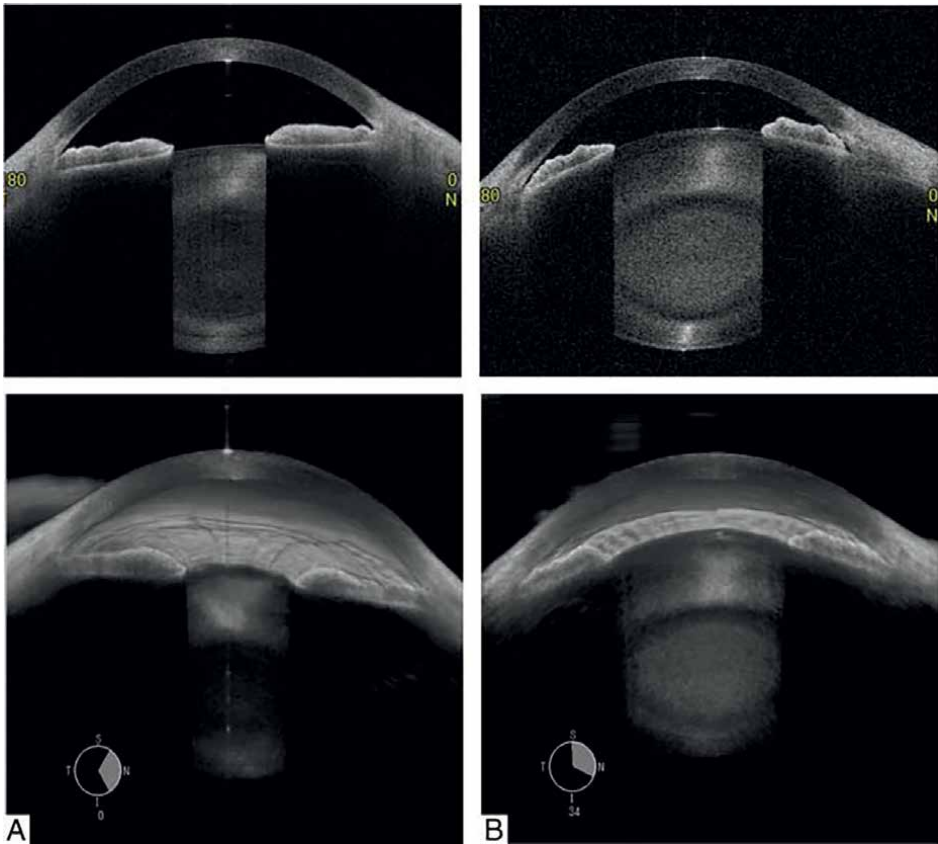


Figure 6.
Casia images. A and B are 3D reconstructions of normal angle and closed angles shown above respectively.

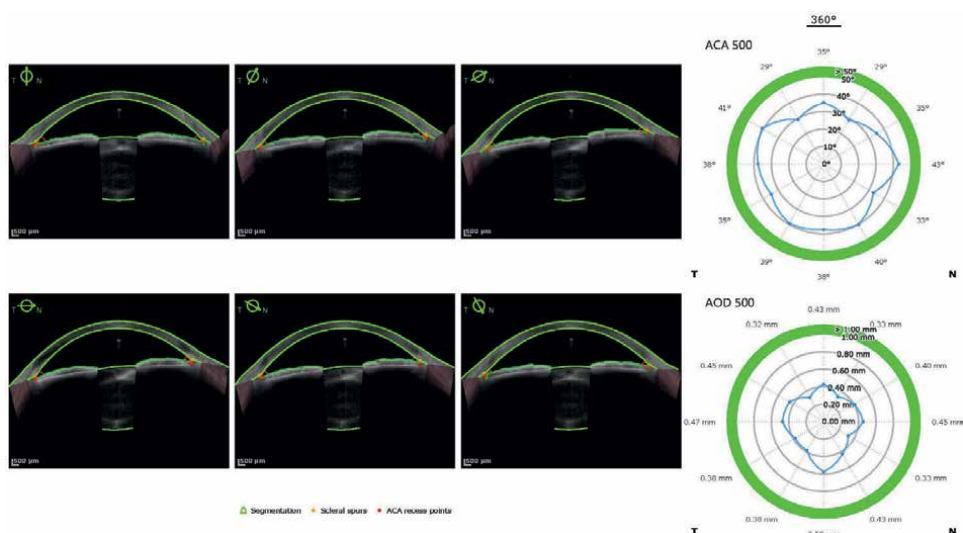


Figure 7.
 Anterior images.

normal individuals [60]. A workable substitute for gonioscopic grading is the measurement of SD-OCT angles in the dark with distant fixation [61]. According to the research of Mukhopadhyaya et al. [36], pilocarpine-induced angle widening identified by SD-OCT may be a reliable objective measure of LPI. Along with gonioscopy, the VH technique, and anterior segment (AS) SD-OCT were used to grade eyes in that investigation. Following pilocarpine drops, the eyes were reviewed. For grading the angles of the anterior chambers, the Shaffer classification was used. Shaffer grades O–I ($\leq 10^\circ$) were deemed as possible closure, grades III–IV (20° – 45°) were considered normal, and grades II ($> 10^\circ$ – 20°) as borderline. It was also noted how much the indentation gonioscopy altered the angle apertures. In a darkened room, AS SD-OCT (AngioVue, Optovue, Inc. USA) was carried out with distant fixation prior to pilocarpine drop instillation and was repeated once pilocarpine drop had produced the maximum amount of miosis. To maximize miosis, the second measurement was conducted in a brightly lit room with close fixation. Measurements of the SD-OCT angle were taken after identification of the scleral spur. Following the application of the pilocarpine drops, eyes with gonioscopically determined smaller beginning angles showed a significant increase in angle OCT values (p -value < 0.000001). The largest disparity between trend lines (pre-pilo vs. post-pilo) was shown at the narrowest angles and became negligible at wide-open angles (**Figure 8**). Normal angle configuration variations with pilocarpine were shown in **Figure 9**, whereas those in questionable cases were shown in **Figure 10**. Various investigations revealed varying degrees of concordance between AS SD-OCT and gonioscopy [62]. Radhakrishnan [63] observed great sensitivity in gathered data across multiple trials, and Nolan et al. [62] found AS-OCT to be quite sensitive. However, Tay et al. [64] discovered that there was little agreement ($\kappa = 0.31$) between AS-OCT and gonioscopy. The receiver operating characteristic (ROC) curve for gonioscopy and angle OCT; however, showed a strong correlation between them ($r = 0.7323$; $p < 0.00001$) with an area under the curve (AUC) of 0.85 (**Figure 11**), according to Mukhopadhyaya et al. [37]. As early as 1992 (Mehrotra) [65], 1995 (Hung) [66], and 1999 (Kobayashi et al.) [67], pilocarpine-induced changes in

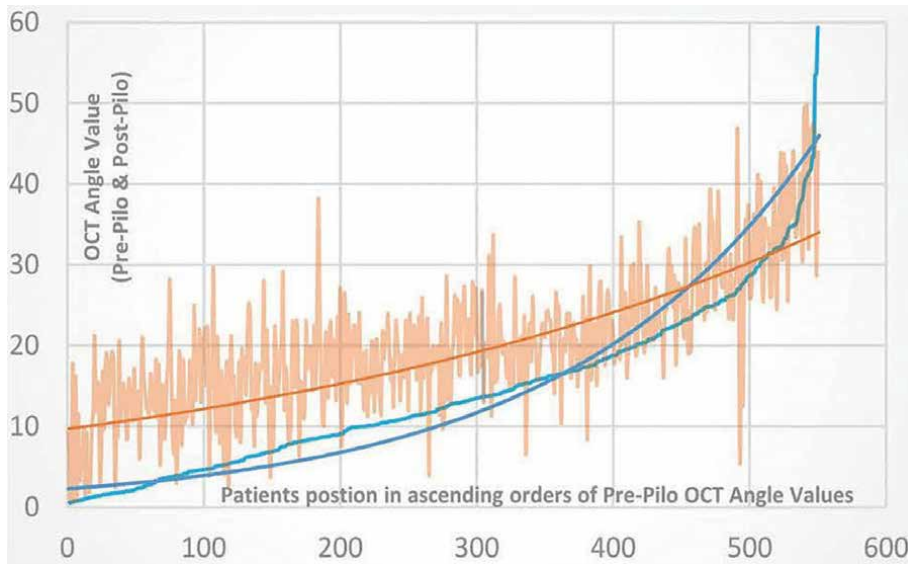


Figure 8. Scatter plots trendlines of OCT angle values (pre-pilo vs. post-pilo). The largest disparity between trend lines (pre-pilo vs. post-pilo) was shown at the narrowest angles and became negligible at wide-open angles [37].

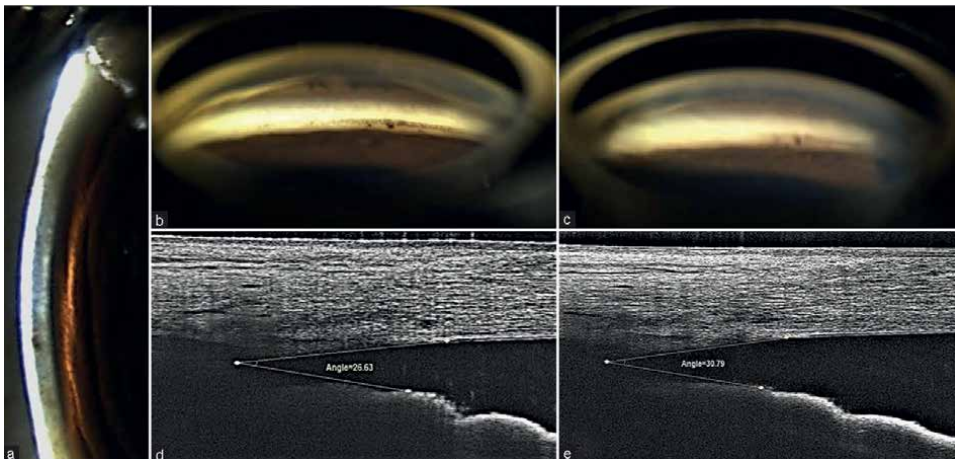


Figure 9. Normal (a) Van Herick limbal AC depth (0.5). (b) Pre-indentation gonioscopy Shaffer's grade III. (c) Post-indentation gonioscopy Shaffer's grade IV. (d) Pre-pilocarpine in dark angle SD OCT. (e) Post-pilocarpine in light angle SD OCT. Please note: Angle did not improve, though the iris is flattened.

anterior chamber angle were investigated using UBM. The study by Kobayashi et al. highlighted the value of pilocarpine-induced increases in anterior chamber angle that were detected by UBM [51], but studies by Merhotra [65] and Hung [66] revealed that pilocarpine decreased the angle depth. They were on ordinary things, though. Thirteen percent (70/539) of the eyes in the study by Mukhopadhyaya et al. [36] had a decrease in angle width. Only nine (12.9%) of these 70 eyeballs had angles less than 10°. AS SD-OCT (AngioVue, Optovue, Inc., USA) was used in their investigation. Only one selected angle could be evaluated at a time by that machine.



Figure 10.
Suspect (a) Van Herick limbal AC depth (<0.25). (b) Pre-indentation gonioscopy Shaffers grade 0. (c) Post-indentation gonioscopy Shaffers grade IV. (d) Pre-pilocarpine in dark angle SD OCT. (e) Post-pilocarpine in light angle SD OCT. Please note: Angle improved and iris is flattened.

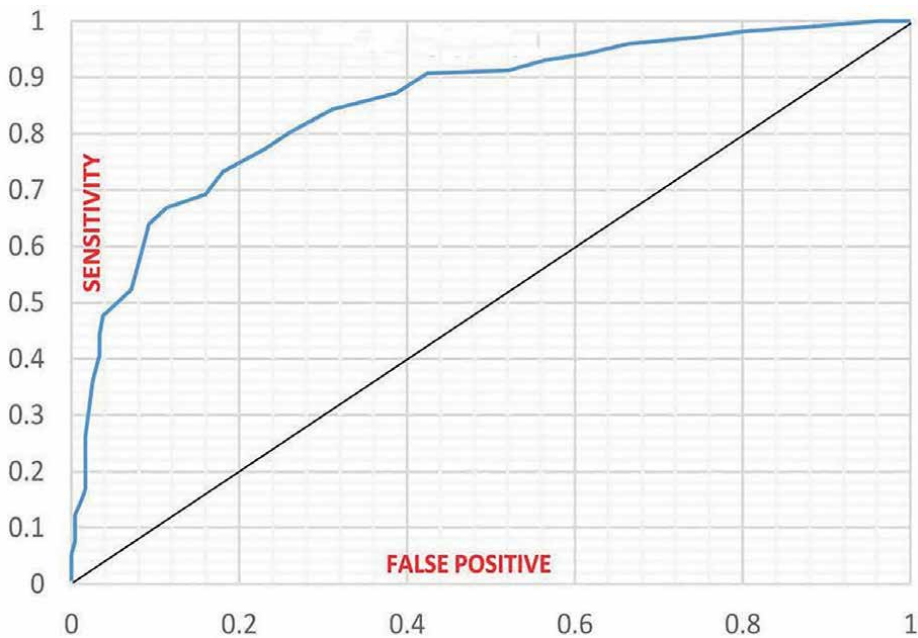


Figure 11.
Area under the curve (AUC) of 0.85 [37].

ANTERION® (Heidelberg Engineering) offers the most crucial anterior segment measures and examinations in a single, modular, upgradable platform by harnessing the potential of high-resolution swept-source OCT pictures. It provides six opposing angles (a total of 12 angles) for evaluating the angles. It displays ACA 500 and AOD 500 (AC depth and angle opening distance at 500 microns) and uses deep learning to identify angle landmarks (scleral spur, Schlemm's canal). ACD,

lens thickness, lens vault, white to white, and axial length are also provided. Thus, it is very easy to register the changes in angle parameters before and after laser peripheral iridotomy, pilocarpine in bright light with near fixation, and pilocarpine in darkness with distant fixation (**Figures 12 and 13**). Deep learning algorithms on the Anterior OCT approximate expert-level measurement of scleral spur-based biometric parameters, and these algorithms are expected to enhance the clinical utility of AS-OCT imaging, especially for evaluating patients with angle closure and performing intraocular lens calculations [52]. A recent study using deep learning algorithms with Anterior System (Heidelberg Engineering) shows potential for improving the clinical value of AS-OCT imaging, particularly for assessing patients with angle closure. Scleral spur-based biometric parameters are measured at an expert level using deep learning algorithms on the Anterior (Heidelberg Engineering) in a separate patient group [52].

The importance of non-contact methods for identifying people at risk of primary angle closure glaucoma was beautifully reviewed and summarized in Cochrane Database of Systematic Reviews by Jindal, Ctori, Virgili, Lucenteforte, Lawrenson [8].

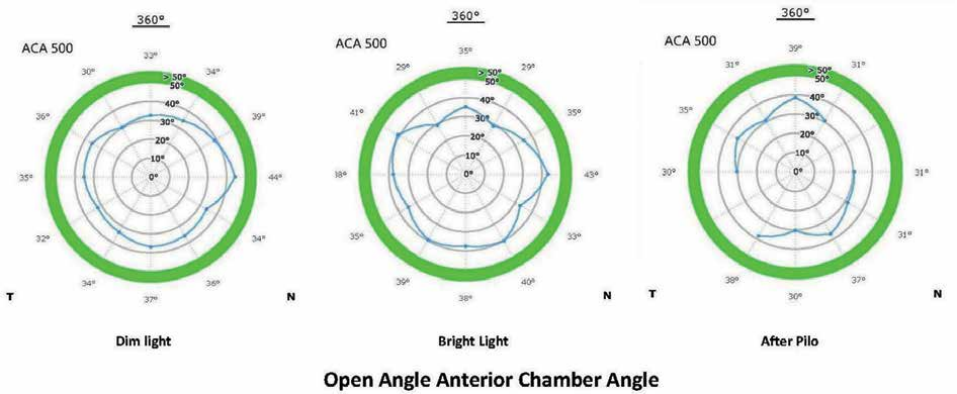


Figure 12.
Angle measurements of open angle in dark, light and after pilocarpine by Anterior.

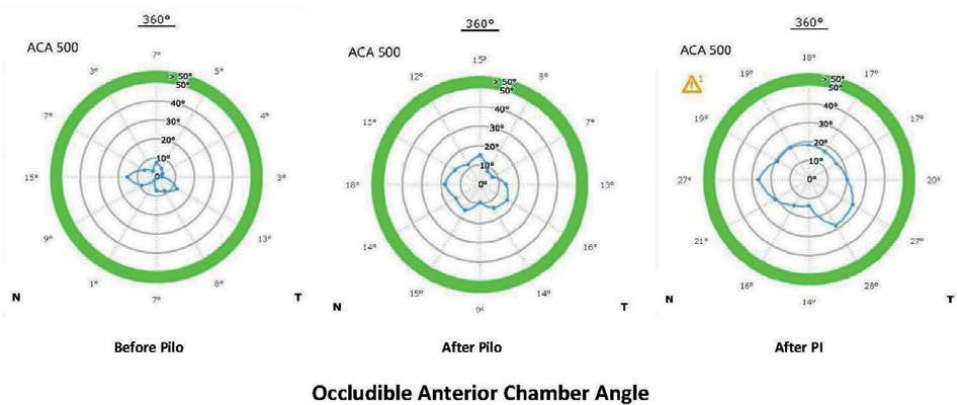


Figure 13.
Angle measurements of occludible angle in dark, light and after pilocarpine by Anterior.

11. Conclusion

Gonioscopy-dependent diagnosis and management of angle closure diseases compels us to risk unintentionally or intentionally missing a significant proportion of glaucoma. Even though gonioscopy is still the gold standard for evaluating glaucoma, its usage is not popular for a number of reasons. When general ophthalmologists do, they are vulnerable to criticism for overtreatment, lack of experience, and procedural flaws. Numerous tools were and are being tried with their advantages and disadvantages in order to provide a clear, objective, repeatable, and documentable assessment of PACG. Results of the usage of these machines are getting robust and encouraging to help diagnose ACG and complement gonioscopy. In several areas, OCT is found to be highly optimal. With OCT noninvasive angiography, it is gradually taking the place of fundus fluorescence/ICG angiography and is now widely accessible and widely used for retinal disorders, glaucoma disk evaluation, and macular ganglion cell status. Instead, it is now recognized as the gold standard for posterior segment diseases. OCTs are now a superior way to assess the cornea. Angle of anterior chamber examinations is now almost entirely devoid of human intervention, thanks to the development of spectral domain and later swept source OCTs, which have superior penetration into opaque structures like the limbus and sclera, as well as the use of artificial intelligence and deep learning. We will continue to overlook the number of patients with angle closure disease who are waiting to become blind in the near future due to the current gonioscopy-dependent management of ACG protocols until the free-hand use of AS-OCT is permitted in the management of ACG by Global Expert Glaucoma Committees with standard operating procedures. In certain PACS circumstances, the widespread use of OCT-directed LPI may lead to overdoing. The risks and benefits should be evaluated. The effects of using AS-OCT in the treatment of angle closure diseases will soon be known.

Author details

Debdas Mukhopadhyay^{1*}, Tamal Roy² and Amitendu Saha¹

1 BKG Malda Eye Hospital Pvt Ltd, Malda, West Bengal, India

2 Raiganj Govt Medical College and Hospital, Raiganj, West Bengal, India

*Address all correspondence to: bkgddmei@gmail.com

IntechOpen

© 2025 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. 

References

- [1] George R, Panda S, Vijaya L. Blindness in glaucoma: Primary open-angle glaucoma versus primary angle-closure glaucoma—A meta-analysis. *Eye*. 2022;**36**:2099-2105
- [2] Tham Y-C, Li X, Wong TY, et al. Global prevalence of glaucoma and projections of glaucoma burden through 2040: A systematic review and meta-analysis. *Ophthalmology*. 2014;**121**:2081-2090
- [3] Seah SK, Foster PJ, Chew PT, et al. Incidence of acute angle closure glaucoma in Singapore. An island-wide survey. *Archives of Ophthalmology*. 1997;**115**:1436-1440
- [4] Foster PJ, Johnson GJ. Glaucoma in China. How big is the problem? *The British Journal of Ophthalmology*. 2001;**85**:1277-1282
- [5] Resnikoff S, Lansingh VC, Washburn L, et al. Estimated number of ophthalmologists worldwide (International Council of Ophthalmology update): Will we meet the needs? *The British Journal of Ophthalmology*. 2020;**104**:588-592
- [6] Quigley H. Understanding the problem of angle-closure Glaucoma explains the role of iris in development of angle closure. *Glaucoma Today*. 2015
- [7] Foster PJ, Aung T, Nolan WP, Machin D, Baasanhu J, Khaw PT, et al. Defining “occludable” angles in population surveys: Drainage angle width, peripheral anterior synechiae, and glaucomatous optic neuropathy in East Asian people. *The British Journal of Ophthalmology*. 2004;**88**:486-490
- [8] Jindal A, Ctori I, Virgili G, Lucenteforte E, Lawrenson JG. Non-contact tests for identifying people at risk of primary angle closure glaucoma. *Cochrane Database of Systematic Reviews*. 2020;**5**:CD012947
- [9] Thomas R, George R, Parikh R, Muliyl J, Jacob A. Five year risk of progression of primary angle closure suspects to primary angle closure: A population based study. *The British Journal of Ophthalmology*. 2003;**87**:450-454
- [10] Wang B, Sakata LM, Friedman DS, Chan Y-H, He M, Lavanya R, et al. Quantitative iris parameters and association with narrow angles. *Ophthalmology*. 2010;**117**(1):11-17
- [11] Tiedeman JS. A physical analysis of the factors that determine the contour of the iris. *American Journal of Ophthalmology*. 1991;**111**(3):338-343
- [12] Zhang Y, Li SZ, Li L, et al. Quantitative analysis of iris changes after physiologic and pharmacologic mydriasis in a rural Chinese population. *Investigative Ophthalmology & Visual Science*. 2014;**55**(7):4405-4412
- [13] Quigley HA, Friedman DS, Congdon NG. Possible mechanisms of primary angle-closure and malignant glaucoma. *Journal of Glaucoma*. 2003;**12**(2):167-180
- [14] Tan RKY, Ng GY, Tun TA, et al. Iris morphological and biomechanical factors influencing angle closure during pupil dilation. *Investigative Ophthalmology & Visual Science*. 2024;**65**(11):7
- [15] Pant AD, Gogte P, Pathak-Ray V, Dorairaj SK, Amini R. Increased iris stiffness in patients with a history of

- angle-closure glaucoma: An image-based inverse modeling analysis. *Investigative Ophthalmology & Visual Science*. 2018;**59**:4134-4142
- [16] Sakai H, Morine-Shinjo S, Shinzato M, et al. Uveal effusion in primary angle-closure glaucoma. *Ophthalmology*. 2005;**112**(3):413-419
- [17] Arora KS, Jefferys JL, Maul EA, Quigley HA. Choroidal thickness change after water drinking is greater in angle closure than in open angle eyes. *Investigative Ophthalmology & Visual Science*. 2012;**53**(10):6393-6402
- [18] Al Owaifeer AM, AlSultan ZM, Badawi AH. Topiramate-induced acute angle closure: A systematic review of case reports and case series. *Indian Journal of Ophthalmology*. 2022;**70**:1491-1501
- [19] Nongpiur ME, He M, Amerasinghe N, Friedman DS. Lens vault, thickness, and position in Chinese subjects with angle closure. *Ophthalmology*. 2010;**118**(3):474-479
- [20] Tan GS, He M, Zhao W, Sakata LM, et al. Determinants of lens vault and association with narrow angles in patients from Singapore. *American Journal of Ophthalmology*. 2012;**154**(1):39-46
- [21] Azuara-Blanco A, Burr J, Ramsay C, Cooper D, Foster PJ, Friedman DS, et al. Effectiveness of early lens extraction for the treatment of primary angle-closure glaucoma (EAGLE): A randomised controlled trial. *Lancet*. 2016;**388**:1389-1397
- [22] De Souza N, Cui Y, Looi S, Paudel P, Shinde L, Kumar K, et al. The role of optometrists in India: An integral part of an eye health team. *Indian Journal of Ophthalmology*. 2012;**60**:401-405
- [23] Yamamoto T, Iwase A, Araie M. The Tajimi study report 2 prevalence of primary angle closure and secondary glaucoma in a Japanese population. *Ophthalmology*. 2005;**112**:1661-1669
- [24] Sawaguchi et al. Prevalence of primary angle closure and primary angle-closure glaucoma in a southwestern rural population of Japan—The Kumejima study. *Ophthalmology*. 2012;**119**:1134-1114
- [25] Paul C, Sengupta S, Choudhury S, Banerjee S, Sleath BL. Prevalence of glaucoma in Eastern India: The Hooghly river glaucoma study. *Indian Journal of Ophthalmology*. 2016;**64**:578-583
- [26] Friedman DS, Chew PTK, et al. Long-term outcomes in fellow eyes after acute primary angle closure in the contralateral eye. *Ophthalmology*. 2006;**113**:1087-1091
- [27] Alsagoff Z, Aung T, Ang LPK, Chew PT. Long-term clinical course of primary angle closure glaucoma in an Asian population. *Ophthalmology*. 2000;**107**:2300-2304
- [28] Ramani KK, Mani B, George RJ, Lingam V. Follow-up of primary angle closure suspects after laser peripheral iridotomy using ultrasound. *Journal of Glaucoma*. 2009;**18**(7):521-527
- [29] Das J, Bhomaj S, Chaudhuri Z, Sharma P, Negi A, Dasgupta A. Profile of glaucoma in a major eye hospital in North India. *Indian Journal of Ophthalmology*. 2001;**49**:25-30
- [30] Pandav SS, Kaushik S, Jain R, Bansal R, Gupta A. Laser peripheral iridotomy across the spectrum of primary angle closure. *Canadian Journal of Ophthalmology*. 2007;**42**:233-237
- [31] Van Herick W et al. Estimation of width of angle of anterior chamber

incidence and significance of the narrow angle. *American Journal of Ophthalmology*. 1969;**68**(4):626-629

[32] Foster PJ, Devereux JG, Alsbirk PH, et al. Detection of gonioscopically occludable angles and primary angle closure glaucoma by estimation of limbal chamber depth in Asians: Modified grading scheme. *The British Journal of Ophthalmology*. 2000;**84**(2):186-192

[33] Thomas R, George T, Braganza A, Muliyl J. The flashlight test and van Herick's test are poor predictors for occludable angles. *Australian and New Zealand Journal of Ophthalmology*. 1996;**24**(3):251-256

[34] Bhartiya S, Shaarawy T. Evaluation of the Van Herick technique for screening for occludable angles in an African population. *Journal of Current Glaucoma Practice*. 2013;**7**(2):88-90

[35] Quigley HA, Friedman DS, Hahn SR. Evaluation of practice patterns for the care of open-angle glaucoma compared with claims data: The glaucoma adherence and persistency study. *Ophthalmology*. 2007;**114**:1599-1606

[36] Stanley J, Huisinigh CE, Swain TA, McGwin J Jr, Oswley C, Girkin CA, et al. Compliance with primary open-angle glaucoma and primary open-angle glaucoma suspect preferred practice patterns in a retail-based eye clinic. *Journal of Glaucoma*. 2018;**27**:1068-1072

[37] Mukhopadhyay D, Patel K, Huda S. Increase in anterior chamber angle depth after topical pilocarpine measured by spectral domain optical coherence tomography: A possible additional indicator for laser peripheral iridotomy in primary angle-closure suspects in an opportunistic set-up. *Indian Journal of Ophthalmology*. 2022;**70**:4174-4179

[38] He M, Foster PJ, Johnson GJ, Khaw PT. Angle-closure glaucoma in East Asian and European people. Different diseases? *Eye*. 2006;**20**:3-12

[39] Rigi M, Bell NP, Lee DA, et al. Agreement between gonioscopic examination and swept source Fourier domain anterior segment optical coherence tomography imaging. *Journal of Ophthalmology*. 2016:1-8

[40] Coleman AL. Risk factor assessment and glaucoma screening. *Ophthalmology Clinics of North America*. 1 Sep 2000;**13**(3):349-359

[41] Kumar AU et al. Agreement of glaucoma specialists and experienced optometrists in gonioscopy and optic disc evaluation. *Journal of Optometry*. 2013;**6**:212-218

[42] Riva I, Micheletti E, Oddone F, Bruttini C, Montescani S, De Angelis G, et al. Anterior chamber angle assessment techniques: A review. *Journal of Clinical Medicine*. 2020;**9**:3814

[43] Saleem MS, Pasquale LR, Sidoti PA, Tsai JC. Virtual ophthalmology: Telemedicine in a Covid-19 era. *American Journal of Ophthalmology*. 2020;**216**:237-242

[44] Phu J, Wang H, Khou V, Zhang S, Kalloniatis M. Remote grading of the anterior chamber angle using gonioscopic photographs and optical coherence tomography: Implications for telemedicine or virtual clinics. *Translational Vision Science & Technology*. 2019;**8**:16

[45] Congdon NG, Spaeth GL, Augsburger J, Klancknik J Jr, Patel K, Hunter DG. A proposed simple method for measurement in the anterior chamber angle biometric gonioscopy. *Ophthalmology*. 1999;**106**:2161-2167

- [46] Thomas R. Letter to the editor biometric gonioscopy for measuring the anterior chamber angle. *Ophthalmology*. 2001;**108**:423-424
- [47] Kaushik S, Jain R, Pandav SS, Gupta A. Evaluation of the anterior chamber angle in Asian Indian eyes by ultrasound biomicroscopy and gonioscopy. *Indian Journal of Ophthalmology*. 2006;**54**:159-163
- [48] Fercher AF, Mengedocht K, Werner W. Eye-length measurement by interferometry with partially coherent light. *Optics Letters*. 1988;**13**(3):186-188
- [49] Sakata LM, Lavanya R, et al. Assessment of the scleral spur in anterior segment optical coherence tomography images. *Archives of Ophthalmology*. 2008;**126**(2):181-185
- [50] Hara N, Benedikt K, Owaki H. CASIA2: Anterior segment 3D swept-source OCT. In: Aramberri J, Hoffer KJ, Olsen T, Savini G, Shammas HJ, editors. *Intraocular Lens Calculations. Essentials in Ophthalmology*. Cham: Springer; 2024. pp. 417-429
- [51] Seager FE, Wang J, Arora KS, Quigley HA. The effect of scleral spur identification methods on structural measurements by anterior segment optical coherence tomography. *Journal of Glaucoma*. 2014;**23**(1):e29-e38
- [52] Bolo K, Apolo Aroca G, Pardeshi AA, et al. Automated expert-level scleral spur detection and quantitative biometric analysis on the ANTERION anterior segment OCT system. *British Journal of Ophthalmology*. 2024;**108**:702-709
- [53] Izatt A, Hee MR, Swanson EA, et al. Micrometer-scale resolution imaging of the anterior eye in vivo with optical coherence tomography. *Archives of Ophthalmology*. 1994;**112**(12):1584-1589
- [54] Radhakrishnan S, Rollins AM, Roth JE, et al. Realtime optical coherence tomography of the anterior segment at 1310 nm. *Archives of Ophthalmology*. 2001;**119**(8):1179-1185
- [55] Leung CK-S, Weinreb RN. Anterior chamber angle imaging with optical coherence tomography. *Eye (London, England)*. 2011;**25**(3):261-267
- [56] Sakata LM, Lavanya R, Friedman DS, et al. Comparison of gonioscopy and anterior segment ocular coherence tomography in detecting angle closure in different quadrants of the anterior chamber angle. *Ophthalmology*. 2008;**115**:769-774
- [57] Gimbert A, Campolmi N, Thuret G. Comparison of two anterior segment OCT CASIA Tomey versus OCT Visante Zeiss. *Acta Ophthalmologica. Abstracts from the 2013 European Association for Vision and Eye Research Conference*. 2013;**91**(s252):1755-3768
- [58] Fahmy RM. Comparative study between Pentacam and anterior segment OCT in measuring anterior segment parameters in myopic patients. *Journal of Medicine and Medical Sciences*. 2020;**11**(1):1-6
- [59] Leung CK, Cheung CY, Li H, Dorairaj S, Yiu CK, Wong AL, et al. Dynamic analysis of dark-light changes of the anterior chamber angle with anterior segment OCT. *Investigative Ophthalmology & Visual Science*. 2007;**48**(41):16-22
- [60] Lin J, Wang Z, Chung C, Xu J, Dai M, Huang J. Dynamic changes of anterior segment in patients with different stages of primary angle-closure in both eyes and normal subjects. *PLoS ONE*. 2017;**12**:e0177769
- [61] Bourne RR, Zhekov I, Pardhan S. Dynamic changes in iris parameters

under physiological conditions
-development of a predictive model
of angle closure risk. Investigative
Ophthalmology & Visual Science.
2019;**60**:6195

[62] Nolan WP, See JL, Chew PT,
Friedman DS, Smith SD,
Radhakrishnan S, et al. Detection of
primary angle closure using anterior
segment optical coherence tomography
in Asian eyes. *Ophthalmology*.
2007;**114**:33-39

[63] Radhakrishnan S. Diagnosing angle
closure: Gonioscopy vs. OCT. Review of
Ophthalmology. 2019. Available from:
<https://www.reviewofophthalmology.com/article/diagnosing-angle-closuregonioscopyvsoc> [Accessed: April 5, 2019]

[64] Tay EL, Yong VK, Lim BA, Sia S,
Wong EP, Yip LW. Agreement of
angle closure assessments between
gonioscopy, anterior segment optical
coherence tomography and spectral
domain optical coherence tomography.
International Journal of Ophthalmology.
2015;**8**:342-334

[65] Mehrotra AS, Gupta I, Chouhan BS.
Ultrasonic study to see the effect of
topical pilocarpine and homatropine
on anterior chamber depth in phakic
cases. *Indian Journal of Ophthalmology*.
1992;**40**:5-8

[66] Hung L, Yang CH, Chen MS. Effect
of pilocarpine on anterior chamber
angles. *Journal of Ocular Pharmacology
and Therapeutics*. 1995;**11**:221-226

[67] Kobayashi H, Kobayashi K, Kiryu J,
Kondo T. Pilocarpine induces an
increase in the anterior chamber angular
width in eyes with narrow angles. *The
British Journal of Ophthalmology*.
1999;**83**:553-558

Glaucoma Pharmacotherapy – Principles and Practice

Ashutosh Dayal

Abstract

Glaucoma is an irreversible disease requiring lifelong treatment. Although various treatment modalities have emerged, topical medications remain the first line of therapy for most cases. Multiple drugs are currently available in the glaucoma armamentarium; hence, knowledge about the mechanisms of action and adverse effects of all the agents becomes essential. With upcoming research and data from various large studies, the guidelines for glaucoma management have undergone a paradigm shift. However, optimizing the treatment can sometimes be challenging. Since target intraocular pressure is dynamic and highly individualized, the risk of under or overtreatment is significant. Moreover, factors such as the risk-to-benefit ratio in terms of adverse effects, disruption in daily activities, and cost of therapy have to be kept in mind while prescribing medical therapy for glaucoma. The treatment of glaucoma needs to be highly individualized – some eyes may need aggressive treatment, while others may not. This section covers some of the basic yet essential information regarding glaucoma pharmacotherapy and practice patterns.

Keywords: glaucoma management, antiglaucoma medications, glaucoma guidelines, target intraocular pressure, pharmacotherapy, maximum medical therapy

1. Introduction

Glaucoma is defined as “chronic progressive optic neuropathy characterized by structural changes in the optic nerve head with retinal ganglion cell loss.” [1] It is associated with characteristic irreversible visual field defects and may progress to blindness if left untreated. Although multifactorial, raised intraocular pressure (IOP) is the most important modifiable risk factor. Hence, lowering IOP remains the mainstay of glaucoma management. The results from Early Manifest Glaucoma Treatment trial have conclusively demonstrated the beneficial effect of IOP reduction in decreasing the rate of disease progression [2].

Glaucoma is the leading cause of irreversible blindness globally, affecting more than 80 million individuals worldwide [3]. This number is expected to rise to almost 111 million by the year 2040 [4, 5]. With such a high morbidity burden, early diagnosis and adequate management of glaucoma become critical to prevent the development of visual disability in such patients. The management of glaucoma revolves around reduction of IOP, which can be achieved either by medications, lasers, surgery, or

a combination of these. The subsequent sections will briefly touch upon the physiology of aqueous humor followed by details about glaucoma pharmacotherapy.

2. Physiology of aqueous humor pathway and glaucoma

2.1 Aqueous humor formation

IOP is directly dependent on the rate of production and outflow of aqueous humor in the eye. The rate of aqueous humor turnover is approximately $2.4 \pm 0.6 \mu\text{L}/\text{minute}$ in an adult eye, with diurnal variations[6]. Aqueous humour is produced in the epithelium of the ciliary processes. It is composed of water, electrolytes, proteins, cytokines, organic solutes, and growth factors necessary to nourish the avascular structures in the anterior chamber. Diffusion, ultrafiltration, and active secretion are three important processes involved in aqueous production. Lipid-soluble substances are passively transported across tissues through diffusion, in accordance with the concentration gradient. Water-soluble substances and proteins, limited by size and charge, are transported through ultrafiltration via fenestrations in the ciliary capillary endothelia. The main site for active secretion is the nonpigmentary epithelium of the ciliary processes and is mediated by protein transporters distributed within the cell membrane. Active secretion accounts for more than 80% of aqueous synthesis [6]. Aquaporins 1 and 4 are water channels that aid in the active transport of fluids across the blood-aqueous barrier, facilitated by the enzyme $\text{Na}^+ \text{K}^+ \text{ATPase}$ located on the ciliary epithelium.

Presence of alpha adrenergic receptors (mainly α_2) in ciliary blood vessels and beta receptors on ciliary epithelium are important for neuronal control regulating aqueous production. Stimulation of α_2 receptors reduces, while stimulation of β_2 receptors increases the rate of aqueous formation. Another enzyme, carbonic anhydrase, located on nonpigmented ciliary body epithelium, forms bicarbonate (HCO_3^-) by reversible hydration of CO_2 , which is then transported across the ciliary epithelium. Bicarbonate plays an important role in aqueous humor production by facilitating the transport of Na^+ ions and regulating pH to facilitate ion transport. The resulting osmotic gradient facilitates water transport through aquaporins. Pharmacological agents inhibiting $\text{Na}^+ \text{K}^+ \text{ATPase}$ (cardiac glycosides, dinitrophenol) or carbonic anhydrase (carbonic anhydrase inhibitors [CAI]) can reduce aqueous humor formation [7].

Aqueous humor traverses the capillary wall, stroma, and epithelial bilayer of the ciliary process to reach the posterior chamber. It flows around the crystalline lens and through the pupil to reach the anterior chamber.

2.2 Outflow of aqueous humor

2.2.1 Conventional pathway

Aqueous humor exits the eye through a conventional (trabecular meshwork) and a nonconventional pathway (uveoscleral outflow). Drainage through the trabecular meshwork into Schlemm's canal accounts for nearly 90% of aqueous drainage.

Trabecular meshwork is a porous structure and acts as a filter that drains aqueous humor passively, depending on the IOP levels [8]. Aqueous humor reaches

Schlemm's canal, a specialized vessel composed of endothelium-lined connective tissue. From Schlemm's canal, collectors drain aqueous humor into the systemic circulation via episcleral veins.

2.2.2 Nonconventional pathway (uveoscleral outflow)

A small amount of aqueous (10%) drains through the nonconventional uveoscleral pathway. The aqueous, instead of entering the trabecular meshwork, passes between the ciliary muscle bundles into the supraciliary and suprachoroidal spaces [9]. It further drains into the sclera, from where it reaches systemic circulation via lymphatics. It is important to note that, in a healthy eye, uveoscleral outflow decreases with age and is considered to be relatively independent of IOP and circadian rhythm [10, 11].

2.3 Pathogenesis of glaucomatous optic neuropathy

2.3.1 Mechanical effect of raised IOP

Raised IOP is the most important, but not the only, cause of glaucomatous damage to the retinal ganglion cell. According to the mechanical theory, a rise in IOP increases the pressure gradient across the lamina cribrosa, leading to pressure-induced backward bowing of the lamina [12]. This results in subsequent deformation and mechanical stress to the retinal ganglion cells. Mechanical stress can induce both direct and indirect damage to the retinal ganglion cells [13]. This stress obstructs both anterograde and retrograde axoplasmic flow of the optic nerve. Obstruction of retrograde axoplasmic flow impedes the movement of neurotrophic factors, resulting in apoptotic cell death [14]. Additionally, deposition of various forms of extracellular matrix proteins alters the biomechanical environment of the optic nerve, leading to changes characteristic of glaucomatous optic neuropathy.

2.3.2 Role of reduced vascular perfusion

Current evidence strongly suggests the role of poor vascular perfusion to the optic nerve head in the pathogenesis of glaucoma [15, 16]. This reduced blood supply leads to oxidative stress and progressive ischemic damage to the retinal ganglion cells. Oxidative stress can reduce energy supplies, hamper intracellular homeostasis of ions such as calcium, promote oxidative damage to proteins, lipids, and DNA, and subsequently induce neurodegeneration.

Hence, ocular perfusion pressure is a key factor in the pathogenesis of glaucomatous optic neuropathy. Ocular perfusion pressure (OPP) can be thought of as the pressure at which blood enters the eye and can be mathematically calculated as [16]:

$$\text{OPP} = 2/3[\text{Diastolic BP} + 1/3(\text{Systolic BP} - \text{Diastolic BP})] - \text{IOP}$$

OPP depends on various ocular and systemic risk factors, including IOP. Raised IOP may cause mechanical compression of ocular vasculature or affect hemodynamic by reducing the perfusion to the optic nerve head and retinal ganglion cells. Hence, IOP has a central role to play in this paradigm as well.

3. Pharmacotherapy for glaucoma

Glaucoma management has evolved significantly over the past few decades owing to the availability of multiple IOP-lowering molecules. As mentioned earlier, the main aim of treatment is to retard disease progression through lowering of IOP. Currently, the treatment options include topical and systemic medications, laser procedures (selective laser trabeculoplasty, laser iridotomy), glaucoma filtering surgeries (trabeculectomy, glaucoma drainage device), and the newer minimally invasive glaucoma surgeries (MIGS). The line of treatment depends on factors such as patient profile, glaucoma severity, and surgeon and patient choices. However, in this chapter, the discussion will be limited to the medical management of glaucoma.

3.1 Prostaglandin analogs

Although nine subtypes of prostaglandin receptors, viz. PGE (EP1-4), PGD (DP1-2), PGFP, PGIP, and Thromboxane A₂ receptors, are found in the human body, only PGE and PGFP are predominantly located within the eye [17]. Prostaglandin analogues bind to receptors located on the cell membrane to elicit their effect. PGF 2 α analogues have demonstrated good affinity for FP, EP1, and EP3 receptors, resulting in an IOP-lowering effect [18]. Clinically used PGF₂ α derivatives are Latanoprost, Bimatoprost, Travoprost, Tafluprost, and Unoprostone. The IOP-lowering effect of prostaglandin analogues is mediated through an increase in uveoscleral outflow. These molecules bind to the EP and FP receptors and cause ciliary muscle relaxation, thereby increasing the nonconventional outflow. Moreover, binding of these molecules to FP receptors induces the expression of matrix metalloproteinase (MMP) and other tissue-remodeling enzymes, which degrade the extracellular matrix within the ciliary spaces and cause dilatation of connective tissue spaces, thereby facilitating aqueous outflow through the uveoscleral pathway. It is interesting to note that, apart from the FP receptor, Bimatoprost has high affinity for PGE₁ and PGE₃ receptors that are located on the trabecular meshwork and Schlemm's canal. It is postulated that modulation of outflow facility through the trabecular meshwork (conventional pathway) might be another mechanism responsible for IOP reduction by prostaglandin analogues [19, 20].

Peak IOP-lowering effect of prostaglandin analogues ranges between 28% and 31% [21] and lasts for roughly 24 hours postinstillation, with a drug washout period of four to six weeks. Prostaglandin analogues have now become the first line of treatment for primary open-angle glaucoma owing to ease of dosing and lack of serious systemic side effects.

Ocular adverse effects include conjunctival hyperemia (maximum with bimatoprost, least with latanoprost), trichomegaly, increased iris pigmentation, periocular iris pigmentation, reactivation of herpetic keratitis, cystoid macular edema and prostaglandin-associated periorbitopathy. No absolute contraindication exists for the use of prostaglandin analogues; however, relative contraindications include eyes with active uveitis, preexisting macular edema, those with a prior history of herpetic uveitis, allergic reaction to the molecule, and in unilateral glaucoma (due to intra and periocular pigmentation).

It is interesting to note that, unlike other classes of antiglaucoma medications, if one molecule seems ineffective in controlling the IOP in a particular patient,

switching to a different molecule from the same class may be attempted before switching to a different class of drugs.

3.2 Beta-adrenergic receptor antagonist (beta blocker)

β -adrenergic receptors play a crucial role in regulating aqueous humor formation. Both β_1 and β_2 receptors are present in the eye, with the latter being more predominant. Upon sympathetic stimulation, these receptors increase aqueous secretion through a cyclic AMP-mediated pathway. β receptor antagonists decrease the rate of aqueous production by reducing the intracellular concentrations of cyclic AMP [22]. These drugs are relatively rapid-acting, with an estimated 20–25% decrease in IOP from the baseline [23]. However, the effect of β -adrenergic receptors on aqueous formation demonstrates diurnal variations. As mentioned earlier, the rate of aqueous formation is higher during the day, owing to higher sympathetic activity, compared to night time. An interesting phenomenon associated with the use of β -adrenergic antagonists is the concept of “escape.” The first dose of beta blocker produces maximum IOP lowering compared to subsequent doses. This rapid reduction in IOP-lowering efficacy over a short duration is termed “beta-blocker escape.” However, this effect seems to stabilize over a certain period of time.

Commercially available beta blockers include Timolol and Levobunolol, which are nonselective, that is, they have equal efficacy for both β_1 and β_2 receptors, and Betaxolol, which is a β_1 -selective molecule.

Beta blockers, though well-tolerated, are occasionally associated with systemic adverse effects that restrict their use in susceptible individuals. These adverse effects occur due to systemic absorption of the drug through conjunctival vessels or nasal mucosa and are attributed to underlying β receptor blockade. These adverse effects include worsening of chronic obstructive pulmonary disease, bradyarrhythmia, worsening of congestive cardiac failure, deranged lipid profile, depression, masking of hypoglycemic symptoms, and erectile dysfunction. Hence, beta-blockers are better avoided in individuals with preexisting COPD, asthma, atrioventricular blocks, decompensated congestive cardiac failure, and dyslipidemia. Although β_1 -selective Betaxolol is comparatively safer in individuals with COPD, caution must be exercised while prescribing. Punctal occlusion after drug instillation can significantly reduce systemic absorption. Ocular side effects, though rare, include dry eye, punctate keratitis, and ocular stinging.

3.3 Alpha adrenergic receptor agonist

IOP-lowering properties of Clonidine were initially described in the 1960s. However, owing to the high incidence of systemic adverse effects, the drug was soon withdrawn. Apraclonidine and Brimonidine are the second and third-generation alpha agonists used in the treatment of glaucoma. Of the two, Brimonidine has a better safety profile and is the preferred molecule. Brimonidine has selective affinity for α_2 receptors and acts by activating presynaptic alpha-2 receptors located in the ciliary epithelium. This causes decreased catecholamine release and cyclic AMP concentration, which, in the ciliary body epithelium, leads to decreased aqueous production. Importantly, alpha-agonists have been shown to increase uveoscleral outflow by modulating the expression of MMP, thereby stimulating the degradation of the extracellular matrix [24]. The latter mechanism is responsible for

the IOP-lowering effect after long-term topical therapy. The onset of action starts within one hour of drug instillation, with peak effect within two to three hours. Adverse effects of topical Brimonidine include systemic hypotension, day time drowsiness, dry eye, dry mouth, fatigue, follicular conjunctivitis, conjunctival hyperemia, periocular pruritus, and drug allergy. Brimonidine can cross the blood-brain barrier, resulting in respiratory depression in young children. Hence, its use is contraindicated in children below two years of age and should be used with utmost caution in children up to six years of age. Similarly, it should be avoided in patients on monoamine oxidase (MAO-A) inhibitors due to the risk of drug interactions. Brimonidine is labeled as Category B and can be used as a first-line treatment for glaucoma in pregnancy [25]. However, it should be discontinued at least two months prior to delivery to prevent any possible postpartum central nervous system depression and apnea in the fetus.

3.4 Carbonic anhydrase inhibitors

Carbonic anhydrase plays a vital role in aqueous humor formation by converting CO₂ into bicarbonate (HCO₃⁻) ions. Bicarbonate is thought to influence fluid transport via pH-dependent sodium transport [26]. Carbonic anhydrase inhibitors (CAI), by preventing the conversion of CO₂ into bicarbonate, reduce the rate of aqueous production. The IOP-lowering effect of CAI (Acetazolamide) has been long known [27]. Currently, systemic (Acetazolamide) and topical (Dorzolamide 2% and Brinzolamide 1%) CAI are approved and commercially available for use in glaucoma. Acetazolamide is a first-generation CAI and inhibits the activity of all isoforms of carbonic anhydrase found in the human body. It is administered systemically and leads to systemic adverse effects and poor long-term compliance. Adverse effects of systemic CAI include paresthesia, hypokalaemia, gastric disturbances, metabolic acidosis, renal calculi, and Stevens-Johnson syndrome (rare). Topical CAI selectively inhibits carbonic anhydrase isoforms II and XII, which are predominantly located on the ciliary epithelium. The onset of action starts within two to three hours of instillation, achieving an IOP reduction of 15–22% from the baseline [26]. Ocular side effects include ocular stinging upon instillation, punctate keratitis, metallic taste in the mouth, and granulomatous anterior uveitis (rare). It can precipitate corneal edema in eyes with compromised endothelial cell count. Hence, caution is advised when using CAI in eyes with low endothelial cell count or those with preexisting corneal edema.

Recently, the neuroprotective role of topical CAI is under evaluation. Experimental studies have demonstrated increased retinal and optic nerve head blood flow in glaucomatous eyes treated with topical CAI. However, the clinical relevance of these findings in terms of neuroprotection still remains unclear. A few randomized trials have shown promising results; on the other hand, the European Glaucoma Prevention Study (EGPS) failed to demonstrate conclusive evidence regarding the neuroprotective effect of CAI [28, 29].

3.5 Rho-kinase inhibitors (ROCK inhibitors)

Rho kinase (ROCK), or Rho protein-associated protein kinase, is a type of serine/threonine kinase. Activated ROCKs increase the phosphorylation of substrates such as myosin light chain and calmodulin, leading to changes in

myoglobin/actin contractility, cell morphology, and matrix synthesis [30]. ROCK inhibitors are a novel class of drugs that block the activation of Rho protein-associated kinase and have been approved for use in glaucoma. These molecules reduce IOP by facilitating aqueous outflow through the trabecular meshwork and decreasing episcleral venous pressure. The mechanism of action involves the inhibition of phosphorylation of the myosin light chain, which leads to reduced resistance in the trabecular meshwork. Moreover, ROCK inhibitors modulate smooth muscle morphology, causing vasodilation and decreased episcleral venous pressure [31].

There is evidence of a possible neuroprotective role for this class of drugs. It is hypothesized that the vasodilatory effect of ROCK inhibitors likely increases optic nerve head perfusion, thereby reducing ganglion cell loss [30]. Also, animal models have demonstrated antiapoptotic properties. However, the clinical implications of these findings are still under evaluation.

Currently, Ripasudil (0.4%) and Netarsudil (0.02%) are the two commercially available molecules. Both have shown good IOP-lowering efficacy and are presently used as adjuvant therapy for glaucoma. ROCK inhibitors have demonstrated a 15–20% drop in IOP from baseline. The recommended doses are two times a day for Ripasudil and once a day for Netarsudil. No serious systemic adverse effects have been reported from either of the molecules. Ocular adverse effects include conjunctival hyperemia, subconjunctival hemorrhages and cornea verticillata. Some cases of reversible reticular or honey comb keratopathy have been reported with the use of Netarsudil.

3.6 Parasympathomimetic agents

Parasympathomimetic agents act upon the cholinergic receptors located on the iris sphincter and ciliary muscles. These agents induce muscarinic M3 receptor-mediated contraction of ciliary smooth muscles. Muscle contractions pull the scleral spur along, resulting in the widening of the trabecular meshwork and increased outflow. The effect of parasympathomimetic agents on the iris sphincter induces miosis, which pulls the peripheral iris away from the trabecular meshwork, thereby widening the angle. The second mechanism is more significant in eyes with narrow angles. Pilocarpine is the best-known molecule of this group, and it has been extensively used for glaucoma management since the 1870s. Pilocarpine demonstrates good efficacy with around a 20–25% drop in IOP from baseline [23]. Local adverse effects associated with pilocarpine include blurred vision due to miosis and accommodative myopia, conjunctival hyperemia, lens opacities, retinal detachments, and precipitation of angle-closure attacks in eyes with iris cysts. Systemic adverse effects, though less common, include headache, intestinal cramps, hypotension, and bronchospasm.

3.7 Newer advances in glaucoma pharmacotherapy

3.7.1 Selective EP2 receptor agonist

Recently, a newer molecule, Omidenepag Isopropyl (OMDI), has been approved for use in glaucoma. It is a nonprostaglandin analog acting on the PGE2 receptors. Upon corneal penetration, OMDI converts into the active metabolite omdidenepag.

This molecule, through its action on PGE2 receptors located within the ciliary body and trabecular meshwork, increases intracellular cyclic AMP, thereby increasing uveoscleral as well as trabecular outflow [32]. The efficacy is similar to that of other prostaglandin analogues. Adverse effects include pain on instillation, conjunctival hyperemia, iris pigmentation, periocular pigmentation, and cystoid macular edema. Interestingly, the incidence of prostaglandin-associated periorbitopathy has not been reported with the use of OMDI, probably as it acts only on PGE2 receptors, unlike conventional prostaglandin analogues [33].

3.7.2 Latanoprostene bunod

Latanoprostene bunod (VYZULTA[®]) is a novel molecule with dual action, recently approved for the management of primary open-angle glaucoma. LBN undergoes hydrolysis in the cornea to latanoprost acid and a nitric oxide (NO)-donating moiety. The latanoprost acid (latanoprost metabolite) increases uveoscleral outflow, while the nitric oxide released promotes trabecular outflow via cytoskeletal rearrangement. Some studies have shown a higher IOP lowering effect when compared to monotherapy with latanoprost or timolol [34, 35].

3.7.3 Intracameral bimatoprost implant (DURYSTA[®])

It is a novel sustained drug delivery system, approved by the FDA for the management of primary open-angle glaucoma and ocular hypertension [36]. It is a biodegradable sustained-release implant containing 10 µg of Bimatoprost that is directly implanted in the anterior chamber. The device releases the drug in a sustained manner and has shown good IOP reduction for a period of 4 to 6 months [37].

4. Goals of glaucoma management

The primary goal of glaucoma management is to reduce the rate of retinal ganglion cell loss, thereby halting disease progression. This can be achieved by lowering IOP. As mentioned above, the benefits of reducing IOP cannot be understated. Modalities to reduce IOP include topical and systemic medications, lasers, and surgery. The Early Manifest Glaucoma Trial, a randomized clinical trial evaluating the role of IOP reduction in glaucoma progression, was one of the early trials to prove the efficacy of IOP reduction. One of the significant findings of the trial was that even a 1 mm Hg reduction in IOP from baseline can reduce the progression of visual field defects by almost 10% [2].

4.1 Concept of “target intraocular pressure”

While treating eyes with glaucoma, the question often arises: how much should the IOP be lowered? IOP lowering should be sufficient to halt disease progression while avoiding over treatment. In recent decades, after analyzing data from various randomized trials, the concept of target IOP was introduced. Target IOP is a presumptive value that is expected to prevent further glaucomatous damage in the diseased eye [38]. In other words, it is the value of IOP that stabilizes the disease. The

World Glaucoma Association has defined target IOP as an “estimate of the mean IOP at which the risk of decreased vision-related quality of life due to glaucoma exceeds the risk of the treatment” [39]. It should be borne in mind that target IOP is not a single fixed value but is highly dynamic and individualized. It varies for different individuals and is dependent on disease severity, life expectancy, rate of disease progression, and the presence of other risk factors such as thin pachymetry and systemic factors [23]. Ideally, target IOP values have to be calibrated individually for each patient, taking into account all the ocular and systemic risk factors for progression, as well as preventing over treatment. Some of the methods mentioned for the estimation of target IOP include:

- **Threshold/absolute cut-off value:** It is a fixed cut-off value of IOP based on disease severity and can be applied to a large group of patients with similar glaucomatous damage. Many studies have reported the cut-off “success” values to be <18 mmHg for early, <15 mmHg for moderate, and <12 mmHg for advanced damage.
- **Percentage reduction:** It is based on a fixed percentage reduction in IOP from baseline. Various “cut-off” values for percentage drop in IOP have been reported in large randomized controlled trials, with varying rates of progression (Refer **Table 1**) [8].
- **Formula-based values:** Attempts have been made to derive a formula for the calculation of target IOP. One of the earliest formulae published was based on patient attributes such as initial pretreatment IOP, Z score (an indicator of disease severity), and burden of therapy (Y factor) [45].

$$\text{Target IOP} = (\text{Initial IOP} \times [1 - \text{initial pressure}/100]) - Z + Y \pm 1 \text{ mmHg}$$

Similarly, the formula used for the Collaborative Interventional Glaucoma Treatment Study (CIGTS) was based on initial or baseline IOP and initial visual field scores (VFI) [8].

However, no conclusive evidence exists to support any of these algorithms for calculating target IOP. Initially, the target IOP should be set considering the patient's disease severity. An initial reduction in IOP of more than 20% from the

Study	IOP reduction	Progression (treatment vs. control)
OHTS[40]	20%	4.4% vs. 9.2%
EMGT[41]	25%	45% vs. 62%
CIGTS[42]	38%	15%
CNTGS[43]	30%	12%vs. 35%
AGIS[44]	40%	No progression

OHTS: Ocular Hypertension Treatment Study; EMGT: Early Manifest Glaucoma Trial; CIGTS: Collaborative Initial Glaucoma Treatment Study; CNTGS: Collaborative Normal Tension Glaucoma Study; AGIS: Advanced Glaucoma Intervention Study

Table 1.
Percentage of intraocular pressure reduction in various landmark trials.

baseline for early glaucoma and more than 30% or around the mid to low teens for moderate to advanced glaucoma is usually recommended [46]. During later follow-ups, the target IOP can be titrated for each eye based on progression analysis. Some of the important factors determining the target IOP include disease severity, life expectancy, rate of progression of visual field loss, baseline IOP, and other risk factors such as thin central corneal thickness, positive family history, etc (See **Figure 1**). [38].

A young patient with advanced visual field loss and rapid deterioration will need a lower target IOP compared to an elderly individual with moderate field loss and no other risk factors.

While determining the target IOP, one should always be wary of “overtreating” the patient. It is always important to consider the risk-benefit ratio and the cost-benefit ratio of the treatment. The potential adverse effects or risks associated with treatment should not outweigh the benefits.

4.2 Problems associated with glaucoma pharmacotherapy

Glaucoma, being a chronic disease, requires lifelong treatment to prevent deterioration of visual function. Presently, topical medications are routinely used as first-line therapy in the management of glaucoma. However, chronic use of topical or

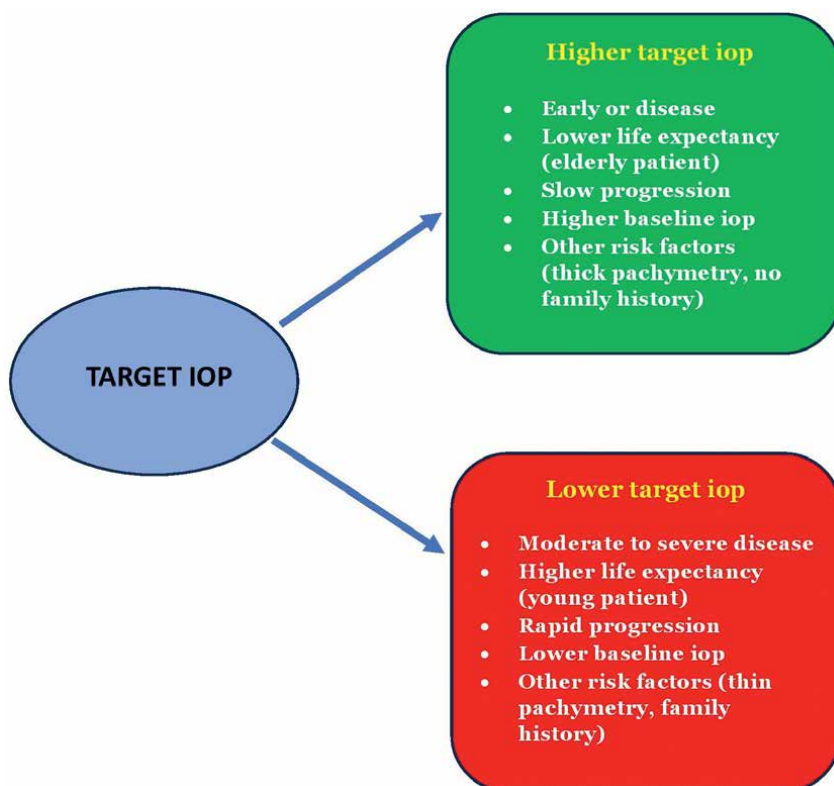


Figure 1.
Factors determining target intraocular pressure.

systemic medications is associated with potential adverse effects that may negatively affect the daily functioning of an individual. The European Glaucoma Society has defined the goal of glaucoma management as “maintaining the patient’s visual function and related quality of life, at a sustainable cost” [38]. Hence, overall quality of life should be given equal emphasis while managing glaucoma.

Drug-related adverse effects: As mentioned previously, chronic use of glaucoma medications is associated with ocular and systemic side effects. These include mild symptoms such as ocular stinging from CAI to beta-blocker-associated exacerbation of COPD. Studies have reported an increased incidence of dry eye and ocular surface disease (OSD) in patients on chronic antiglaucoma therapy [47, 48]. Changes at the cellular level, including conjunctival stromal thickening and loss of goblet cells, are associated with long-term use of antiglaucoma medications [49]. Other adverse effects, such as day time drowsiness (brimonidine) and conjunctival hyperemia (brimonidine and ROCK inhibitors), might negatively affect the professional and social functioning of an individual.

Role of preservatives: Preservatives are additives added to extend the shelf-life of an ophthalmic preparation. However, these preservative agents destabilize the cell membrane, causing reduced cell surface adhesion in healthy corneal and conjunctival tissue. This may give rise to OSDs, including superficial punctate keratitis, corneal erosions, papillary conjunctivitis, and dry eye with low tear film break-up time [50]. Chronic exposure to preservatives over time accentuates the symptoms of OSD, thereby resulting in ocular discomfort [51].

Although preservative-free preparations are now commercially available, their long-term superiority is still not conclusively proven.

Frequent drug administration: Occasionally, patients require multiple antiglaucoma agents to achieve the “target IOP.” However, this results in an increase in the number of bottles and frequency of instillation. Higher frequency of drug administration can impair daily functioning and may lead to treatment noncompliance. Similarly, for elderly patients with movement disorders, such as tremors or Parkinson's disease, self-instillation of topical medication frequently might be a tedious task. Commercially available fixed-dose combinations should be preferred wherever multiple drugs are prescribed.

Cost of treatment: Since glaucoma patients need lifelong treatment and follow-up, the overall recurrent cost of treatment can be a significant factor affecting treatment compliance. This factor is important in developing and underdeveloped countries, which lack social security for all.

The above-mentioned factors do play an important role in affecting the quality of life of the patients, apart from the visual field disability caused by glaucoma per se. These factors can occasionally lead to poor treatment compliance, which can further deteriorate the disease and should be considered while initiating pharmacotherapy for glaucoma.

The newer surgical techniques, such as MIGS and selective laser trabeculoplasty (SLT), have been advocated as the first-line treatment by some authors. These procedures are relatively free from some of the problems associated with long-term medication use. However, these procedures have their own set of limitations, and therefore, for the time being, topical glaucoma medications still remain the most favored first-line therapy for glaucoma management.

4.3 Strategies for glaucoma management

- **Patient selection:** Proper patient selection is essential before starting topical medication. Basic queries that one may ask are “whom to treat” and “how much to treat?” Patient factors that may influence the choice of therapy include systemic and ocular conditions, severity and rate of progression of glaucoma, compliance, and the choice of the patient. As mentioned in the previous section, patients with movement disorders and advanced disease might find the instillation of medications difficult; early surgical treatment might be considered for them. Similarly, professionals with long working hours or excessive traveling are likely to miss medication, leading to non-compliance. A minimally invasive glaucoma surgery or an SLT might be a better first-line option in such cases. SLT can be considered as a first-line therapy for glaucoma in pregnancy, wherein most available medications have a doubtful safety profile.
- **Drug selection:** Selection of a drug usually depends on the drug profile as well as the patient profile. The safety profile of the medication should match the systemic and ocular status of the patient. For example, one would avoid prescribing a beta blocker to an individual with COPD due to the risk of exacerbation. Similarly, prostaglandin analogues should be avoided in unilateral glaucoma in view of the risk of periocular pigmentation. Although any of the topical agents can be used as the first-line drug, factors such as dosing schedule, efficacy, and adverse effects usually play a part in the selection of the drug. The medication selected should have a good safety and tolerability profile, be affordable, and have the greatest chance of reaching the target IOP [46]. Prostaglandin analogues are usually preferred as first-line medication due to ease of dosing (once a day), good efficacy, and no systemic adverse effects [52]. In the event of a contraindication to prostaglandin analogues, a beta blocker or a CAI can be used as the first-line drug.
- **Medication should be prescribed as monotherapy initially, except in cases of very high IOP and advanced field loss, where it might be necessary to start with more than one agent.** The minimum strength and dose of medication required to achieve the desired therapeutic outcome should be advised.
- **Assessment of efficacy and tolerance:** Patients should be reviewed to assess efficacy and tolerability of the medication. A drug is considered effective if the IOP reduction after treatment is comparable to the published range for that drug [23] (e.g., 20–25% for timolol). However, it is important to note that efficacy should be assessed after at least two to four weeks of starting the treatment. A drug is considered ineffective if the IOP-lowering response is inadequate (less than 20% from baseline).
- **If the response to the medication is ineffective or inadequate, treatment adherence and the method of instillation should be checked.** Lid closure for at least two minutes postinstillation and punctal occlusion should be demonstrated to all patients at the first visit in the clinic.

- **Inadequate response to a drug:** In case of an inadequate response, it is advisable to switch to a molecule from a different class as monotherapy, instead of adding a second drug to the existing one. However, individual variability exists in response to different prostaglandin analogues. An individual may be more responsive to one prostaglandin analog than the others, and hence, switching to a different molecule from the same class (prostaglandin analog) can be attempted in such cases.
- **Adding a second medication:** The addition of a second molecule is recommended if the reduction in IOP is insufficient to reach target IOP levels, despite good efficacy observed with the first molecule. The second drug should not have the same pharmacological action as that of the first drug. The patient should be reassessed for efficacy and tolerability. In case the second medication shows efficacy, a fixed-dose combination can be considered, in view of better tolerability, an easier dosing regimen, and lesser exposure to preservatives.
- **If the combination therapy fails to achieve the desired IOP goal,** despite both molecules demonstrating good efficacy, a third molecule may be added. However, it should be borne in mind that the efficacy of adjuvant molecules decreases as the number of drugs increases.
- **Other treatment modalities,** such as selective laser trabeculoplasty and MIGS, can be used as adjuvants for IOP control in patients not achieving target IOP with two or more medications or those who are intolerant to topical medications.
- **At baseline and subsequent follow-up,** eyes should be evaluated for signs of OSD, such as dry eye, punctate keratitis, allergic conjunctivitis, and meibomian gland dysfunction.
- **In case of preexisting OSD or allergy to any preservative,** the use of preservative-free formulations is recommended.

4.4 Role of preservative-free preparations

The deleterious effect of preservatives on the ocular surface has been extensively discussed in the literature. It is more commonly reported in patients with glaucoma, as they have to use topical medications containing preservatives for many years. Consequently, preservative-free preparations of common antiglaucoma medications are commercially available. Studies have demonstrated comparable IOP-lowering efficacy of preparations with and without preservatives. Hence, the question arises: Should preservative-free preparations be used universally for all patients? Eyes with preexisting OSD have demonstrated better OSD scores and tear break up time with the use of preservative-free medications when compared to those with preservatives. However, in eyes without preexisting OSD, no conclusive difference has been observed [53, 54]. Owing to the limited availability and higher cost of preservative-free medications, the use of preservative-free preparations is recommended for eyes with preexisting OSD, those with allergies to preservatives, and those on multiple

medications. Considering the cost-benefit analysis, conclusive evidence for the universal use of preservative-free preparations, especially for those without OSD, is currently lacking.

5. Conclusion

Patients with glaucoma require lifelong treatment, which might need modification intermittently during the course of treatment. Thus, the knowledge of using topical medications is mandatory for every clinician. It should be kept in mind that the primary aim of glaucoma management is to reduce disease progression without affecting the quality of life of the patients. Studies have associated glaucoma with psychological effects; hence, a holistic approach to glaucoma care that includes instructions for the instillation of medications and motivational counseling should be a part of routine glaucoma practice [55, 56].

Author details

Ashutosh Dayal
Subodh Agarwal Memorial (SAM) Eye Hospital, Lucknow, India

*Address all correspondence to: adayal007@gmail.com

IntechOpen

© 2025 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. 

References

- [1] Mahabadi N, Zeppieri M, Tripathy K. Open Angle Glaucoma [Internet]. StatPearls Publishing; 2024. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK441887/> [Accessed: 2025-July-6]
- [2] Heijl A. Reduction of intraocular pressure and glaucoma progression: Results from the Early Manifest Glaucoma Trial. *Archives of Ophthalmology*. 2002;**120**(10): 1268–1279
- [3] Quigley HA. The number of people with glaucoma worldwide in 2010 and 2020. *British Journal of Ophthalmology*. 2006;**90**(3):262–267
- [4] 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**:2081–2090
- [5] Pascolini D, Mariotti SP. Global estimates of visual impairment: 2010. *British Journal of Ophthalmology*. 2012;**96**(5):614–618
- [6] Gabel B, Kaufman P. Aqueous humor hydrodynamics. In: Hart WM, editor. *Adler's Physiology of the Eye*. St Louis: Mosby; 2003
- [7] Goel M, Picciani RG, Lee RK, Bhattacharya SK. Aqueous humor dynamics: A review. *The Open Ophthalmology Journal*. 2010;**4**(1):52
- [8] Sihota R, Angmo D, Ramaswamy D, Dada T. Simplifying “Target” intraocular pressure for different stages of primary open-angle glaucoma and primary angle-closure glaucoma. *Indian Journal of Ophthalmology*. 2018;**66**(4):495
- [9] Nilsson SFE. The uveoscleral outflow routes. *Eye*. 1997;**11**(2):149–154
- [10] Brubaker RF. Measurement of uveoscleral outflow in humans. *Journal of Glaucoma*. 2001;**10**(5):S45–48
- [11] Liu H, Fan S, Gulati V, Camras LJ, Zhan G, Ghate D, et al. Aqueous humor dynamics during the Day and Night in healthy mature volunteers. *Archives of Ophthalmology* 2011;**129**:269–275
- [12] Jonas JB, Berenshtein E, Holbach L. Anatomic relationship between lamina cribrosa, intraocular space, and cerebrospinal fluid space. *Investigative Ophthalmology & Visual Science*. 2003;**44**(12):5189–5195
- [13] Halpern DL, Grosskreutz CL. Glaucomatous optic neuropathy: Mechanisms of disease. *Ophthalmology Clinics of North America*. 2002;**15**(1):61–68
- [14] Pease ME, McKinnon SJ, Quigley HA, Kerrigan-Baumrind LA, Zack DJ. Obstructed axonal transport of BDNF and its receptor TrkB in experimental glaucoma. *Investigative Ophthalmology & Visual Science*. 2000;**41**(3):764–774
- [15] Cherecheanu AP, Garhofer G, Schmidl D, Werkmeister R, Schmetterer L. Ocular perfusion pressure and ocular blood flow in glaucoma. *Current Opinion in Pharmacology*. 2013;**13**(1):36
- [16] Weinreb R, David G, Gupta N, Liebmann J, Ritch R, Varma R. Ocular

- Perfusion Pressure in Glaucoma [Internet]. Available from: <https://www.nyee.edu/health-professionals/cme/enduring-activities> [Accessed: 2025-June-24]
- [17] Subbulakshmi S, Kavitha S, Venkatesh R. Prostaglandin analogs in ophthalmology. *Indian Journal of Ophthalmology*. 2023; **71**(5):1768
- [18] Winkler NS, Fautsch MP. Effects of prostaglandin analogues on aqueous humor outflow pathways. *Journal of Ocular Pharmacology and Therapeutics*. 2014;**30**(2–3):102
- [19] Wang JW, Woodward DF, Stamer WD. Differential effects of prostaglandin E2 -sensitive receptors on contractility of human ocular cells that regulate conventional outflow. *Investigative Ophthalmology & Visual Science*. 2013;**54**(7):4782
- [20] Christiansen GA, Nau CB, McLaren JW, Johnson DH. Mechanism of ocular hypotensive action of bimatoprost (Lumigan) in patients with ocular hypertension or glaucoma. *Ophthalmology*. 2004;**111**(9):1658–1662
- [21] Van Der Valk R, Webers CAB, Jsag S, 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**(7):1177–1185
- [22] Grieshaber MC, Flammer J. Is the medication used to achieve the target intraocular pressure in glaucoma therapy of relevance? – An exemplary analysis on the basis of two beta-blockers. *Progress in Retinal and Eye Research*. 2010; **29**(1):79–93
- [23] Spaeth GL. European glaucoma society terminology and guidelines for glaucoma, 5th edition. *British Journal of Ophthalmology*. 2021;**105**(Suppl 1):1–169
- [24] Oh DJ, Chen JL, Vajaranant TS, Dikopf MS. Brimonidine tartrate for the treatment of glaucoma. *Expert Opinion on Pharmacotherapy*. 2019;**20**(1):115–122
- [25] Salim S. Glaucoma in pregnancy. *Current Opinion in Ophthalmology*. 2014;**25**(2):93–97
- [26] Stoner A, Harris A, Oddone F, Belamkar A, Vercellin ACV, Shin J, et al. Topical carbonic anhydrase inhibitors and glaucoma in 2021: Where do we stand? *British Journal of Ophthalmology* 2021;**106**:1332
- [27] Becker B. Decrease in intraocular pressure in man by a carbonic anhydrase inhibitor, diamox. *American Journal of Ophthalmology*. 1954;**37**(1):13–15
- [28] Martínez A, Sanchez-Salorio M. Predictors for visual field progression and the effects of treatment with dorzolamide 2% or brinzolamide 1% each added to timolol 0.5% in primary open-angle glaucoma. *Acta Ophthalmologica*. 2010;**88**(5):541–552
- [29] Miglior S. Results of the European glaucoma prevention study. *Ophthalmology*. 2005;**112**(3):366–375
- [30] Wang J, Wang H, Dang Y. Rho-Kinase inhibitors as emerging targets for glaucoma therapy. *Ophthalmology and Therapy*. 2023;**12**(6):2943
- [31] Sit AJ, Aihara M, Khawaja AP, Lin SC, Mansouri K, Miki A, et al.

Clinical implications of lowering episcleral venous pressure in the management of glaucoma and the use of Rho kinase inhibitors. *Survey of Ophthalmology* 2025;**70**:918–929

[32] Santen Pharmaceutical Co., Ltd.; UBE Corporation. Santen and UBE Received FDA Approval for OMLONTI® (Omidenepag Isopropyl Ophthalmic Solution) 0.002% for the Reduction of Elevated Intraocular Pressure in Patients with Primary Open-Angle Glaucoma or Ocular Hypertension. 2022. Available from: <https://www.glaucoma.org/glaucoma/glaucoma-facts-and-stats.php> [Accessed: 2025-June-28]

[33] Matsuo M, Matsuoka Y, Tanito M. Efficacy and patient tolerability of omidenepag isopropyl in the treatment of glaucoma and ocular hypertension. *Clinical Ophthalmology*. 2022;**16**: 1261–1279

[34] Weinreb RN, Ong T, Sforzolini BS, Vittitow JL, Singh K, Kaufman PL, et al. A randomised, controlled comparison of latanoprostene bunod and latanoprost 0.005% in the treatment of ocular hypertension and open angle glaucoma: The VOYAGER study. *British Journal of Ophthalmology* 2015;**99**:738–745

[35] Weinreb RN, Scassellati Sforzolini B, Vittitow J, Liebmman J. Latanoprostene bunod 0.024% versus timolol maleate 0.5% in subjects with open-angle glaucoma or ocular hypertension: The APOLLO study. *Ophthalmology*. 2016;**123**(5):965–973

[36] Shirley M. Bimatoprost implant: first approval. *Drugs & Aging*. 2020;**37**(6):457

[37] Teymoorian S, Craven ER, Nguyen L, Werts E. Real-world study of the effectiveness and safety of

intracameral bimatoprost implant in a clinical setting in the United States. *Clinical Ophthalmology*. 2023;**18**: 187–199

[38] European Glaucoma Society. European glaucoma society terminology and guidelines for glaucoma, 4th edition - Chapter 3: Treatment principles and options supported by the EGS foundation. *The British Journal of Ophthalmology*. 2017;**101**(6):130–195

[39] Weinreb RN, Brandt JD, Garway-Heath D, Medeiros FA, editors. WGA Consensus Series 4: Intraocular Pressure. Kugler Publications; 2007

[40] Artes PH, Chauhan BC, Keltner JL, Cello KE, Johnson CA, Anderson DR, et al. Longitudinal and cross-sectional analyses of visual field progression in participants of the ocular hypertension treatment study (OHTS). *Archives of Ophthalmology* 2010;**128**:1528

[41] Öhnnell H, Heijl A, Brenner L, Anderson H, Bengtsson B. Structural and functional progression in the early manifest glaucoma trial. *Ophthalmology*. 2016;**123**(6):1173

[42] Musch DC, Gillespie BW, Niziol LM, Lichter PR, Varma R. Intraocular pressure control and long-term visual field loss in the collaborative initial glaucoma treatment study. *Ophthalmology*. 2011;**118**(9):1766

[43] Anderson DR. Collaborative normal tension glaucoma study. *Current Opinion in Ophthalmology*. 2003;**14**(2):86–90

[44] Gaasterland DE, Ederer F, Beck A, Costarides A, Leef D, Closek J, et al. The Advanced Glaucoma Intervention Study (AGIS): 7. The relationship between

control of intraocular pressure and visual field deterioration. American Journal of Ophthalmology 2000;**130**:429–440

[45] Jampel HD. Target pressure in glaucoma therapy. Journal of Glaucoma. 1997;**6**(2):133–138

[46] Asia-Pacific Glaucoma Society Issuing Body. Asia Pacific Glaucoma Guidelines. 3rded. Amsterdam, The Netherlands: Kugler Publications; 2016.

[47] Leung EW, Medeiros FA, Weinreb RN. Prevalence of ocular surface disease in glaucoma patients. Journal of Glaucoma. 2008;**17**(5): 350–355

[48] Mathews PM, Ramulu PY, Friedman DS, Utine CA, Akpek EK. Evaluation of ocular surface disease in patients with glaucoma. Ophthalmology. 2013;**120**(11): 2241–2248

[49] Mastropasqua L, Agnifili L, Mastropasqua R, Fasanella V. Conjunctival modifications induced by medical and surgical therapies in patients with glaucoma. Current Opinion in Pharmacology. 2013;**13** (1):56–64

[50] Dayal A. Psychosocial aspects of glaucoma. In: Lanza M, editor. Ocular Hypertension - the Knowns and Unknowns. London: IntechOpen; 2021. p. 73-79. Available from: <https://www.intechopen.com/chapters/76382> [Accessed: 2025-December-14]

[51] Kalyani VS, Dayal A, Chelerkar V, Deshpande M, Chakma A. Assessment of psychosocial impact of primary glaucoma and its effect on quality of life of patients in Western India. Indian

Journal of Ophthalmology. 2020;**68** (11):2435–2438

[52] Gedde SJ, Vinod K, Wright MM, Muir KW, Lind JT, Chen PP, et al. Primary open-angle glaucoma preferred practice pattern®. Ophthalmology. 2021;**128**(1):P71–P150

[53] Steven DW, Alaghband P, Lim KS. Preservatives in glaucoma medication. British Journal of Ophthalmology. 2018;**102**(11):1497

[54] Skov AG, Rives AS, Freiberg J, Virgili G, Azuara-Blanco A, Kolko M. Comparative efficacy and safety of preserved versus preservative-free beta-blockers in patients with glaucoma or ocular hypertension: A systematic review. Acta Ophthalmologica. 2022;**100**(3):253–261

[55] Dayal A, Kalyani VKS, Chelerkar V, Deshpande M. Prevalence of anxiety and depression in patients with primary glaucoma in Western India. Journal of Glaucoma. 2022;**31** (1):37–40

[56] Rezapour J, Nickels S, Schuster AK, Michal M, Münzel T, Wild PS, et al. Prevalence of depression and anxiety among participants with glaucoma in a population-based cohort study: The Gutenberg health study. BMC Ophthalmology. 2018;**18**(1):157

Systematic Review on the Modern Strategies in Glaucoma Treatment – The Role of Optometrists

Kingsley Ekemiri

Abstract

As the global population continues to age, there is an increasing emphasis on managing age-related health conditions, among which glaucoma is particularly prominent. Optometrists play a significant role in the timely detection and management of glaucoma. Therefore, this review is aimed at examining the role of optometry in the management of glaucoma. A search of PubMed, PsycINFO, SCOPUS, and Google Scholar identified articles from 1990 onward, focusing on the role of optometry in glaucoma management. The JBI checklists were used to appraise the quality of the studies, and a narrative synthesis was conducted. A total of 11 original, peer-reviewed articles published from November 1993 up to January 2025 were identified. The identified roles of optometry in glaucoma management include screening and managing affected individuals using available diagnostic equipment such as CCT, gonioscopy, tonometry, and ophthalmoscopy. Numerous studies highlight their capacity to perform advanced diagnostic procedures and effectively screen glaucoma patients, with a high level of agreement with ophthalmologists on various aspects of patient evaluation and management. Thus, utilizing the skills and capacities of optometry professionals helps to improve vision-related quality of life and achieve better patient outcomes.

Keywords: optometry, role, review, glaucoma, management

1. Introduction

Glaucoma describes a group of neuropathies characterized by progressive degeneration of retinal ganglion cells and optic nerve atrophy, and it is a leading cause of irreversible blindness in the developed world [1]. Glaucoma-induced visual impairment seriously affects the quality of life and healthy life expectancy of patients, while also placing a significant burden on families and healthcare systems [2].

The risk factors most commonly associated with glaucoma include a family history of the disease, advanced age, male sex, myopia, elevated intraocular pressure, and high blood pressure [3–5].

The age-standardized global prevalence of glaucoma is approximately 3.54% in the population aged 40 years and above, and it is expected to increase to 112 million people by 2040 due to the rapid increase in global population aging [6].

The available treatments cannot cure existing optic nerve damage or reverse visual field loss; however, they can help control disease progression through medication, laser treatment, or incisional glaucoma surgeries to prevent further vision loss, with the support of an inter-professional healthcare team for optimal treatment outcomes [7].

Poor management of glaucoma results in a decline in patients' physical capabilities, affecting activities of daily life such as reading, watching TV, and perceiving objects in their peripheral vision. Additionally, glaucoma patients may face an increased risk of falls and accidents due to these impairments, and patients should be linked to vision rehabilitation and psychosocial support services [8–10].

Despite these, the diagnostic evaluation and management of glaucoma rely on several key factors that must be considered to establish a diagnosis and determine the target intraocular pressure. These factors include intraocular pressure, ocular function, and eye morphology, as well as enhanced optometric services facilitated through inter-professional collaboration [11–13].

Besides, vision loss from glaucoma can be minimized by recognizing systemic conditions and medications that increase a patient's risk of glaucoma and by referring high-risk patients for a complete ophthalmologic examination [14].

As the global population continues to age, there is an increasing emphasis on managing age-related health conditions, among which glaucoma is particularly prominent. Optometrists play a significant role in glaucoma detection and management. By utilizing advanced diagnostic technologies, they can identify risk factors and provide timely interventions, greatly improving patient outcomes. Furthermore, optometrists can facilitate ongoing management strategies for those diagnosed with glaucoma [15–17]. However, there is evidence disparity regarding their scope of practice, so this systematic review is conducted to investigate the available evidence of the optometrist's role in the management of glaucoma.

1.1 Review questions

- What are the roles of optometry in modern Strategies for Glaucoma treatment?
- How much is the diagnostic agreement between an optometrist and an ophthalmologist?

2. Methods and materials

The updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines were used to report the findings of this systematic review [17, 18].

2.1 Eligibility criteria: Inclusion criteria

- The review will include studies conducted among patients with glaucoma.
- The review will include studies dealing with modern strategies for glaucoma management.
- The review will include studies conducted on the role of optometrists in the management of glaucoma.
- Only articles published in the English-language.
- All types of studies assessing the role of optometry in modern strategies for glaucoma treatment will be included in the review, whereas studies addressing the traditional role and systematic review articles were excluded.

2.2 Information sources and search strategy

The search strategy was designed to identify both published and unpublished studies after 1990 related to the role of optometry in glaucoma treatment strategies. A three-step method was used: a preliminary PubMed search was conducted to identify keywords and index terms, a second search across databases was performed using these terms, and a review of reference lists was undertaken for additional studies. Keywords included glaucoma OR ocular disease OR silent thief of sight OR ocular hypertension OR eye disease OR ophthalmic condition OR optometrist OR eye care professionals OR role. To identify the studies, PubMed, PsycINFO, SCOPUS, and Google Scholar databases were utilized.

2.3 Selection process and data extraction

Four reviewers individually evaluated the titles and abstracts of identified studies for eligibility. Then, the full texts of the studies were independently assessed by all reviewers. Any discrepancies between the reviewers were resolved through consultation with a fifth reviewer/author. Subsequently, four reviewers independently conducted the data extraction. The authors' names, study design, study setting, sample size, impacts of modern strategies, types of modern strategies, and the role of optometry were extracted using a Microsoft Excel 2010 spread sheet. Differences in data extraction were resolved through consensus among the assessors.

2.4 Outcomes

This review explored the roles of optometry in modern strategies for glaucoma treatment and diagnosis, in agreement with ophthalmologists.

2.5 Study risk of bias assessment

Risk of bias for each included study was assessed independently by the authors using the JBI Critical Appraisal Checklist for qualitative studies [19]. The JBI checklist consists of methodology alignment, data collection and analysis, result

interpretation, researcher influence, sample representativeness, ethical issues, and conclusions. All studies included in this study were determined to have a low risk of bias. Any differences in assessing the risk of bias between the reviewers were resolved through discussion.

2.6 Data analysis and synthesis

Literature identified in this study was analyzed to evaluate the extent of available evidence, quantified by the number of publications. Key variables, including sample size, study design, and the roles of optometry, were considered. Extracted data were organized into a structured spreadsheet table summarizing the results of the included studies. Narrative synthesis was conducted, detailing aspects such as study design, study setting, sample size, role of optometry, and diagnosis agreement. By summarizing the key findings, this review provides insights into the current evidence on the role of optometry in glaucoma management strategies. Descriptive statistics were computed to summarize the quantitative findings.

3. Results

3.1 Study selections and extractions

Four electronic databases were searched: PubMed (n = 78), PsycInfo (n = 19), Scopus (n = 42), and Google Scholar (n = 26), resulting in 165 articles. After removing 22 duplicate articles, 143 unique articles remained for screening based on titles and abstracts. Sixty-four publications that did not meet the inclusion criteria were excluded before data extraction. Subsequently, a full-text review was conducted on the remaining 79 articles, resulting in 11 studies for data extraction and further analysis (**Figure 1**).

3.2 Characteristics of included studies

A total of eleven [12, 20–29] original, peer-reviewed articles published from November 1993 up to January 2025 were identified, focusing on the role of optometry in glaucoma management that met the inclusion criteria. The selected articles were published from 1990 onwards. Notably, 81.8% (9 articles out of 11) were published after 2000. Cross-sectional studies constituted the largest subset of studies (n = 7, 63.6%), and most of the studies were conducted in the United Kingdom (n = 9 out of 11, 81.8%). The study populations comprised patients, optometrists, and ophthalmologists (**Table 1**).

3.3 The role of optometry in modern strategies for glaucoma management

This systematic review synthesizes evidence from studies about the role of optometrists in modern strategies of glaucoma management and organizes findings systematically by various factors, including study design, sample size, roles performed by optometrists, and diagnostic agreement with ophthalmologists. Different cross-sectional studies and editorial notes were

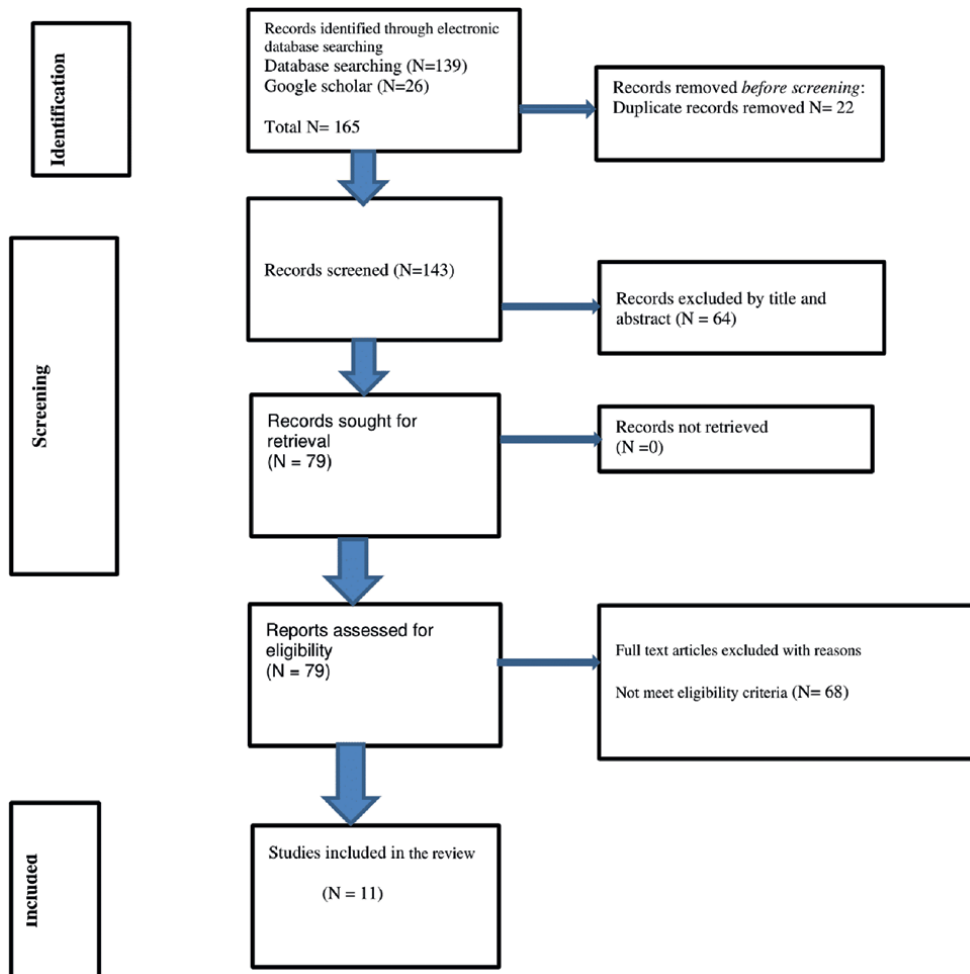


Figure 1.
 PRISMA Flowchart describing the selection of studies on the role of optometrist in management of glaucoma.

systematically reviewed. From the included studies, an editorial note by Krishnakumar R et al. highlights the expanding role of optometrists in glaucoma clinics. Besides conducting routine examinations, they are increasingly involved in advanced diagnostic procedures, such as gonioscopy using the Goldmann 4-mirror gonioscope.

A similar study conducted by Willis CE et al. revealed some remarkable findings regarding intraocular pressure (IOP) assessments in clinical practice. An impressive 95% of practitioners applied age criteria when measuring IOP, and 82% selected visual field testing based on appropriate clinical guidelines. Their study showed that 45% of practitioners considered an IOP of 25 or 26 mmHg to be the threshold for referral when no risk factors were present. Moreover, 89% of respondents indicated that they would refer patients for further evaluation if visual field defects and disc cupping were evident.

Authors	Publication year	Sample size	Study setting	Study design
Krishnakumar R, et al.	2016	–	United Kingdom	Editorial
Kotecha A	2009	–	United Kingdom	Review
Banes MJ, et al.	2000	54 patients	United Kingdom	Cross-sectional
Gunn PJ, et al.	2022	90 optometrists	United Kingdom	Survey
Jamous KF, et al.	2014	574 participants from Australia and 244 from New Zealand.	Australia and New Zealand	Cross – sectional
Ryan B, et al.	2025	802 patients	United Kingdom	Cross – sectional
BSc (Horn) PhDMBCO JW	1993	50 optometrists	United Kingdom	Survey
Willis CE, et al.	2000	171 optometrists	United Kingdom	Survey
Strong NP.	1992	147 optometrists	United Kingdom	Survey
Ho S, A Vernon S.	2011	140 patients	Nottingham	A single masked comparison study
Harper R, et al.	2016	70 optometrists	United Kingdom	Survey

Table 1.
Characteristics of the study on the role of optometry in modern management strategies for glaucoma.

A study by Ryan B et al. further supports the notion that optometrists are well-equipped and possess the required skills and qualifications to provide enhanced optometric services for glaucoma. Their findings emphasize the readiness of optometrists to take on more expanded roles in patient care.

Moreover, research by BSc (Horn), PhD, MBCO, JW showed that all optometrists have access to screening facilities such as tonometry and ophthalmoscopy. Markedly, 73% of them also offer visual field testing. They routinely perform optic disc examinations on patients, and intraocular pressure (IOP) is measured for all patients aged 40 and above, with selective assessments for younger individuals based on optic disc appearance. Additionally, they provide a referral service, with the referral rate rising to 90% if the discs appear suspicious. Most practitioners also indicated readiness to perform visual field tests for patients who have an IOP exceeding 25 mmHg, regardless of their disc status.

In another study by Strong NP, it was shown that all optometrists routinely examine the optic disc of every patient they see. Although the optometrists use tonometry selectively based on various factors, including age, family history, and disc appearance, they also reported that while 88% possess field testing equipment, the type of apparatus is often not optimal for effective general population screening, with only 38% having automated or semi-automated perimetry available. The study emphasized that an IOP threshold of 27 mmHg was the cutoff for referral in

80% of cases, provided that there was no evidence of disc cupping; this threshold decreased to 24 mmHg if cupping was suspected.

Furthermore, a study by Harper R et al. reported that the majority of optometrists (96% of 70 respondents) approved their engagement in extended roles. Remarkably, glaucoma was identified as the primary extended service offered, with 92% of practitioners providing such services. A similar result by Gunn PJ and colleagues further demonstrated the extended roles of optometrists in managing patients with glaucoma.

However, despite the capability and readiness of optometrists to deliver a range of diagnostic tests for glaucoma, some studies have highlighted potential instrumental barriers, such as advanced IOP measurement devices and CCT, as reported by a study by Kotecha A. A nearly similar study by Jamous KF et al. echoed these sentiments, indicating that while optometrists are generally well-equipped for glaucoma assessments, a notable exception lies in performing gonioscopy.

Also, studies have evaluated the diagnostic agreement between optometrists and ophthalmologists regarding patient evaluation and management. Remarkably, a study by Banes MJ demonstrated agreement between optometrists and experienced ophthalmologists in various aspects of patient assessment and management. Similarly, a study by Ho S and Vernon S indicated a striking agreement (>88%) between optometrists and ophthalmologists in areas such as visual field interpretation, medical and surgical management decisions, scheduling of subsequent appointments, and the ordering of visual field tests (**Table 2**).

4. Discussion

This review provides evidence on the role of optometry in glaucoma management, focusing on the screening and management of affected individuals using available diagnostic equipment such as CCT, gonioscopy, tonometry, and ophthalmoscopy.

Traditional optometry's role in glaucoma care focuses on early detection, diagnosis, and initial management, often involving eye drop prescriptions; however, modern optometry encourages collaborative care, where optometrists work closely with ophthalmologists and other healthcare providers to ensure holistic patient care using advanced diagnostic modalities and treatment options [30–32].

Nowadays, eye care services have grown significantly, particularly with the increasing roles of optometrists in performing essential diagnostic and therapeutic procedures, such as CCT, gonioscopy, tonometry, and ophthalmoscopy, which highlight the expanding scope of practice for optometrists beyond traditional routine eye examinations, as evidenced by this review [33].

Optometrists play a vital role in the early detection and ongoing monitoring of glaucoma. This review points out that optometrists are not only trained to perform comprehensive glaucoma screenings but are also equipped to make timely referrals to ophthalmologists when necessary.

On the other side, as studies indicate, the economic burden associated with glaucoma management can vary significantly between optometric and ophthalmological care. Optometry services often have lower costs than specialized ophthalmological interventions; if optometrists are supported to further enhance their diagnostic capabilities, this could include advanced training, access to the latest

Authors	Role of optometrists
Krishnakumar et al. [20]	In the glaucoma clinic, in addition to performing routine procedures, optometrists are engaged in additional diagnostic procedures such as gonioscopy using a Goldmann 4-mirror gonioscope and may indicate or perform any additional tests that may be needed.
Kotecha [21]	Most primary care optometrists will not have access to these new IOP measurement devices and may not have the instrumentation available to measure CCT.
Banes et al. [22]	The results show there was a high level of agreement between the optometrist and the 'gold standard' of the experienced ophthalmologist in all aspects of patient evaluation and management. This demonstrates that the optometrist was capable of undertaking routine glaucoma assessments and making good clinical decisions.
Willis et al. [23]	One practice lacked a tonometer, and one practice lacked visual field instrumentation. Age criteria were used by 95% of practitioners for measuring intraocular pressure (IOP), and 82% used appropriate selection criteria for visual field testing. An IOP of 25 or 26 mmHg was used by 45% of practitioners as the threshold for referral if there were no risk factors; 89% would refer at any level if a visual field defect and disc cupping were present. The results confirm that the majority of optometrists are well-equipped for the screening of glaucoma.
Jamous et al. [24]	Optometrists were well-equipped to perform glaucoma assessments, with the possible exception of gonioscopy. Advanced imaging modalities were not yet fully integrated into optometric practice.
Ryan et al. [12]	The workforce survey confirms that optometrists possess the skills and qualifications and are willing to deliver these enhanced optometric services.
BSc (Horn) PhDMBCO JW [25]	The results demonstrated that all respondents have facilities for screening by tonometry and ophthalmoscopy, with 73% also having facilities for visual field testing. All responding optometrists undertake optic disc examination on all patients. Intraocular pressure (IOP) was measured on all patients aged 40 years and over, with selective testing of those patients less than 40 years of age, depending on disc appearance. Seventy-six per cent of respondents would refer for IOP > 24 mm Hg if optic discs Were normal; whereas, if optic discs were suspicious, 90% would refer for an IOP > 21 mm Hg. All indicated that they would test visual fields of patients with IOP > 25 mm Hg, irrespective of disc appearance or family ocular history of glaucoma. The majority of optometrists would refer for characteristic field losses, for optic disc changes, including a C/D ratio > 0.6 or a C/D asymmetry of 0.2 or 0.3.
Strong NP. [26]	All respondents examine the optic disc of all patients. tonometry is available, but most use it selectively based on age, family history, and disc appearance. Although 88% have field testing apparatus, this is usually not of a type likely to be effective in screening a general population; 38% have automated or semiautomated perimetry. The criterion level of IOP at which 80% of respondents would refer was 27 mm Hg in the absence of disc cupping, falling to 24 mm Hg if cupping was suspected. Over 80% would refer any patient with a field defect, irrespective of IOP.
Ho and Vernon [27]	There was a high degree of agreement (>88%) in terms of visual field interpretation, medical and surgical management decisions, timing of the next appointment, and ordering of visual field tests.
Harper et al [28]	A substantial majority of respondents ($N = 67/70$, 96%) indicated that optometrists undertook extended roles. Glaucoma is the leading extended role service provided by optometrists, with 92% of respondents providing extended role services.
Gunn et al. [29]	There was an increase in the proportion of units delivering extended roles, with glaucoma (88%) remaining the most common extended role.

Table 2.
Summary of the role of optometry in modern management strategies for glaucoma.

screening technologies, and updated clinical guidelines that reflect current best practices, which will relieve patient burden [34, 35].

The review included studies conducted in high-income countries, specifically the United Kingdom, Australia, and New Zealand. This highlights a regional focus on the role of optometry in the management of glaucoma. Despite this, the studies provide valuable insights into the role that optometrists play in diagnosing and managing glaucoma. However, it is difficult to apply these findings to low-income countries because of variations in healthcare infrastructure, resource availability, and cultural contexts. As a result, careful consideration is necessary before applying these insights to low-income countries, and further research to address the unique challenges and needs of lower-income settings is essential to incorporate optometrists into modern management strategies for glaucoma.

5. Conclusion

The changing role of optometrists in glaucoma care is becoming increasingly significant, as evidenced by numerous studies highlighting their capacity to perform advanced diagnostic procedures and effectively screen for the condition. With a high level of agreement observed between optometrists and ophthalmologists on various aspects of patient evaluation and management, it is clear that optometrists are well-equipped to make critical clinical decisions in the realm of glaucoma assessment.

In spite of the qualifications and willingness of optometrists to deliver enhanced optometric services, challenges remain, particularly regarding access to advanced diagnostic tools and equipment. Addressing these instrumental barriers is therefore necessary.

Also, the findings stress the importance of collaboration between optometrists and ophthalmologists in improving patient outcomes in glaucoma management. By leveraging the strengths of each profession, the healthcare system can enhance its capacity to effectively identify and manage this significant eye condition, ultimately benefiting patient care and preserving vision for those at risk.

Acknowledgments

The author gratefully acknowledges the contributions of researchers and clinicians whose work formed the foundation of this review. Special appreciation is extended to academic and clinical colleagues within the Optometry Unit, Faculty of Medical Sciences, The University of the West Indies, St. Augustine, for their valuable insights, guidance, and professional support throughout the development of this manuscript.

Conflict of Interest

The authors declare no conflicts of interest.

Author details

Kingsley Ekemiri

Optometry Unit, Faculty of Medical Sciences, The University of the West Indies,
St. Augustine, Trinidad and Tobago

*Address all correspondence to: iamekemiri@gmail.com

IntechOpen

© 2025 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. 

References

- [1] Križaj D What is glaucoma? Webvision: The organization of the retina and visual system [Internet]. 2019
- [2] Welp A, Woodbury RB, McCoy MA, Teutsch SM. National Academies of Sciences, Engineering, and Medicine, Committee on Public Health Approaches to Reduce Vision Impairment and Promote Eye Health. The Impact of Vision Loss. In Making Eye Health a Population Health Imperative: Vision for Tomorrow. Washington, DC: National Academies Press (US); 2016
- [3] Lee SS, Mackey DA. Glaucoma - risk factors and current challenges in the diagnosis of a leading cause of visual impairment. *Maturitas*. 2022;**163**:15–22. DOI: 10.1016/j.maturitas.2022.05.002
- [4] McMonnies CW. Glaucoma history and risk factors. *Journal of Optometry*. 2017;**10**(2):71–78
- [5] Shan S, Wu J, Cao J, Feng Y, Zhou J, Luo Z, Song P, Rudan I, Global Health Epidemiology Research Group. Global incidence and risk factors for glaucoma: A systematic review and meta-analysis of prospective studies. *Journal of Global Health*. 2024;**14**:04252
- [6] Tham Y-C, Li X, Wong TY, Quigley HA, Aung T, Cheng C-Y. Global prevalence of glaucoma and projections of glaucoma burden through 2040: A systematic review and meta-analysis. *Ophthalmology*. 2014;**121**(11):2081–2090
- [7] Dietze J, Blair K, Zeppieri M, Havens SJ, Adams M. Glaucoma (Nursing). In *InStatPearls* [Internet]. Treasure Island (FL): StatPearls Publishing; 2024. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK568748/>
- [8] Ayele FA, Zeraye B, Assefa Y, Legesse K, Azale T, Burton MJ. The impact of glaucoma on quality of life in Ethiopia: A case-control study. *BMC Ophthalmology*. 2017;**17**:1–9
- [9] Ramulu PY, Mihailovic A, West SK, Gitlin LN, Friedman DS. Predictors of falls per step and falls per year at and away from home in glaucoma. *American Journal of Ophthalmology*. 2019;**200**:169–178
- [10] Huang W, Gao K, Liu Y, Liang M, Zhang X. The adverse impact of glaucoma on psychological function and daily physical activity. *Journal of Ophthalmology*. 2020;**2020**:19606420
- [11] Schuster AK, Erb C, Hoffmann EM, Dietlein T, Pfeiffer N. The diagnosis and treatment of glaucoma. *Deutsches Arzteblatt International*. 2020;**117**(13):225
- [12] Ryan B, Jones M, Anderson P, Reynolds R, Nicholls REM, Cullen K, Davies M, North R, Molik B, Wallace C. Hospital to community in Wales: What is the value of optometrists playing a greater role in managing neovascular AMD and glaucoma in primary care? *Ophthalmic and Physiological Optics*. 2025;**45**(1):280–293
- [13] Ferrito ML Improving care for adults with visual impairment through interprofessional education
- [14] Stein JD, Khawaja AP, Weizer JS. Glaucoma in adults—screening,

diagnosis, and management: A review. *Jama*. 2021;**325**(2):164–174

[15] Zhang Y, Huang S, Xie B, Zhong Y. Aging, cellular senescence, and glaucoma. *Aging and Disease*. 2024;**15**(2):546

[16] Unterlauff JD, Böhm MR. Role of the aging visual system in glaucoma. *Der Ophthalmologe*. 2017;**114**:108–113

[17] Gibson T. Optometry's role in managing patients with glaucoma. *Clinical and Experimental Optometry*. 2016;**99**(1):1–3

[18] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *bmj*. 2021;**372**:n71. DOI: 10.1136/bmj.n71

[19] Porritt K, Gomersall J, Lockwood C. JBI's Systematic Reviews. *AJN the American Journal of Nursing*. 2014;**114**(6):47–52

[20] Krishnakumar R, Anuradha N, Hussaindeen MJ, Sailaja MV. Role of optometrist in eye hospitals. *Medical & Vision Research Foundations*. 2016; **34**(1):1–4. Available From: <https://www.semanticscholar.org/paper/32153473>

[21] Kotecha A. Detection of glaucoma by the primary care optometrist. *Optometry Practice*. 2009;**10**(2):51–64

[22] Banes MJ, Culham LE, Crowston JG, Bunce C, Khaw PT. An optometrist's role of co-management in a hospital glaucoma clinic. *Ophthalmic and Physiological Optics*. 2000;**20**(5):351–359. DOI: 10.1136/bjo.2005.082388

[23] Willis CE, Rankin SJ, Jackson AJ. Glaucoma in optometric practice: A survey of optometrists. *Ophthalmic and Physiological Optics*. 2000;**20**(1):70–75

[24] Jamous KF, Kalloniatis M, Hayen A, Mitchell P, Stapleton FJ, Zangerl B. Application of clinical techniques relevant for glaucoma assessment by optometrists: Concordance with guidelines. *Ophthalmic and Physiological Optics*. 2014;**34**(5):580–591

[25] BSc (Horn) PhDMBCO JW. BAppSc ST. Glaucoma screening by optometrists. *Clinical and Experimental Optometry*. 1993;**76**(6):199–207

[26] Strong NP. How optometrists screen for glaucoma: A survey. *Ophthalmic and Physiological Optics*. 1992;**12**(1):3–7

[27] Ho S, A Vernon S. Decision making in chronic glaucoma – Optometrists vs ophthalmologists in a shared care service. *Ophthalmic and Physiological Optics*. 2011;**31**(2):168–173

[28] Harper R, Creer R, Jackson J, Ehrlich D, Tompkin A, Bowen M, Tromans C. Scope of practice of optometrists working in the UK Hospital Eye Service: A national survey. *Ophthalmic and Physiological Optics*. 2016;**36**(2):197–206

[29] Gunn PJG, Creer RC, Bowen M, Tromans C, Jackson AJ, Tompkin AP, Harper RA. Scope of practice of optometrists working in the UK Hospital Eye Service: Second national survey. *Ophthalmic and Physiological Optics*. 2022;**42**(3):428–439

[30] Harper R. Glaucoma and optometry: Recognition, challenges and opportunities.. *Ophthalmic and Physiological Optics*. 2011;**31**(4): 327–329

[31] Machon K. Optometrists' scope of practice. *Clinical and Experimental Optometry*. 2017;**100**(3):201–202

[32] Hui A, Jalbert I. Ocular therapeutics: From special interest to standard care. *Clinical and Experimental Optometry*. 2021;**104**(3):265–266

[33] Khan RH. A study on the role of optometrists in abilities in the public and private sectors. *European Journal of Molecular & Clinical Medicine*. 2023;**10**(01):2023

[34] Usgaonkar UP, Naik R, Shetty A. The economic burden of glaucoma on patients. *Indian Journal of Ophthalmology*. 2023;**71**(2):560–566

[35] Soroka M. Comparison of examination fees and availability of routine vision care by optometrists and ophthalmologists. *Public Health Reports (Washington, D.C.: 1974)*. 1991;**106**(4):455

Edited by Felicia M. Ferreri

This Edited Volume, *Glaucoma - Exploring Medical Therapies and Surgical Treatments*, is a collection of peer-reviewed chapters that provide a comprehensive overview of recent developments in glaucoma research. The book comprises single chapters authored by various researchers, edited by an expert in the field. All chapters are complete in themselves but united under a common research study topic. This publication aims to provide a comprehensive overview of recent research by international authors in ophthalmology and to open new avenues for further development.

Published in London, UK

© 2026 IntechOpen

© Marvin S.T. Pineda / iStock

IntechOpen

