Current Practices in Ophthalmology
Series Editor: Parul Ichhpujani

Parul Ichhpujani *Editor*

Glaucoma

Springer

Current Practices in Ophthalmology

Series Editor

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Foreword

Dr. Parul Ichhpujani has—in this text—condensed current teaching about most of the new technologies and concepts in the field of glaucoma. This is a great accomplishment and a useful one.

She set herself a difficult task, as basic concepts about glaucoma, what it is, and how it is best diagnosed and treated are in transition and new technologies arrive daily! Those relatively new to the field may find it hard to believe that as recently as 50 years ago, the diagnosis of glaucoma was "easy"; one simply measured the pressure within the eye! That sadly incorrect method of thinking lingers on, unfortunately. Also, there was a widespread belief that the size of the optic nerve head "cup" was of essential importance in diagnosing and following patients with glaucoma. However, it is now clear that the size of the cup is poorly correlated with diagnostic and functional status and that "cup/disc ratios" should no longer be used; they mislead more than help. It is the pattern of the nerve appearance that is hugely helpful. Some authors now use phrases such as "pressure-independent" glaucoma, while others believe that pressure is in some way always at least partially responsible for the damage that occurs in glaucoma. One of the essential pieces of information—the appearance of the anterior chamber angle—is today incorrectly evaluated in over two-thirds of individuals!

As a result, blindness from primary angle closure glaucoma is the leading cause of permanent blindness—despite being easy to diagnose and treat successfully! Most of those (perhaps more than 90%) with glaucoma do not even get diagnosed, and for the relatively few that do, treatment options are so wildly diverse that the practitioner must wonder what to do.

What is certain is that thinking and acting regarding glaucoma are in a messy transition.

This book is a highly informative read for all interested in the field. The chapters are well-referenced, allowing the reader to go beyond the helpful material in the chapters themselves.

To me the major things to stress are:

- Prior methods of basing diagnosis and care on average values did not and still do not work; data must be personalized. Mean eye pressure, isolated measurement of retinal nerve fiber layer thickness, central corneal thickness, and cup/disc ratios are useless or worse, because they divert the examiner from what is truly essential.
- To be useful, data must be *valid* (i.e., accurate, consonant with reality) and *relevant* (i.e., pertinent for the person being considered). They should also be the result of *socially responsible* data acquisition methods. Valid, irrelevant, unsustainable data should not be obtained. Prior to recommending any test or procedure, the physician needs to ask the following: "Will the data obtained be accurate and relevant for this particular person, and is the cost justified?" Unless the answers to the two questions are a solid "yes," the test or procedure should not be done, unless scientifically sound methods are applied to study the validity, relevance, and sustainability of what is being considered.
- While there is as great deal still to learn, present methods, when applied well, work well for most individuals. There is no substitute for an empathetic, comprehensive, history designed to find symptoms and establish their chronology; an accurate, sensitive means of assessing visual ability; an accurate gonioscopy; a correct evaluation of pupillary responses; an estimate of the intraocular pressure with a simple instrument such as an applanation tonometer or the fingers; and a meticulous evaluation of the optic nerve head through a dilated pupil. There is still truth in the old saying that "the time to try a treatment is before learning that it does not work."
- One of the most exciting next steps is the confirmation by Caprioli and others that following adequate lowering of intraocular pressure fields improves. While this has been suggested in the past, few believed it. The reality of disc improvement has been proven since von Jaeger reported it in 1869; but even now, few recognize that it is common. The clinical implication of this improvement is that it may allow, for the first time, a valid, relevant method of determining how much the intraocular pressure needs to be lowered in order to assure the best chance of no further disease progression.

Those who have the good sense to read this text from start to finish will be better able to determine what they need to do to obtain and interpret and use data that are most likely to be valid, relevant, and socially responsible, so they can be of most help to patients, and, also, to understand better what questions need to be asked and how best to try to answer them.

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About the Editor

Parul Ichhpujani is currently an Associate Professor in the Department of Ophthalmology at Government Medical College and Hospital, Chandigarh, India. She takes care of the glaucoma and neuro-ophthalmology services at her center. She has done her glaucoma training from Advanced Eye Centre, Postgraduate Institute of Medical Education and Research, Chandigarh, India, and a subsequent clinical research fellowship, under Dr. George L. Spaeth, at Wills Eye Institute, Philadelphia, USA.

She is the member of associate advisory board and education committee of the World Glaucoma Association. She is the associate managing editor of the *Journal of Current Glaucoma Practice*, the official journal of the International Society of Glaucoma Surgery, and is an assistant editor for glaucoma section of the *Indian Journal of Ophthalmology*. She was enlisted in the Powerlist 2015 of *"Best 40 ophthalmologists under 40." She is an Associate Advisory Board member of World Glaucoma Association.*

She is an avid researcher and an academician having co-authored three books, *Pearls in Glaucoma Therapy, Living with Glaucoma, and Smart Resources in Ophthalmology*; and edited five books, *Expert Techniques in Ophthalmology, Glaucoma: Basic and Clinical Perspectives, Manual of Glaucoma, Clinical Cases in Glaucoma: An Evidence Based Approach, and Glaucoma: Intraocular Pressure and Aqueous Dynamics.*

She has contributed several research articles and book chapters in national as well as international books. Dr. Ichhpujani has lectured at regional, national, and international surgical meetings. She serves as a reviewer for many ophthalmology journals.

What's New in Pathogenesis of Glaucoma

1

Parul Ichhpujani and Suresh Kumar

Glaucoma is an optic neuropathy due to progressive damage to retinal ganglion cells (RGCs), which results in characteristic cupping of the optic nerve head (ONH) and corresponding visual field defects. Despite years of research, the mechanism(s) underlying glaucomatous optic neuropathy (GON) remain unclear. It is believed that the lamina cribrosa is the primary site of injury, and raised intraocular pressure (IOP) is a major risk factor. Three theories have been widely accepted and they include the biomechanical, vascular, and biochemical theories [1].

Biomechanical Theory

Lamina cribrosa: According to this theory, IOP above the tolerable threshold of the ONH resistance results in deformation of the lamina cribrosa and the glial support framework of the anterior part of the optic nerve. Astrocytes and lamina cribrosa cells can sense strain through integrin receptors that tie their cytoskeletons directly to the adjacent fibrillar extracellular matrix. Elevated IOP leads to backward bowing, stretching, and compression of laminar plates within the lamina cribrosa, resulting in elongation of its pores, compression of the nerve fibers resulting in axoplasmic flow stasis in the RGC axons, and eventually RGC death and GON. Remodelling of the lamina cribrosa may predispose to localized compartment syndrome like situation when perfusion pressure lowers. These changes are associated with disk hemorrhages and visual field damage. These are also interpreted as a variant of limited anterior ischemic optic neuropathy like situation with venous congestion in a structurally altered ONH with narrowed pores in the lamina

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cribrosa [2]. With advancement in clinical imaging techniques, lamina cribrosa changes are detectable with optical coherence tomography (OCT) and can be used for diagnosis and management of glaucoma.

Role of intracranial pressure and trans-lamina cribrosa pressure difference: Another concept suggests that compression of the anterior part of optic nerve is also influenced by intracranial pressure (ICP) that may vary according to or independently of IOP fluctuations. Lamina cribrosa forms a pressure barrier between the high-pressure, intraocular space and the low-pressure, retrobulbar cerebrospinal fluid (CSF) space. The difference between the IOP and ICP across the lamina cribrosa is known as the trans-lamina cribrosa pressure difference (TLCPD) [3].

Clinical significance of TLCPD:

- Since the retinal and choroidal venous blood drains through the CSF space, therefore elevated CSF pressure may partly account for increased incidence of choroidal thickening and retinal vein occlusions [4].
- Studies have shown that the lamina cribrosa is significantly thinner in highly myopic eyes vis-a-vis mild or moderately myopic eyes, leading to steep trans-lamina cribrosa pressure gradient, which may explain why high myopes are more susceptible to glaucomatous damage [5].
- In advanced stage of glaucoma, lamina cribrosa becomes markedly thinner; therefore the TLCPD occurs over a shorter distance, resulting in a steeper trans-lamina cribrosa pressure gradient [4].

NTG versus HTG versus OHTN: Recent clinical studies have shown that patients with normal tension glaucoma (NTG) had significantly lower CSF pressure and a higher TLCPD when compared to subjects with no glaucoma. Therefore, it is plausible that a low CSF pressure may be associated with NTG. Low nocturnal systemic blood pressure could physiologically be associated with a low CSF pressure, which results in an abnormally high TLCPD, and this is akin to a similar scenario wherein the IOP is elevated and CSF pressure is normal. This concept explains why patients with NTG have relatively low systemic blood pressure and why eyes with NTG and HTG show similarities in ONH appearance, unlike eyes with a direct vascular optic neuropathy.

Studies have shown that chronic elevation of IOP in animals with experimentally induced ocular hypertension (OHTN) results in RGC death. Recent studies have reported that ICP is higher in patients with OHTN compared with controls [6]. This elevated ICP may be protective for the ONH by decreasing the TLCPD, thus explaining why despite elevated IOP most OHTN patients do not develop POAG. The lamina cribrosa is located more deeply in HTG than in NTG eyes and in NTG eyes than in healthy controls based on enhanced-depth imaging on spectral domain OCT (EDI-SDOCT) measurements. EDI-SDOCT has shown that the lamina cribrosa depth is a helpful parameter to differentiate HTG from normal eyes, but does not reach a good level of diagnostic accuracy for detecting NTG [7].

Vascular Theory

Elevated IOP also causes intraneural ischemia resulting from decreased ONH perfusion. Vascular perfusion of the ONH depends on three factors: systemic blood pressure, IOP, and the autoregulatory mechanism. Intraneural capillary perfusion pressure in the ONH is equal to the systemic blood pressure minus the IOP. Thus either decreased blood pressure or increased IOP leads to drop in the perfusion pressure of the ONH vasculature [8].

Additionally, IOP fluctuation results in vascular dysregulation which is worse than reduced circulation due to a stable elevated IOP or arteriosclerosis. Compromised ocular blood flow leads to reperfusion injury which, because of its repetitive nature, is detrimental. In NTG, endothelin-1 (ET-1) may have both a local and systemic component of vascular dysregulation, while in HTG, effect of ET-1 may be primarily localized to ocular tissue. Thus, ET-1 antagonism may be developed as a possible new approach for the treatment of both NTG and high-tension glaucoma (HTG) [9].

Neurochemical Theory

Since mechanical and vascular theories failed to explain glaucomatous optic neuropathy in all cases of glaucoma, the possible role of neurochemical mechanisms leading to glaucomatous neurodegeneration have been explored. These biochemical mechanisms include the role of reactive oxygen species (ROS), nitric oxide (NO), excitatory amino acids, caspases, protein kinases, tumor necrosis factor-alpha, metalloproteins, and neurotrophins [10].

An unstable ocular perfusion, an unstable oxygen supply, and a dysfunctional autoregulation result in oxidative stress and release of ROS within the axons of the ONH [11]. The increased outflow resistance can be explained by apoptosis and inflammation at the level of the TM, secondary to ROS stimulation.

Role of mitochondria: RGC mitochondrial dysfunction increases with glaucoma progression, and this leads to an imbalance in ROS production and detoxification. Müller cells have to work harder to maintain the level of chemicals released from activated microglia and astrocytes to nontoxic levels for the already compromised RGCs.

As the disease progresses, Müller cells are increasingly overburdened and are unable to cope with the neurochemical overload in the extracellular space, which leads to overstimulation of receptors associated with RGCs. Individual RGCs with defined receptor profiles are stimulated at different times by these neurochemicals which causes calcium influx that results in mitochondrial collapse and cell death [12].

Role of immune system: The eye is an immune-privileged site and ocular structures are protected from immune reactions and innate pathogens. However, injury or disease result in breakdown of the blood-retina barrier or changes in cytokine milieu and thus may compromise this immune privilege.

NO- and ROS-induced damage causes antigen-specific immune activation in retina [13]. These insults act through common final pathways that activate cellular proteases and eventually cause neuronal programmed cell death. So, these retinal proteins may be related to the development of GON.

However, there is also an opposing view that immune responses in glaucoma may be both neuroprotective or neural destructive [14]. For example, T-cell-mediated immune responses may initially be beneficial to limit neurodegeneration, but secondary recruitment of circulating T cells through an antigen-mediated process results in chronic autoimmune neurodegeneration. This in turn is associated with a failure to control stress-induced and aberrant immune response cascade.

Is It Apt to Label Glaucoma, "Ocular Alzheimer's"?

Research has shown that glaucoma patients are four times more likely to have dementia. RGC death in glaucoma is hypothesized to involve chronic amyloid β neurotoxicity, which causes apoptosis by binding to neurotrophin receptor $p75^{NTR}$ or through the accumulation of protein aggregates mimicking Alzheimer's disease at the molecular level, which is also being explored.

Glymphatic Theory

Another recent hypothesis is the existence of an ocular "glymphatic system," analogous to the "glymphatic system" in the brain [15, 16]. The retina is an extension of the CNS and shares embryological, anatomical, and physiological similarities to the brain; therefore, it seems plausible that the branches of the central retinal vessels in the retina are also surrounded by paravascular spaces with the same properties as the paravascular spaces in the brain.

Hu and coworkers have used multimarker immunohistochemistry to show evidence of a glymphatic system in mice, primates, and human retinas [17]. They found an $AQP4^{+}$ glial network ensheathing the entire retinal vascular system. Löffler and colleagues have also provided support for lymphatic structures in mice retinas similar to the glymphatic system in the brain [18].

In glaucomatous eyes, altered lamina cribrosa framework may mechanically interfere with the glymphatic flow through it by decreasing the elimination of neurotoxic substances, such as amyloid β, and resulting in subsequent GON.

This paravascular flow restriction may be in proportion to the amount of the TLCPD. Wostyn and coworkers have hypothesized that restriction of normal glymphatic flow at the level of the lamina cribrosa may lead to progression of glaucoma in patients with nocturnal hypotension and systemic hypertension [15].

Though a lot of research has been carried out to ascertain the precise pathogenesis of glaucoma, but the results have not yet been clinically utilized in management of glaucoma to halt or reverse the disease progression. However the future seems to be bright for deciphering the elusive pathways that define the disease. Figure 1.1 broadly elucidates the various theories for pathogenesis of glaucoma.

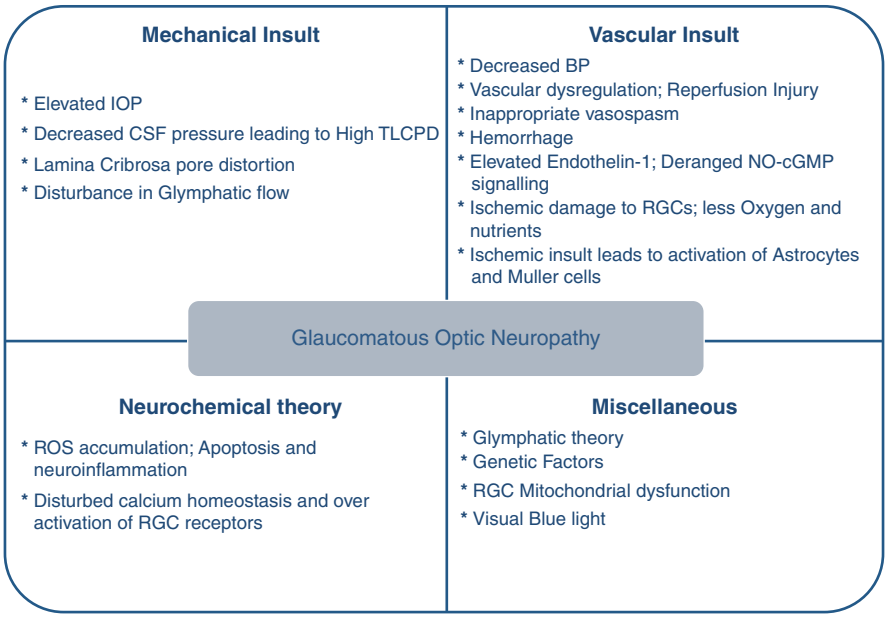

Fig. 1.1 Summary of theories for pathogenesis of glaucoma

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What's New in Structural Tests for Glaucoma

2

Carina Torres Sanvicente and M. Reza Razeghinejad

Glaucoma is defined as a progressive optic neuropathy characterized by degeneration of retinal ganglion cells resulting in a distinct appearance of the optic disc and concomitant pattern of visual field loss [1, 2]. The currently accepted gold standards for glaucoma diagnosis and management are detecting structural changes of the optic disc and nerve fiber layer and standard automated perimetry to assess the optic nerve function. The management of glaucoma relies on the change or progression of optic neuropathy over time; therefore, the need for a reliable, repeatable, and reproducible test of the optic nerve and retinal nerve fiber layer (RNFL) structure is paramount. The fast-pace improving technology has much contributed to testing of glaucoma; however, the slow progressive nature of the disease requires consistency of the results and also the comparability of technologies when evaluating patients longitudinally [3]. Peripapillary RNFL analysis using optical coherence tomography (OCT) is the most commonly used scanning protocol for glaucoma diagnosis and management. However, other modalities of OCT including the ganglion cell analysis, OCT angiography, and anterior segment OCT have added a lot to this field. In this chapter, the novel available OCT technologies for structural testing in glaucoma are presented.

Posterior Segment OCT

OCT was first described in 1991 [4, 5]. Over time and after significant advancement, it has become the technology of choice in structural evaluation of glaucoma [6]. Nowadays, the most commonly used OCT machines for evaluation of optic

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nerve head (ONH), RNFL, and ganglion cell layer (GCL) are Fourier domain or spectral domain-OCTs (SD-OCT). SD-OCT is an ultrahigh-speed OCT system that acquires depth profiles at a wavelength of 840 nm, at the speed of 10,000–29,300 scans per second [7]. It has supplanted the use of time domain-OCT (TD-OCT) providing faster scans (68 times) and a higher axial resolution of 5 μm, compared to 10 μm for TD-OCT [6]. SD-OCT allows cross-sectional and three-dimensional visualization of retina and optic nerve [8].

Swept-source OCT (SS-OCT) applies a short-cavity swept laser with a tunable wavelength of operation, instead of the diode laser used in SD-OCT [9, 10]. This new technology has increased imaging depth by using a center wavelength of 1050 nm and a sweeping range of 100 nm [10]. High-resolution imaging of deep ocular structures such as the choroid and lamina cribosa (LC) as well as high-quality wide-angle images (up to 12 × 12 mm), capturing optic disc and macula in one frame, are among the capabilities of this machine [10].

Peripapillary Retinal Nerve Fiber Layer

Measurement of RNFL thickness with SD-OCT has enabled quantitative and objective assessment of glaucomatous structural damage [3]. Excellent reproducibility and repeatability has been shown for both generalized and focal RNFL defects detection [3]. It has become the gold standard OCT parameter in diagnosis and follow-up of glaucoma patients. Individual results are compared to a normative database (Figs. 2.1a, 2.2, and 2.3), and, in the printout, the average and sectorial RNFL thickness measurements as well as symmetry between both eyes are presented. The role of OCT in detecting glaucoma progression varies widely with the stage of the disease [11]. Reports on progression are available for most SD-OCT machines, by analyzing RNFL, ONH, and GCL. The changes recorded for these parameters are analyzed based on the event and/or trend analysis (Figs. 2.4, 2.5, and 2.6). Event analysis is based on the difference between measurements and considers the change as progression when it reaches a certain threshold (usually set by the test-retest repeatability and reproducibility) (Fig. 2.4a). Trend analysis is based on a linear regression between the parameter of interest and time (Fig. 2.4b, c). It is especially useful when estimating the rate of disease progression [12].

A recent meta-analysis on the diagnostic ability of commercially available OCT devices (Zeiss Stratus, Zeiss Cirrus, Heidelberg Spectralis, Optovue RTVue, and Topcon 3DOCT) showed that the average, superior and inferior RNFL measurements had the best diagnostic ability [13]. Both SS-OCT and SD-OCT show comparable diagnostic ability using these parameters [10].

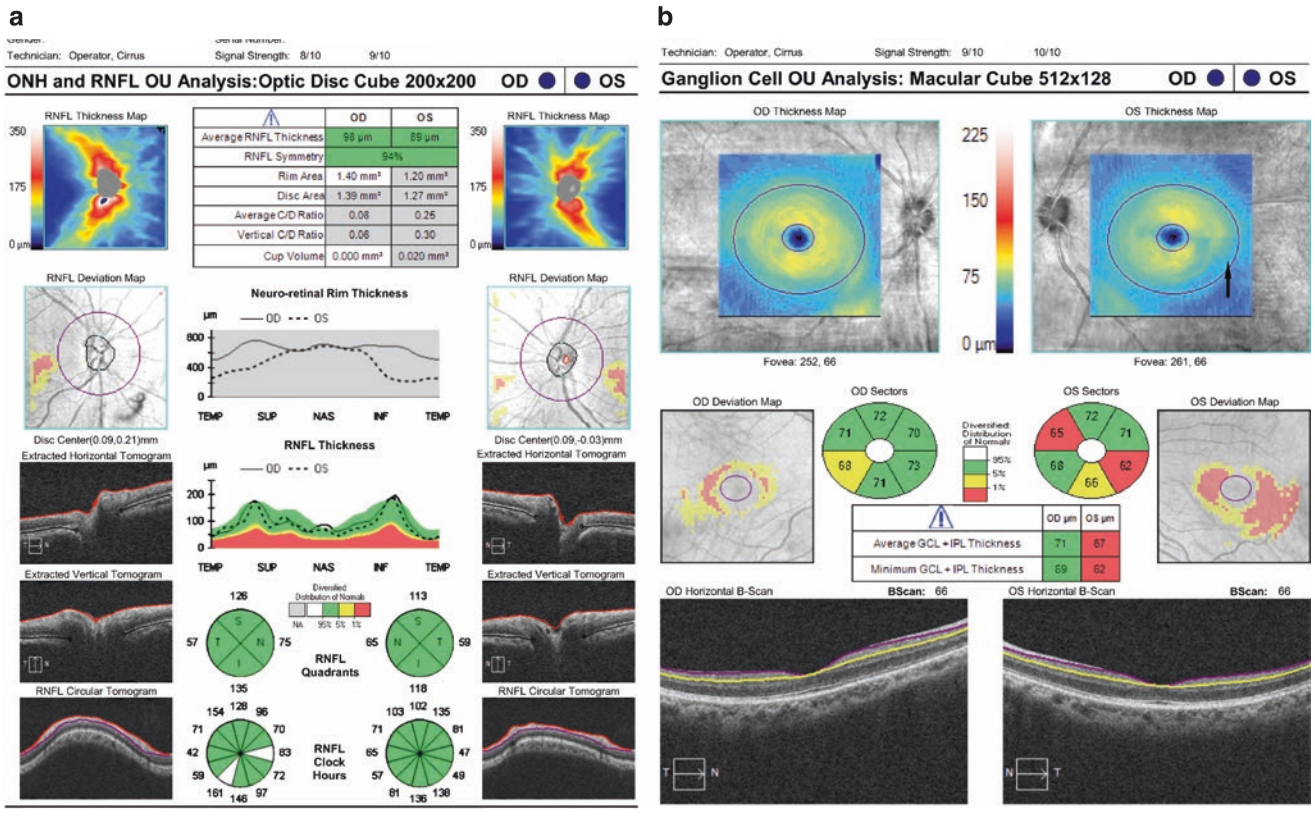

Fig. 2.1 (**a**) Printout of the cirrus spectral domain optical coherence tomography (Carl Zeiss Meditec, Inc.) of the retinal nerve fiber layer (RNFL) and optic nerve head (ONH) parameter showing an intact RNFL and ONH. (**b**) Printout of the ganglion cell analysis of the same patient showing the discrete pattern of ganglion cell and inner plexiform layer thinning in the macular vulnerability zone (arrow) compatible with early glaucoma damage

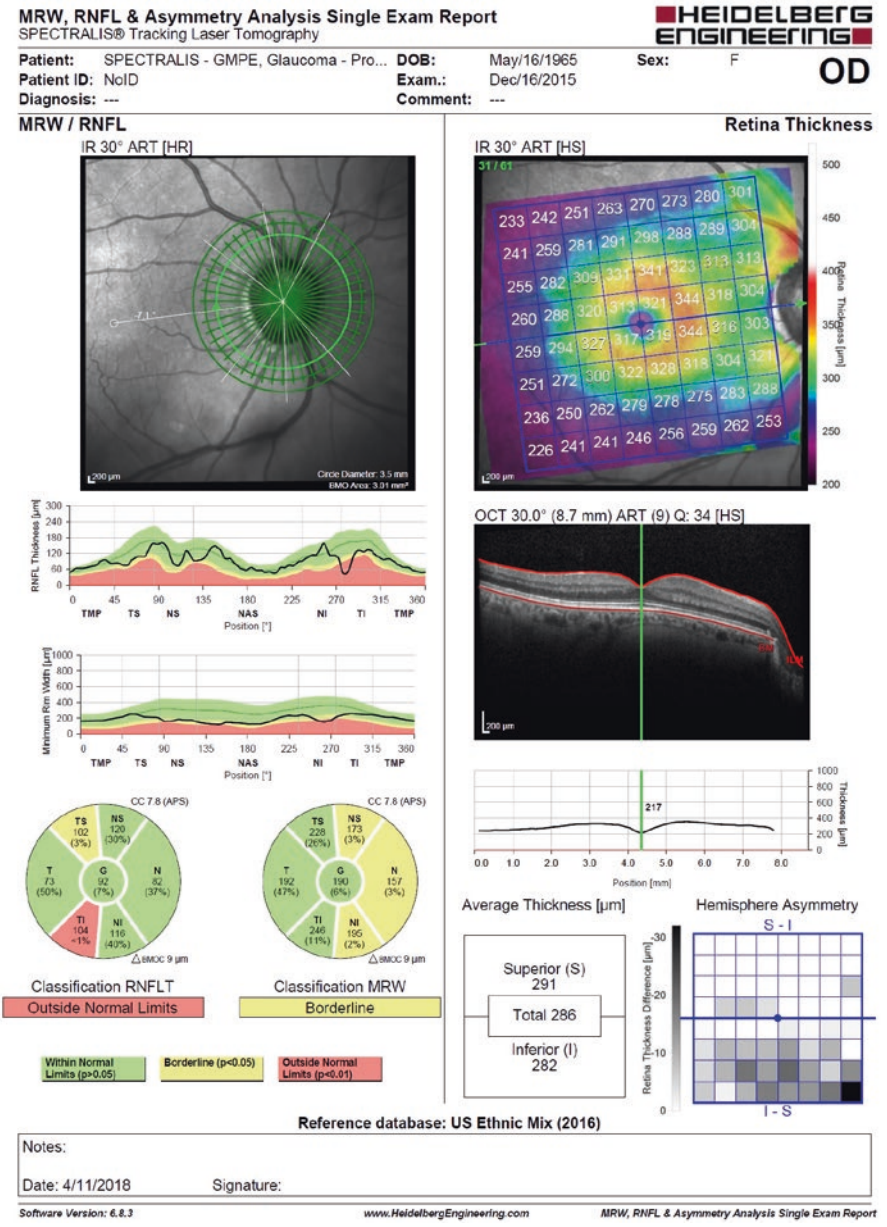

Fig. 2.2 Printout of the spectralis optical coherence tomography (Heidelberg Engineering, Inc.) of retinal nerve fiber layer and macular thickness (asymmetry analysis). Image courtesy of Heidelberg Engineering, Inc.

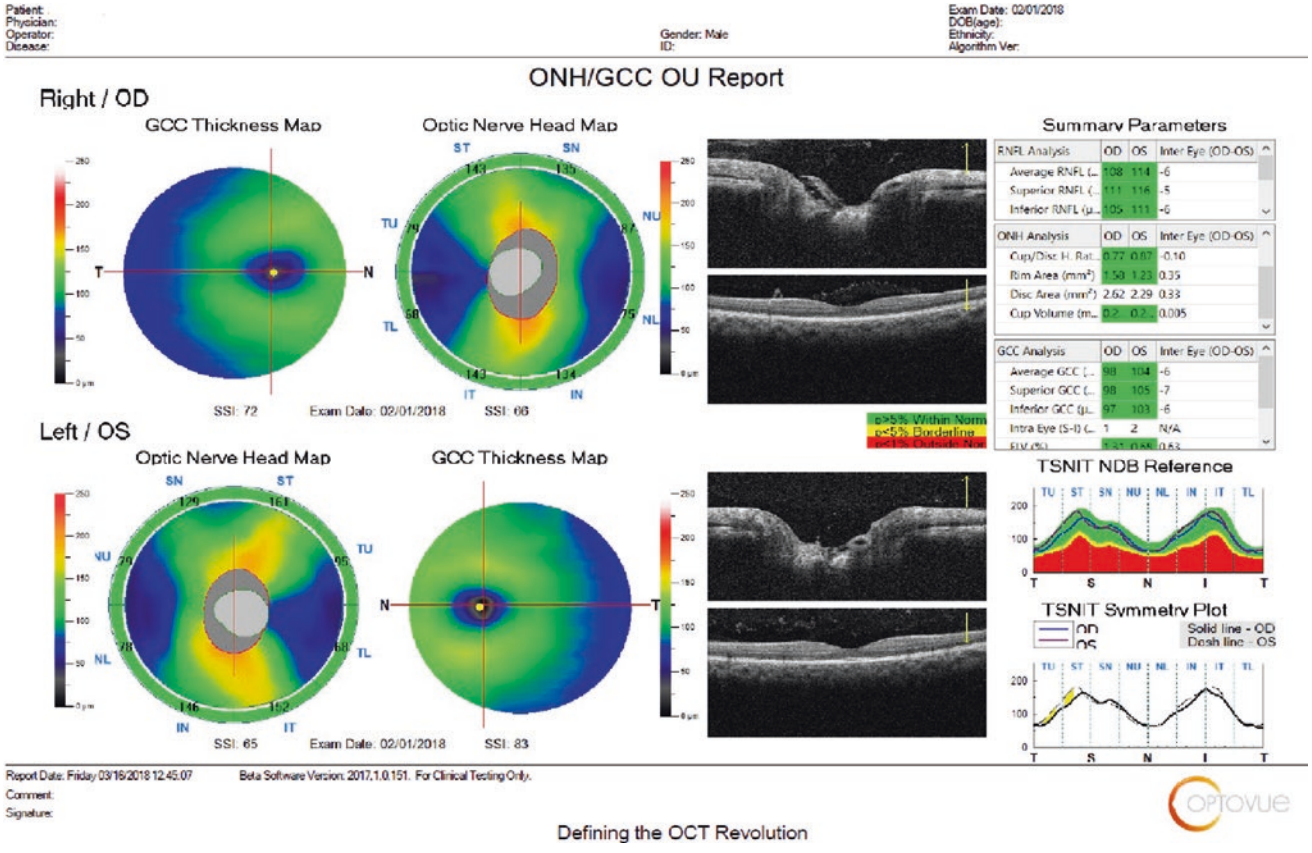

Fig. 2.3 Printout of the Optovue avanti spectral domain optical coherence tomography (Optovue, Inc.) of retinal nerve fiber layer, optic nerve head, and ganglion cell complex of a patient with ocular hypertension

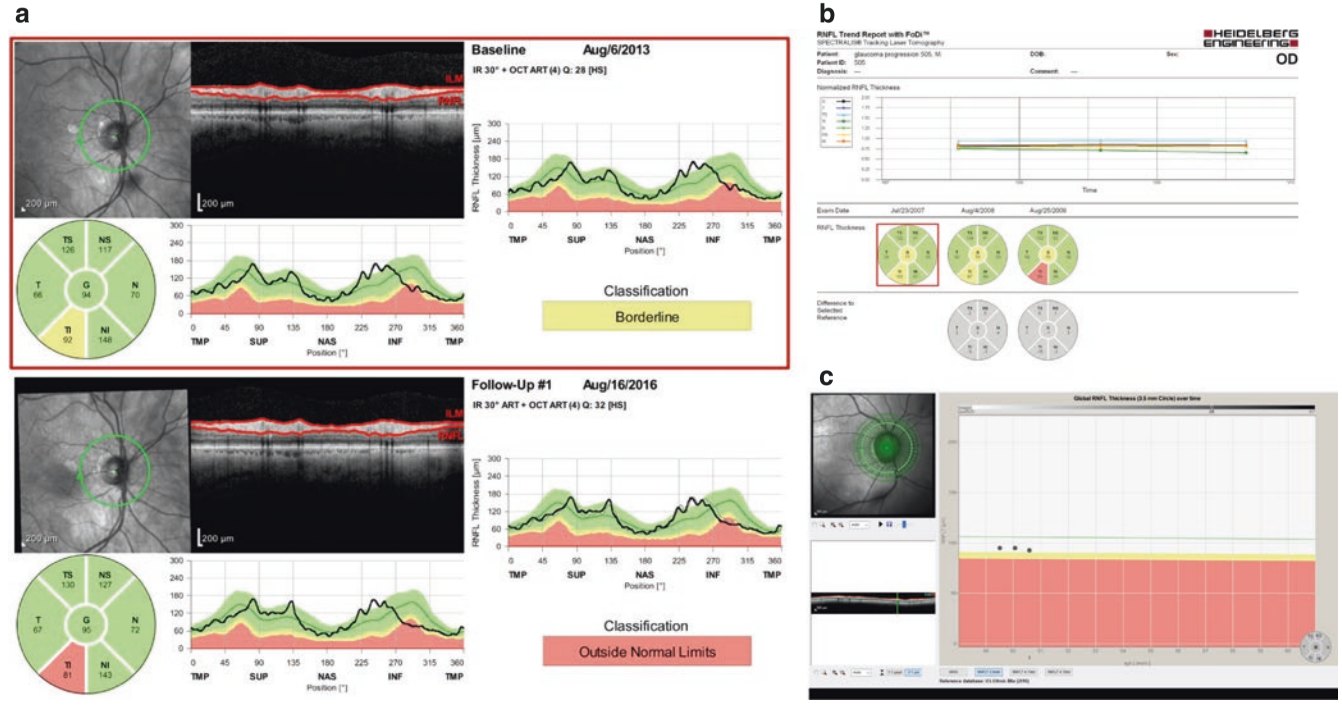

Fig. 2.4 (**a**–**c**) Progression analysis printout of Spectralis optical coherence tomography (Heidelberg Engineering, Inc.). Images courtesy of Heidelberg Engineering, Inc.

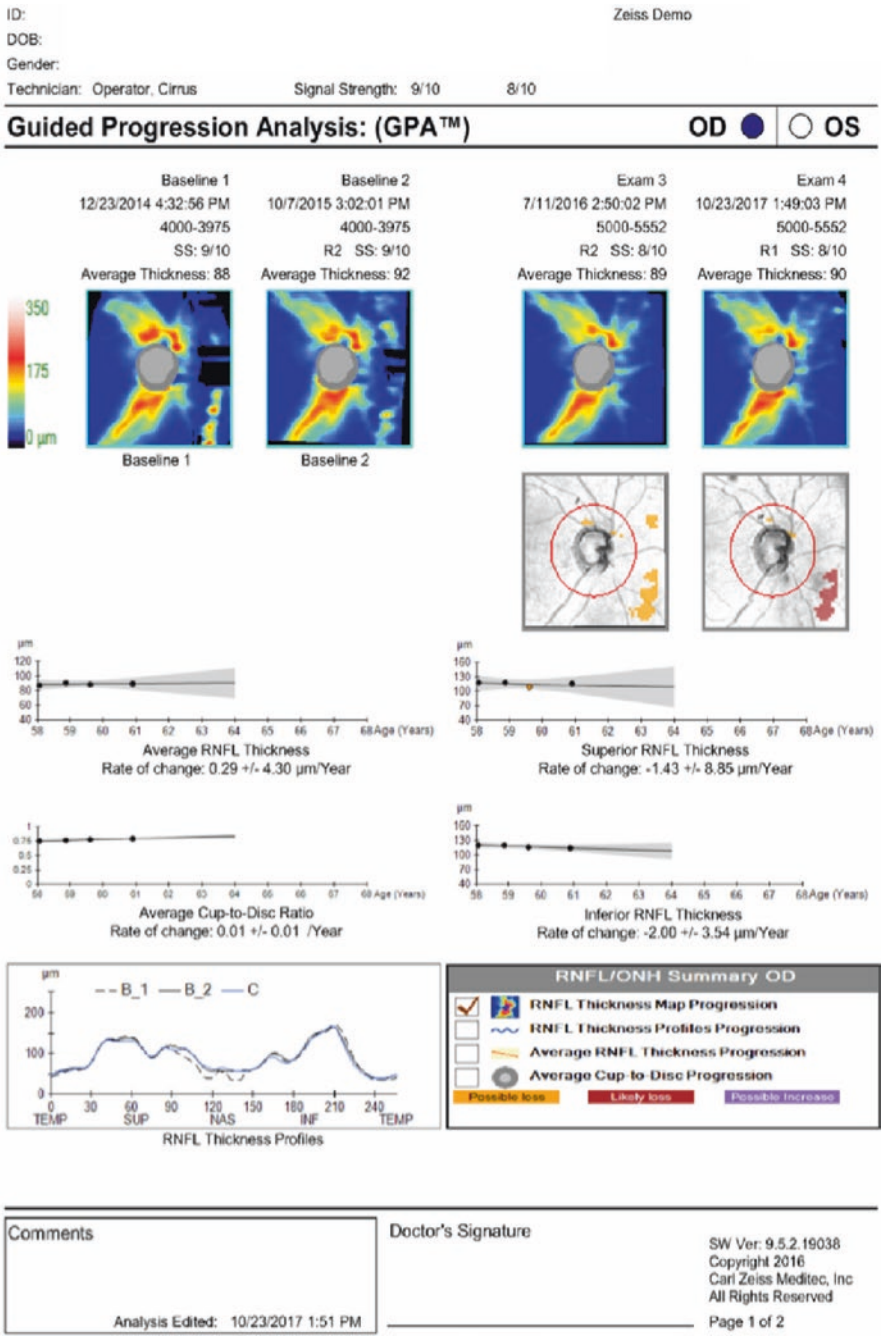

Fig. 2.5 Guided progression analysis (Carl Zeiss Meditec, Inc.) using retinal nerve fiber layer and optic nerve head parameters

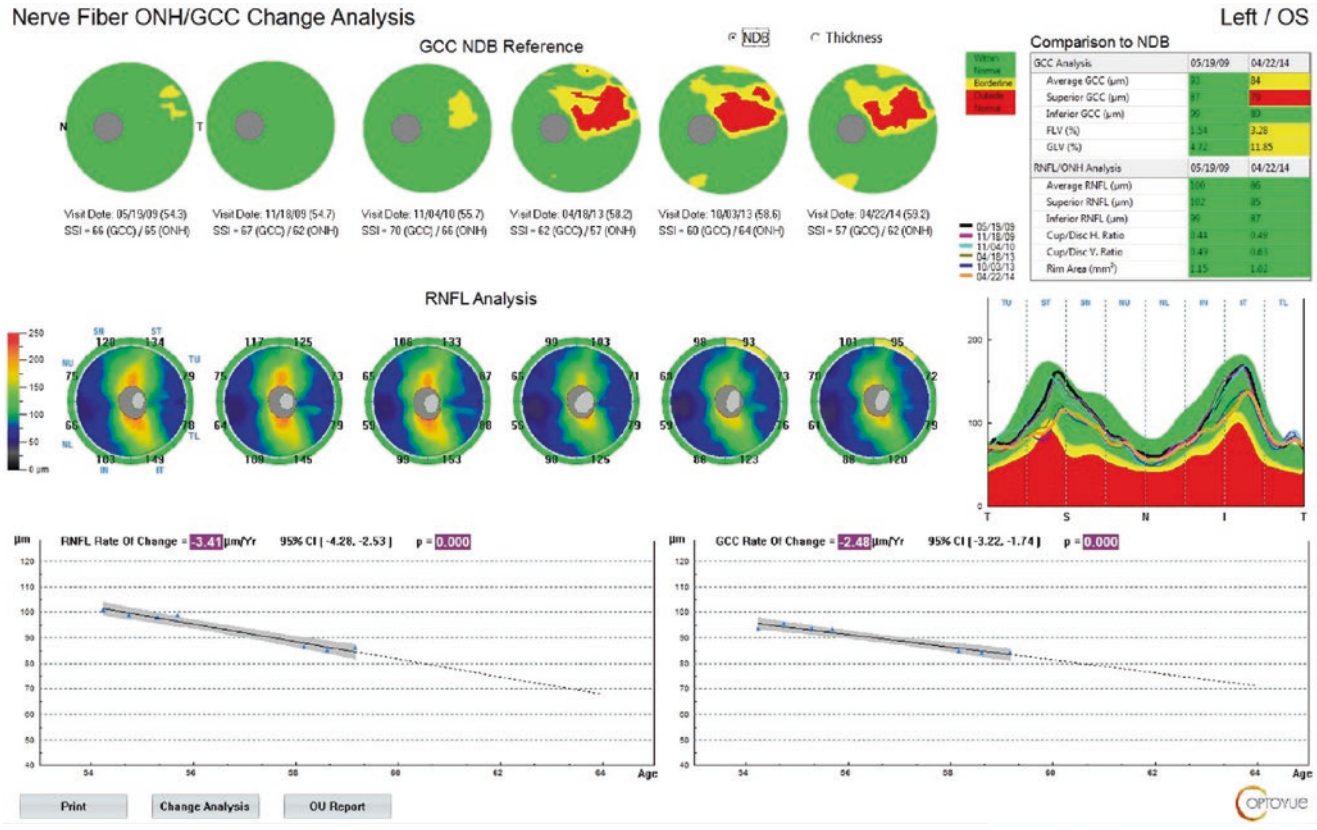

Fig. 2.6 Trend analysis report on ganglion cell complex and retinal nerve fiber layer change using avanti optovue optical coherence tomography (Optovue, Inc.)

Optic Nerve Head

Evaluation of the ONH is also possible using OCT and has been tremendously improved with the use of SD-OCT. Cirrus HD-OCT (Carl Zeiss Meditec, Inc.) uses the disc cube protocol, which scans 200 A scans and 200 B scans and over a 6.0 mm^2 area centered on the ONH [14]. Some parameters yielded by this scan are disc and rim area (mm^2), cup-to-disc (CD) ratio, vertical CDR, and cup volume (mm^3) (Fig. 2.1a, central top box). Spectralis OCT (Heidelberg Engineering, Inc.) ONH protocol consists of 193 B-scans centered in the ONH with a field of view of 20° × 20° (corresponding approximately to an area of 6.0 mm^2) [15]. It evaluates the following parameters: rim area, volume, and thickness. Avanti OCT (Optovue, Inc.) evaluates rim, disc, and CD ratio areas (mm^2), horizontal CD, vertical CD, as well as cup volume (mm^3) (Fig. 2.3, right middle box).

Classical two-dimensional ONH OCT uses a reference plane 150 μm above the retinal pigment epithelium/Bruch's membrane (RPE/BM) complex, which may be affected by variable cup anatomy [16]. Removing this source of variability can make the test more reproducible and reliable for detection of progression [17]. Analysis of the optic nerve with 3D SD-OCT yields two parameters that appear to bring advantages on diagnostic ability of 2D RNFL and ONH analysis: the minimum distance band (MDB) and the minimum rim width [18]. The MDB is a parameter derived from a densely sampled scan (512 A-lines in the 193 B-scans, averaging 193 raster scans) found on the Spectralis SD-OCT and quantifies three-dimensional neuroretinal rim tissue using the position of the disc margin through the accurate delineation of the internal limiting membrane (ILM) and RPE/BM complex. Unlike previously used ONH OCT parameters, MDB is not defined by an arbitrary reference [15]. A similar parameter, called the Bruch's membrane opening-minimum rim width (BMO-MRW), uses 24 radial scans and one circumpapillary B-scan centered on the ONH and measures the minimum distance between Bruch's membrane opening and the ILM (Fig. 2.7) [19]. Both three-dimensional SD-OCT parameters performed better than two-dimensional ONH OCT parameters for glaucoma detection. When compared to two-dimensional RNFL thickness measurements, MDB and BMO-MRW had better or equal diagnostic performance, depending on the quadrant evaluated [16].

Retinal Ganglion Cell Layer

Improved scan quality and segmentation introduced the use of macular parameters in the management of glaucoma [20]. Fifty percent of the retinal ganglion cells (RGCs) are in the macular area; these cells appear to have larger cell bodies than the periphery. Macular parameters have shown to be less affected by structural variability than the peripapillary area and also have high reproducibility [20]. The majority of commercially available SD-OCT machines have protocols of macular measurements for glaucoma assessment (Table 2.1) (Figs. 2.1b, 2.2, and 2.3). GCA analysis showed comparable or superior diagnostic ability for detecting early glaucoma to

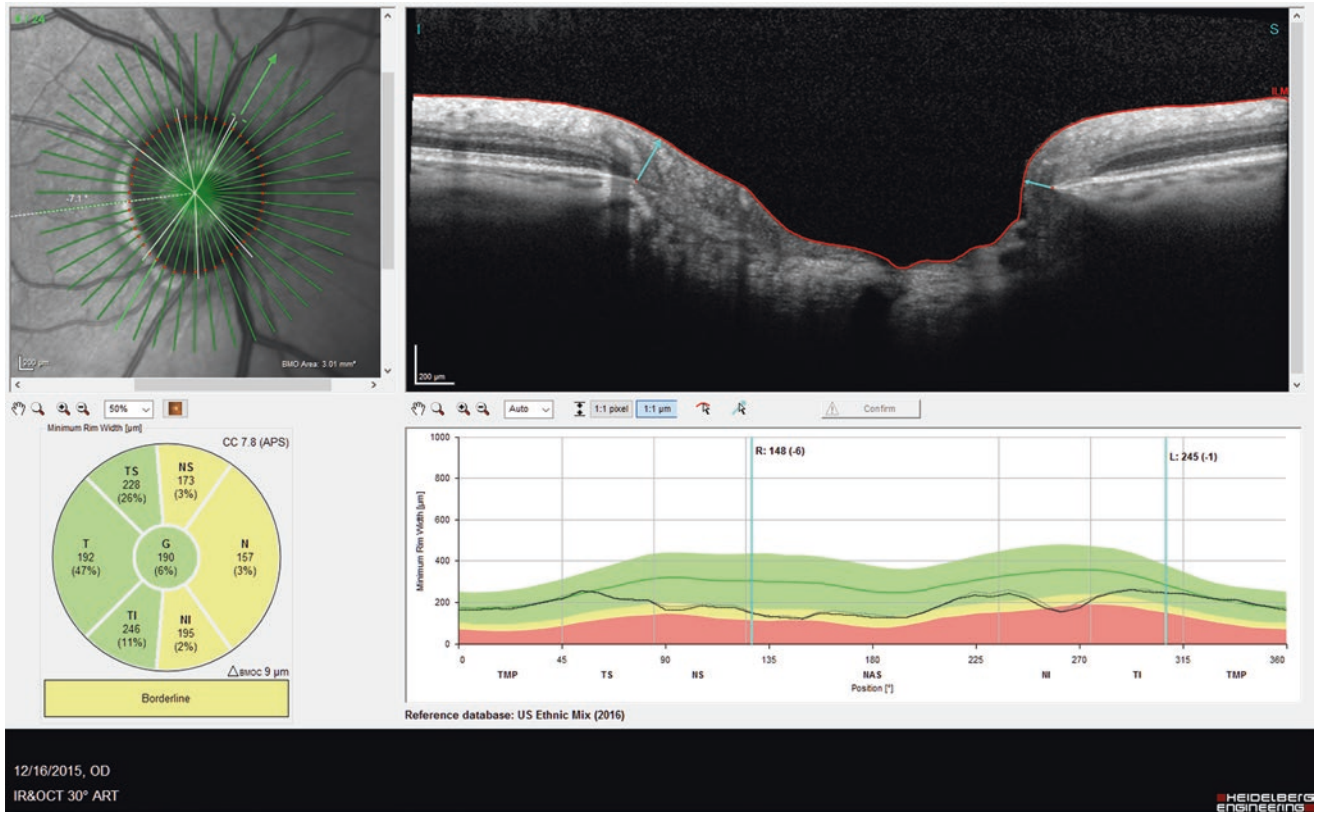

Fig. 2.7 Minimum rim width measurements of the optic nerve head using Spectralis OCT. Blue arrows measuring the minimum distance from Bruch's membrane to the internal limiting membrane (Heidelberg Engineering, Inc.). Images courtesy of Heidelberg Engineering, Inc.

Table 2.1 Commercially available SD-OCT with macular scan protocols for detecting glaucomatous damage

	Cirrus HD-OCT	Spectralis OCT	RTVue FD-OCT	Topcon 3D-OCT
Manufacturer	Carl Zeiss Meditec, USA	Heidelberg Engineering, Germany	Optovue, USA	Topcon, Japan
Scan speed (A-scans/s)	27,000	27,000	26,000	27,000
Axial resolution (μm)	5	3.9	5	5–6
Transverse resolution (μm)	15	14	15	20
Grid dimensions (mm)	6 × 6	8 × 8	7 × 7	6 × 6
Center	Fovea	Fovea	1 mm temporal to the fovea	Fovea
Layers measured	GCIPL = GCL + IPL	Separate measurements of retinal layers	GCC = GCL + IPL + RNFL	RNFL, GCIPL, GCC

SD spectral domain, *OCT* optical coherence tomography, *GCL* ganglion cell layer, *IPL* inner plexiform layer, *GCIPL* ganglion cell-inner plexiform layer, *GCC* ganglion cell complex, *RNFL* retinal nerve fiber layer

RNFL and ONH measurements (Fig. 2.1, showing normal RNFL and abnormal GCA) [21–23].

GCIPL parameters had better diagnostic ability than peripapillary RNFL in detecting structural changes in those with central visual field defects [24]. A study with follow-up of 3 years revealed a possible temporal relation between structural damage to the macular vulnerability zone (MVZ), as assessed by GCIPL, preceding RNFL defects in the corresponding area [25]. The CGIPL thickness measurements have also shown to be useful in detecting progression in advanced glaucoma, when RNFL and ONH parameters may have reached the floor effect [26–28].

Macular parameters may be affected by structural changes and other ocular pathologies [29–31]. However, in high myopic eyes, retinal ganglion cell parameters, especially the inferotemporal GCIPL thickness, have shown one of the best diagnostic abilities for perimetric and preperimetric glaucoma [32, 33]. Diagnostic performance of this parameter is similar between SD-OCT and SS-OCT. [34]

Most SD-OCTs use macular measurements for glaucoma progression detection (Fig. 2.6). In fact, a report using trend-based analysis showed that the rate of GCIPL thinning was significantly faster in patients experiencing glaucoma progression than those without progression [35]. A longitudinal study showed that the progression analysis using the GCIPL was possible even in advanced cases and could predict visual field defects better than RNFL change analysis [36].

Lamina Cribosa

Lamina cribosa (LC) is an area of interest in the pathogenesis of glaucoma [37]. However, standard SD-OCTs are not able to provide a reliable and reproducible image of this structure. Enhanced-depth imaging (EDI) was developed by Spaide et al. by placing an SD-OCT machine closer to the subject's eye and obtaining an inverted image, thereby obtaining images of more posterior structures [37, 38]. LC thickness measurement using EDI has shown comparable ability to peripapillary RNFL thickness in detecting patients with glaucoma and showed greater ability in diagnosing early normal tension glaucoma [37].

Imaging of the LC yields qualitative and quantitative data, such as its morphology, posterior displacement, thickness, and presence of LC focal defects (holes, disinsertions) [39]. These parameters have shown good intra-observer reproducibility for both EDI and swept-source technologies [40]. Studies have shown a significant association between focal LC defects and concomitant localized RNFL thinning and longitudinal progression of the disease [39, 41, 42]. Further research on LC evaluation may lead to incorporating LC assessment in the clinical practice of glaucoma management.

Evaluation of the three-dimensional microarchitecture and automated segmentation of the LC in vivo has been possible using either SS-OCT or a combination of SD-OCT and adaptive optics (AO) [43]. AO employs a wavefront sensor and corrector that measures and corrects for monochromatical optic aberrations in real time. AO has been incorporated in many ophthalmic imaging modalities, such as fundus photography, scanning laser ophthalmoscopy, and OCT, successfully diminishing artifacts and increasing image quality [44]. The pairing of AO with SD-OCT has enabled substantial improvement in lateral and axial resolution of the scans, with visualization of discrete structures, such as individual retinal ganglion cells and photoreceptors [44, 45]. Widespread incorporation of AO still encounters some limitations, such as the need for robust image processing, limited field of view and extended acquisition time.

OCT Angiography

Retinal and optic nerve head vascular perfusion is classically assessed by fluorescein angiography (FA) [46–49]. More recently, noninvasive methods such as Doppler OCT used SD acquisition to detect Doppler frequency shift of backscattered light and obtain blood flow images [50]. However, with these methods, only the superficial vessels supplied by the central retinal artery are visualized. Since the blood to the ONH is also supplied by the posterior ciliary arteries, a method for assessing the deep microcirculation was sought after [51]. Jia et al. developed the split-spectrum amplitude-decorrelation angiography (SSADA) algorithm that enables the quantification of peripapillary and optic nerve blood flow using high-speed OCT [52, 53].

With OCT angiography (OCTA) technology, noninvasive quantification and description of blow vessels in all layers of the ONH (including the LC) is possible (Fig. 2.8). Through the flow index parameter, a significant difference between normal

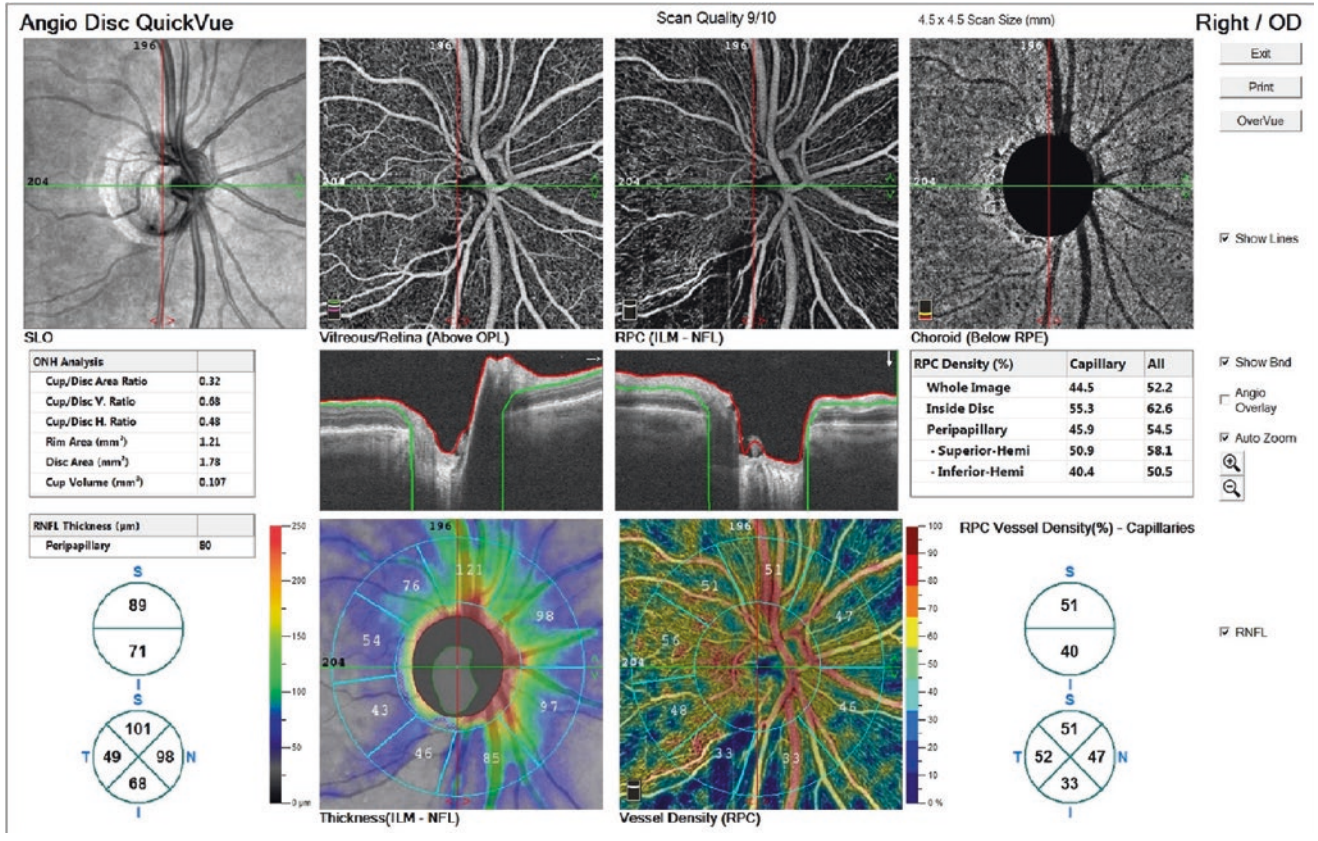

Fig. 2.8 Optical coherence tomography angiography of the optic nerve and peripapillary area taken with the Avanti Angiovue (Optovue, Inc.) showing decreased vessel density in the inferior peripapillary area in a patient with glaucoma. Images courtesy of Optovue, Inc.

and glaucomatous eyes has been demonstrated. This parameter also showed a strong correlation with the visual field pattern standard deviation [52]. OCTA has great value in detecting changes in the peripapillary vasculature, using the flow index and vessel density parameters in glaucoma patients. Both mentioned parameters were independently correlated with the mean deviation and pattern standard deviation of visual field [54]. A study on longitudinal macular vessel density change concluded that patients diagnosed with glaucoma had significant decrease in vascular density than controls or glaucoma suspects. Further longitudinal research may show a temporal, or even, causal relationship between vascular dropout and RNFL loss.

Anterior Segment OCT

Anterior segment OCT (AS-OCT) is an imaging modality to assess the anterior segment structures qualitatively and quantitatively [55]. A higher light wavelength (1.3 μm) is utilized for scan acquisition of the anterior segment [56].

Angle Assessment

High-resolution cross-sectional images of the cornea and angle structures, including the iris root, angle recess, anterior ciliary body, scleral spur, and, in some cases, the Schlemm's canal is possible. Quantitative evaluation of the angle with AS-OCT is dependent on the visualization of certain anatomic landmarks, most commonly, the scleral spur, or Schwalbe's line [57, 58]. The following quantitative parameters have been described using this technology (Fig. 2.9) [59]:

- Angle opening distance (AOD): perpendicular distance between a point 500 μm (AOD 500) or 750 μm (AOD 750) anterior to the scleral spur and opposing iris
- Angle recess area (ARA): the triangular area bounded by the AOD 500 (ARA 500) or 750 (ARA 750), the anterior iris surface, and the inner corneoscleral wall

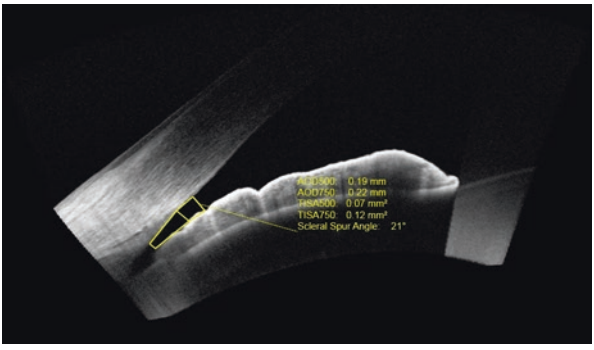

Fig. 2.9 Anterior segment optical coherence tomography imaging with the Cirrus HD-OCT 5000 (Carl Zeiss Meditec, Inc.) showing the parameters used for analysis of the anterior segment angle. Images courtesy of Carl Zeiss Meditec, Inc.

– Trabecular space area (TISA): trapezoidal area bounded by the AOD 500 (TISA 500) or 750 (TISA 750), anterior iris surface, inner corneoscleral wall, and the perpendicular distance between the scleral spur and opposing iris

However, visualization of key delimiting structures may not be possible in up to 28% of eyes [60]. In such cases, it is still possible to qualitatively assess iridocorneal apposition in most images. AS-OCT also reveals the configuration of the peripheral iris and its relationship to the trabecular meshwork. A closed angle is defined by the presence of contact between the iris and angle wall anterior to the scleral spur. The diagnostic ability of AS-OCT for angle closure depends on the scanning protocol, with the inferior quadrant-only protocol showing the highest area under the receiving operating characteristic curve [61].

Iris Angiography

The advancements of OCTA allows imaging and characterization of the vasculature of the iris [62]. Compared to the iris FA, OCTA provides more detailed imaging of the iris vasculature [63]. This technique has been applied to evaluate anterior segment tumors, assessment of anterior segment ischemia and uveitis [64–70]. It is an invaluable imaging tool in patients with spontaneous hyphema without a history of trauma, surgery, or angle or iris neovascularization and high intraocular pressure to detect vascular pathologies like iris hemangiomatosis (Fig. 2.10) [66].

Further research will likely show the valuable role of anterior segment OCTA in the field of glaucoma. Possible applications would be in patients with pseudoexfoliation, pigmentary glaucoma, and iridocorneal endothelial syndrome, among other types of secondary glaucoma.

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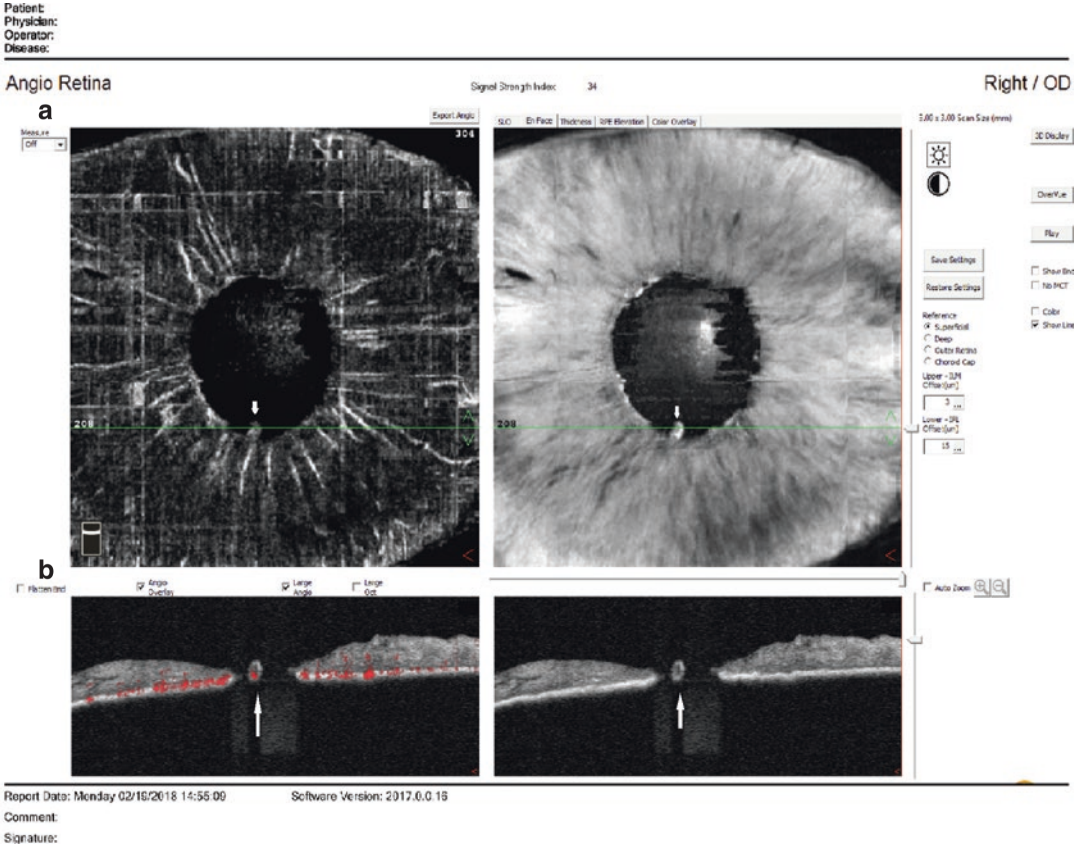

Fig. 2.10 Optical coherence tomography angiography of the iris showing iris hemangiomatosis (arrows) in the (**a**) en face and (**b**) B-scan images taken with the Avanti Angiovue (Optovue, Inc.). Images courtesy of Shields and Shields MD PC

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What's New in Functional Tests for Glaucoma

3

Zakieh Vahedian and Ghasem Fakhraie

Although various structural tests are aimed to diagnose glaucoma before functional impairment has occurred, the main goal of various treatments is to preserve functional vision and ability of the patient. Therefore, functional tests are very important to help us understand how the patients with glaucoma see the world and what difficulties they face in their daily life. Moreover, these information help scientists develop visual aid to help the patients have an easier, independent life.

Four main functional test groups, which can be done for glaucoma patients, include:

1. Contrast sensitivity tests
2. Perimetry
3. Electrophysiologic tests
4. Color vision test

Contrast Sensitivity

Contrast is the amount of lightness or darkness of an object against its background. Contrast sensitivity allows us to discriminate things with different shades of the same color. Therefore, it is important in many visual functions such as detecting motion, dark adaptation, pattern recognition, visual field, and acuity. Contrary to Snellen acuity, which measures central vision quantitatively, contrast sensitivity tests give us a better understanding of how the patient sees.

In glaucoma patients, binocular contrast sensitivity and visual acuity are strongly correlated with daily living activities; even more than amount of visual field impairment or optic disc damage [1]. In contrast to visual acuity, which is affected late in the course of glaucoma, contrast sensitivity damage occurs early (even in ocular

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hypertension or preperimetric stages) [2–4] and can be very valuable in assessment of functional disability of these patients. That is why even very early stage glaucoma patients may have difficulty in reading, driving at night, recognizing facial expressions, and many other tasks despite normal visual acuity [1, 5–7]. It should be kept in mind that both central and peripheral contrast sensitivity are reduced in glaucoma and contribute to patients' abilities to perform their daily tasks [2, 8, 9].

Different tests are available to measure contrast sensitivity with their own advantages and disadvantages [3–5, 10–14]; talking about all of them is beyond the scope of this chapter. In summary, these tests can be categorized into three groups:

1. ***Grating charts*** including Arden, Ginsburg, Cambridge, Vistech, Functional Acuity Contrast Test (FACT), and Vector Vision's CSV 1000 tests [11]
2. ***Letter charts*** such as Pelli-Robson, Regan, and Mars tests [11]
3. ***Mobile/computer-based tests*** like mobile app Aston test [15], ClinicCSF App [16], the Spaeth/Richman Contrast Sensitivity (SPARCS) test [17, 18], Freiburg Visual Acuity and Contrast Test (FrACT), Holladay automated contrast sensitivity system, and many other contrast sensitivity charts that are converted to be used on computer monitors [11]

Although many investigators have used contrast sensitivity tests in an attempt to diagnose glaucoma before occurrence of visual field defects, none of these tests have had enough sensitivity or specificity for early detection of this disease [13, 14, 19–21].

Herein, we discuss SPARCS and mobile apps, which are gaining popularity in clinical practice of glaucoma patients.

SPARCS (Spaeth/Richman Contrast Sensitivity)

In general, a clinically applicable test should be user-friendly, inexpensive, valid, and reliable. Most of the contrast sensitivity tests lack at least one of these characteristics. To address this issue, George Spaeth and his colleagues have designed a test named SPARCS that is an internet-based self-administered method of contrast sensitivity assessment. It has multiple answer choices and uses bracketing technique to reach contrast threshold in each location [17, 22, 23].

The test measures both central and peripheral contrast sensitivity (one central and four peripheral locations, i.e., superonasal, superotemporal, inferonasal, and inferotemporal) and has been used to discriminate different ocular diseases such as macular degeneration [24, 25] or cataract [26], from normal people. It is very simple to use and is easily accessible via the internet; it just needs a relatively cheap hardware without any specific software (only a web browser) [23]. Because this test does not have any optotypes, words, or letters, patient's literacy is not required. Corrected refractive errors either myopia or hyperopia do not influence the results [23].

Although SPARCS test results are significantly correlated with other tests such as Pelli-Robson (PR), which is a very reliable test of central contrast sensitivity, its

reliability is higher than PR and has better test-retest agreement [23]. The SPARCS test designers have claimed that their test is very specific and relatively sensitive for finding patients with glaucoma. In their study, all glaucoma patients with some optic nerve damage scored worse than most control people, some patients with minimal glaucomatous optic nerve damage scored well overlapping with controls though. They have suggested this test to be used as a home screening test or in following patients with definite diagnosis of glaucoma [17].

The worse SPARCS test scores, the more vision-related disability the glaucoma patients experience in their life. Therefore, this test can be used to get an impression of vision-related quality of life of these patients (Figs. 3.1 and 3.2) [27, 28].

Mobile Apps

Two mobile apps have recently been introduced to measure contrast sensitivity:

clinicCSF

It is an app compatible with both Android and iOS operating systems and is written by pure mobile ActionScript3.0 code. clinicCSF displays nine patches of sinusoidal gratings with spatial frequencies of 3, 6, 12, and 18 cpd. The app should be presented at 2 m from the subject; therefore an examiner is needed to hold the tablet at this distance and press the button corresponding to the patient's response. The stimuli are presented in various orientations (vertical and oblique) with different psychophysical methods to achieve the CSF threshold in the two versions (ClinicCSF. v1and .v2) [16].

This app has been shown to be similar to FACT test when using the same contrast sensitivity steps. For more details please refer to reference number [16].

Aston Contrast Sensitivity App

This app is designed for both near and far contrast sensitivity measurement and can be installed on iPad. It presents the contrasts and spatial frequencies at once by a swept frequency design. The patient should mark the boundary between the visible and invisible gratings. This app has been shown to have a good inter-test repeatability and validity [15].

Some clinicians have found significant improvement of contrast sensitivity with IOP reduction either surgically [29] or medically (may be due to neuroprotective effects of some agents such as brimonidine or carbonic anhydrase inhibitors) [30–33].

Perimetry

Visual field testing (perimetry) is one of the main diagnostic and follow-up tests in glaucoma, which characterizes the location and depth of vision loss. Standard automated perimetry (SAP) which is a static visual field testing (as opposed to kinetic perimetry) is the standard tool in functional assessment of glaucoma

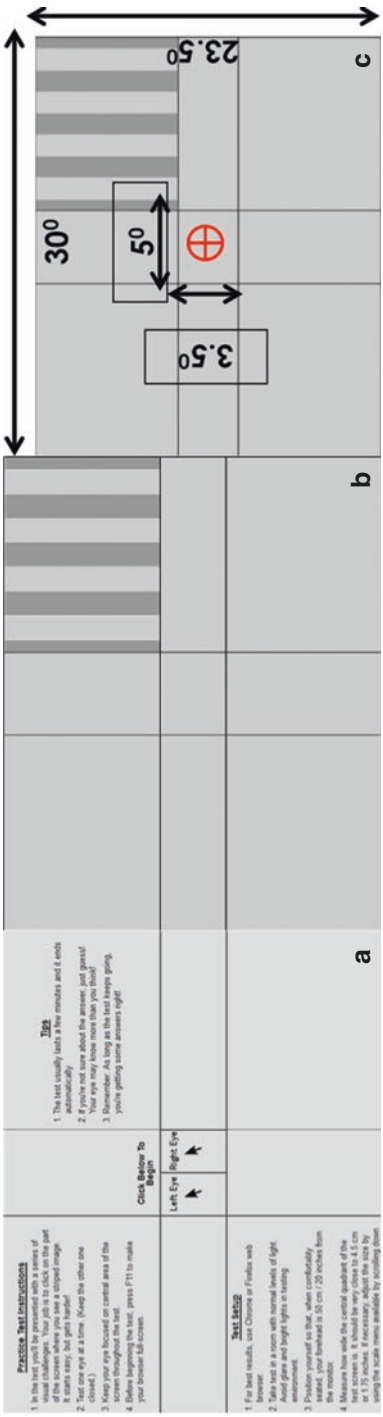

Fig. 3.1 SPARCS. (**a**) Instruction screen. (**b**) Testing screen. (**c**) Degrees of vision represented by testing screen

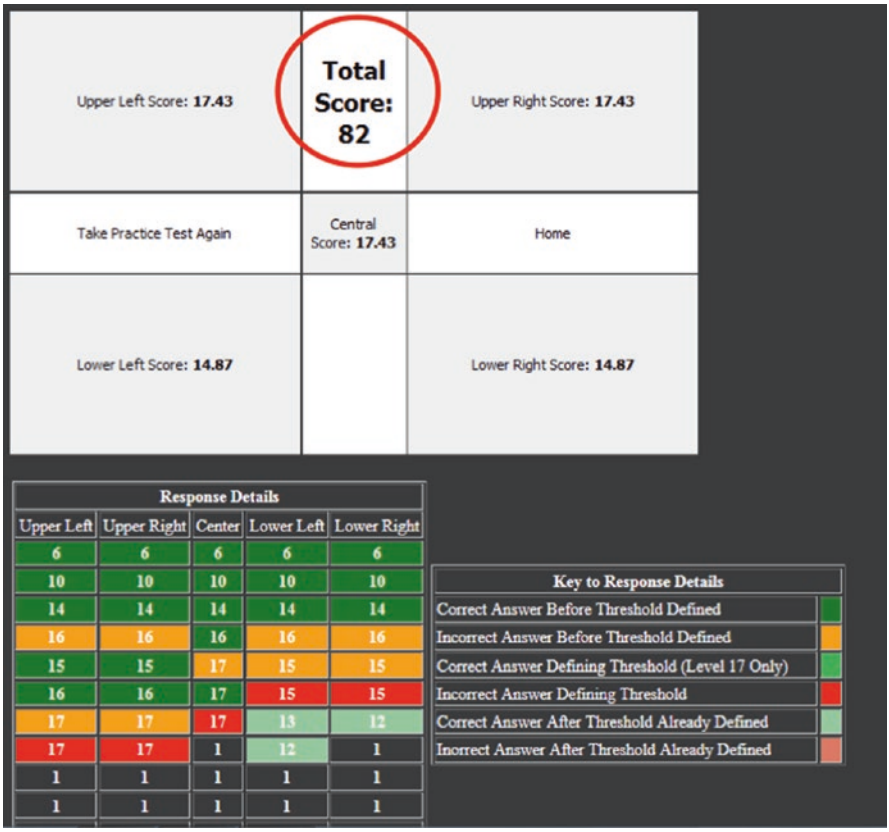

Fig. 3.2 SPARCS test results (Image courtesy: Dr. Parul Ichhpujani)

patients. It has long been used in clinical settings despite its many drawbacks such as subjectivity, being lengthy and the results affected by patients' learning. Over the years many innovations have been made in order to improve its efficiency and lessen its flaws and difficulties.

Electronic Visual Field Tests

Many electronic forms of visual field testing have been developed. They can be used at home via personal computers, various tablets including iPad, or portable brain-computer interfaces.

Herein, we discuss some of these tests:

Peristat

Peristat is a computer-based virtual perimetry that is suprathreshold, achromatic, and static. It has a patient-friendly system and uses internet for working (it is available at http://www.keepyoursight.org for free). The test uses four levels of standardized

threshold stimuli and is originally designed for screening. It optimally detects moderate to severe scotomas. The threshold of the central 24° of the field horizontally and 20° vertically is measured, and fixation loss and false-positive and false-negative indices are used for assessment of reliability. A target of 3 mm in diameter is presented within 6° intervals. An alert patient can easily perform this test in less than 5 min for each eye [34, 35].

It has been shown to be reasonably reliable for self-screening of populations while being inexpensive and cost-effective in large scale [34]. It has been shown to have a good correlation with Humphrey visual field in terms of number of abnormal points and an acceptable area under ROC curve compared to other visual field tests in both mild and moderate to severe glaucoma (Fig. 3.3) [35].

Visual Fields Easy (VFE)

This is a free iPad application and, as Peristat, is good for suprathreshold screening of visual field [36] and can be freely downloaded and used. Ninety six test points (24 in each quadrant) spread in central 30° are tested from 33 cm distance. The fixation target is red and is first placed in the lower left corner and the patient's eye and head are centered on it. After testing one quadrant, the fixation target is moved to the lower right corner to evaluate another quadrant. The same procedure is done for all quadrants. Goldmann Size V stimulus is presented with 16 dB intensity. The background luminance of 10 cd/m^2 (31.5 asb) is used. Reliability of the test is assessed by false-positive and false-negative indices [37]. This test is good for detection of moderate to advanced glaucoma, and the number of missed points correlates with MD and PSD in Humphrey visual field test [37]. It has a reasonable sensitivity, specificity, and positive and negative predictive values. Therefore, although the test does not replace SAP, it is a good tool to be used in poor countries or places where SAP is not available (Fig. 3.4) [38].

Melbourne Rapid Fields (MRF)

This iPad application is a threshold perimetry; hence it can be used for detection and monitoring of visual field status in glaucoma. It evaluates 66 test points distributed over central 30° from fixation. It can easily be performed at home or remote areas with little financial resources [39]. Because the iPad screen is not big enough to test all the 30° with patient fixating on one target, areas more than 18° from fixation should be evaluated by changing the fixation point location (on the four corners of the screen) [40]. False-positive and false-negative indices are calculated for reliability assessment. The test takes less than Humphrey to be completed. Its results are highly correlated with Humphrey results with similar test-retest reliability [41]. Global indices such as MD, PSD, and VFI are also highly correlated in two perimeters [40].

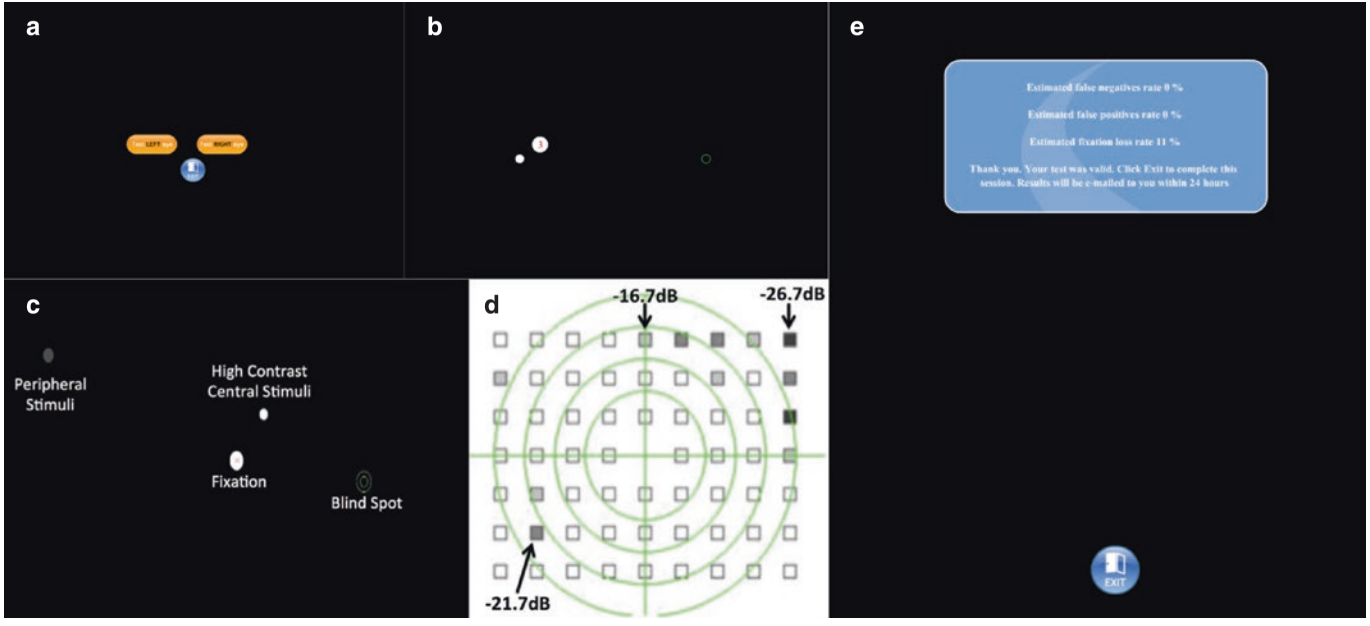

Fig. 3.3 Peristat online perimetry. (**a**) Test screen at the beginning. (**b**) Test screen when patient is undertaking the test. (**c**) Patient fixes on a central white circle at such a distance that the blinking green circles would disappear in the blind spot. High contrast stimuli are initially presented in the central visual area to establish a baseline response pattern followed by peripheral stimuli of varying intensity. Patient must respond to each stimulus by pressing the computer space bar. (**d**) The errors are recorded to create a plot of visual field defects at −16.7, −21.7, and −26.7 dB contrast sensitivities. (**e**) End of test. Results are interpreted by an expert and e-mailed to the patient within 24 h

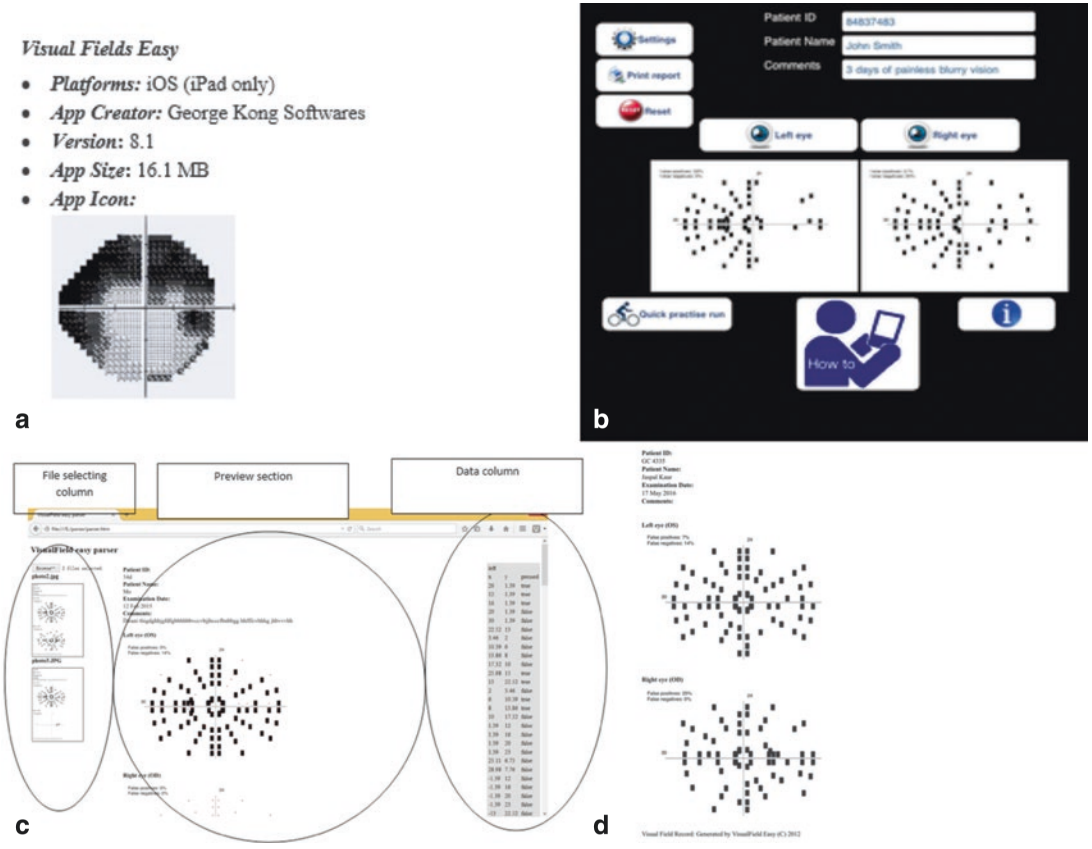

Fig. 3.4 Visual fields easy. (**a**) App details. (**b**) Test screen. (**c**) Data analysis. (**d**) Test result (Source: DOI: https://doi.org/10.13140/RG.2.2.36476.64640; Permission to use by Dr. Parul Ichhpujani)

nGoggle

All the above-mentioned forms of perimetry are subjective and hence affected by the patients' compliance, cooperation, and alertness. A portable brain-computer interface (BCI) has recently been validated to address this problem. nGoggle (NeuroGoggle) is a BCI that can assess visual field using multifocal steady-state visual evoked potentials (mfSSVEP) and therefore is completely independent from patient's responses. The platform is portable and consists of wireless, wearable dry electroencephalograph and electrooculography combined with a head-mounted display (HMD) that is cellphone-based. It detects mfSSVEP waves as a result pattern reversal visual stimuli. The field of view is divided into 20 sectors; each of them flickers at a specific frequency. The device can distinguish glaucomatous optic neuropathy from normal in clinics. It may be used as a home-based test in future [42].

Compass Perimetry

Maintaining proper fixation is essential for having a reliable visual field test. Therefore, monitoring how the patient fixates on the proper target is important for assessment of the reliability of the test. Fundus tracking (microperimetry) is a new technique for eye tracking that has been recently introduced. A new instrument, called Compass (CenterVue, Padova, Italy), uses this technique for fixation monitoring. In this device, a scanning ophthalmoscope takes infrared and color images of the fundus without pupillary dilation. An automated perimeter and an eye tracker are also included in the device. If any eye movement (fixation loss) occurs, the device automatically compensates for it and therefore all the stimuli are exactly presented at predefined retinal locations. Central 24° or 30° of visual field (points 6° apart) with full threshold strategy can be evaluated. Other grids are continuously being developed for this device. In a dark room, the patient puts his or her chin and forehead on the corresponding places. Because the stimulus is directly presented on the retina, no corrective lens is needed and the device automatically compensates for any refractive errors if present. The 24-2 grid has 54 locations, and similar to Humphrey perimeter, Goldmann III stimulus with 200 ms duration, background luminance of 31.4 asb, and maximum luminance of 10,000 asb are used. Although compass perimetry has a good correlation with Humphrey visual field analyzer [43] and despite the very similarities, these two cannot be used interchangeably because of threshold sensitivities and global indices have wide limits of agreement [44].

MP-3 Micoperimetry

In MP-3 micoperimetry, unlike other perimeters in which the target is presented on a screen, the stimulation target is projected onto the retina. This microperimeter that is manufactured by Nidek Company, Japan, uses a fundus camera with 45° field of view. The retinal position is tracked automatically with an infrared image; therefore, the stimulated point is precisely determined and the effects of eye movements are eliminated. No mydriasis is needed for this perimetry. Like Humphrey visual field

analyzer, the background luminance is 31.5 asb and the device presents the target in 0–34 dB intensities [45, 46]. In this modality of visual field testing, central 10° of vision is tested (56 test points in a 2 by 2 grid) and has been shown to have similar test-retest reproducibility to Humphrey central 10-2 perimetry, with a greater relationship with structural tests [45]. Even, this test was more reproducible than octopus perimetry in a study performed by Palkovits, S. and colleagues [46].

MAIA™ (Macular Integrity Assessment)

MAIA is another type of microperimetry in which central 10° of the visual field is assessed using a 68-point grid. The fixation target is a red circle with 1° diameter. Goldman Size III stimuli is usually presented against a background with a luminance of 1.27 cd/m^2. It has been shown to have a good structure-function relationship similar to Humphrey analyzer [47–49].

Contrast Sensitivity Perimetry (CSP)

High variability of conventional perimetry in areas of glaucomatous defect, on one hand, and poor agreement between perimetric and structural findings in a great percentage of glaucoma patients, on the other hand, have led Swanson WH and his colleagues to invent a new test named contrast sensitivity perimetry (CSP). They first have tested CSP on 20 glaucomatous and 20 normal patients and have found less test-retest variability in areas of glaucomatous field defect than standard automated perimetry (SAP) and at the same time better agreement than SAP with rim area measured with HRT [9]. They then developed a second generation of CSP named CSP-2 which uses variable-sized stimuli and are more blur resistant [50] and are less affected by reduced retinal illumination, e.g., during miosis [51]. A custom-built testing station based on the Visual Stimulus Generator (VSG2/5, Cambridge Research Systems Ltd., Cambridge, UK) is used. It has a 21-in. cathode-ray tube display with 800 by 600 pixels resolution. The test is done at 33 cm from the patient and tests 57 locations in central field. The background luminescence is 40-cd/m^2. The stimuli are Gabor horizontal grating patches with a range of spatial frequencies (0.5 cpd at center and 0.14 cpd at 21° from fixation) [52]. Compared with SAP, frequency doubling perimetry (FDP), and retinal nerve fiber layer (RNFL) thickness, deeper defects in CSP-2 and FDP than SAP in areas with mild RNFL thinning and greater residual function in areas of severe RNFL loss have been reported [52]. Because of the advantages of CSP-2, this test may become more popular in future to assist clinicians in early diagnosis of glaucoma with more certainty [52].

Pattern Noise (PANO)

This as another relatively new perimetric device that is financially affordable in low-income regions. An ordinary laptop is needed for running the software. A chin rest is used to fix patient's head relative to the screen. The test is done at 25 cm distance and the stimuli are presented in 54 locations distributed over 30° nasal and 24°

temporal to fixation (similar to central 24-2 program of HFA). Each target is 5-by-5 degrees and is made of bright/dark pixels. The contrast level between these pixels is measured. Each target can have 63 different contrast levels. The pixel flickers with a frequency of 18 Hz. The background is gray. PANO test results significantly correlate with optic nerve head morphology [53].

As can be expected, the more frequent visual field testing is done, the earlier we can detect glaucoma progression [54]. On average, testing three [55] or even two [56] times a year provides good sensitivity and specificity for detection of any significant progression in disease status while having reasonable financial burden. The notable point here is that even detecting rapid progression during the first 2 years of follow-up does not necessarily mean true progression, because of the few number of tests performed during this short period of time. Therefore, any visual field progression found during a short time interval should be confirmed with other test [57]. Frequent (weekly) home monitoring is another option that allows for earlier detection of glaucoma progression than office tests performed twice a year; in fact it can reduce the time needed for catching of rapid progression by two-thirds. The home tests may not be cost-effective or easy though [58]. Many of the previously mentioned perimetric tests can be done at home easily with some patient education and may become handy in disease monitoring in future.

Apart from new perimetric methods mentioned above, some innovations have been made in traditional visual field testing techniques and analyses to enhance its efficacy, reliability, and ease of use.

Central Versus Peripheral Testing

Traditionally, testing central 10° of visual field has been used to monitor advanced stages of glaucoma in which more peripheral visual field has been lost. Recently, more attention has been paid to this region in early stages of glaucoma. Macular damage both structurally and functionally does occur in early glaucoma or even glaucoma suspects [59–62]. Inferior macular region (corresponding to superior central visual field) is especially vulnerable to early glaucomatous damage [62–64]. Therefore, central visual field testing can assist clinicians in detection and follow up of early glaucoma patients [65, 66]. This is especially important because central damage has a large impact on quality of life of these patients, even more than peripheral damages [67–69]. Indeed, some studies have found that central 24-2 testing can miss abnormalities present in central 10-2 tests [70, 71]; some other studies have shown that defects in central points of 24-2 tests can strongly predict 10-2 defects though [72, 73]. Therefore, more studies are required to answer this question whether testing central 10° of field should replace 24° or it may delay detection of non-central damages [73].

On the other hand, testing more peripheral locations (outside the central 24° or 30° which are usually tested) has also gain attention. Some clinicians believe that some patients may have abnormal peripheral visual field while still are normal in central 24° of vision [74, 75] and central and peripheral visual fields are just moderately related [76] and these patients may have difficulty in daily life such as maintaining their postural stability [77]. Other investigators, however, have stated that

although some disagreement exists between central 24° and more peripheral visual field, testing central 24° of field can reflect the damage present in peripheral locations. Therefore, the usefulness of testing peripheral visual field for early detection and follow-up of glaucoma should be evaluated more in future [78].

New Strategies for Threshold Measurement

Because better thresholding algorithms lessen measurement variability, some investigators have tried to improve these algorithms.

1. Having more stimulus points around the scotoma or areas of visual field loss improves precision in the scotoma edges. In fact, the 6° by 6° inflexible grid which is used in ordinary 24-2 and 30-2 programs of Humphrey visual field analyzer does not allow us to precisely depict the edges of scotoma and longitudinal changes in them. Therefore many investigators have used spatial information to condense test locations in the regions they want. In Scotoma-oriented perimetry (SCOPE), first, traditional static automated perimetry is performed and then the examiner depicts the areas of visual field defects as the region of interest (ROI) and adds more stimuli in these regions to enhance the spatial resolution [79, 80]. Similar to SCOPE, in field-oriented perimetry (FOP), more test locations are added by operator in visual field areas corresponding to suspicious lesions of optic disc or retinal nerve fiber layer [81–84]. Similarly an automated approach can be used to detect ROI and add test more test points in these regions. In the gradient-oriented automated natural neighbor approach (GOANNA), there is a large pool of 150 test points located 3° from each other. The test begins with this pool and as proceeds, the device automatically selects further locations in a manner that more test points are located around areas of visual field defect. This selection is done in a manner that the test time is no longer than testing a fixed pattern of locations such as Zippy Estimation by Sequential Testing (ZEST). Central 21° of the field is tested; in nasal side, it is extended to 27° [85, 86].
2. Some algorithms are designed to reduce the test time. For example, Spatially Weighted Likelihoods in ZEST (SWeLZ) is designed to reduce the test time compared to ZEST with similar precision and accuracy of threshold estimation. In this algorithm, intensity and order of each stimulus presentation is determined automatically from spatial information of previous presentations [87]. Another algorithm named spatial entropy pursuit (SEP) is also aimed to increase the speed of ZEST by using neighboring test points to estimate the sensitivity of related locations [88].
3. In Structure-ZEST (SZEST) and Structure Estimation of Minimum Uncertainty (SEMU), structural information are used to predict thresholds of test locations [89, 90].

Improvements in Progression Analysis

1. Two methods of progression analysis are available in static automated perimetry devices: (1) trend-based analysis which calculates the amount of change in global indices such as mean deviation (MD) or visual field index (VFI) over time

and (2) event-based which analyzes pointwise change using guided progression analysis (GPA).

Because pointwise measurements have large variability, trend-based analysis becomes handy, but, since the global indices are used in the trend-based method, this method is not sensitive to small amounts of local change, which is usually the case in early glaucoma. On the other hand, global indices are affected by some factors that cause generalized depression of sensitivity such as miosis and cataract; hence their change is not specific to glaucoma. Having the shortcomings of these two methods in mind, one may seek an alternative analysis that has the advantages of them yet avoiding the disadvantages. Therefore, some researchers have used pointwise analysis of visual field clusters. In this method, visual field is divided into small clusters (sectors) and a trend analysis is done for each sector. Several clustering methods based on anatomy of the retinal nerve fiber layer [91], rates of progression [92–94], and cross-sectional correlation of test points [95, 96] are present; discussing them is beyond the scope of this chapter. Octopus perimeter has a software named *EyeSuite* in which the visual field is divided into ten anatomy-based clusters and has been shown to be useful for detection of progression, even in early glaucoma, on time with good specificity [97, 98].

2. Analysis with Non-Stationary Weibull Error Regression and Spatial Enhancement (ANSWERS): This is a novel analytical technique that uses differing levels of nonstationary measurement variability (increasing test retest variability in area of visual field defect as glaucoma progresses) and spatial correlations. It has been shown to be very sensitive to visual field progression and prediction of the future status of the patient [99, 100].
3. Some researchers have got benefit from artificial intelligence to detect progression in longitudinal visual fields (Gaussian mixture-model with expectation maximization (GEM) and variational Bayesian independent component analysis mixture-models (VIM) for detecting glaucomatous progression along VF defect patterns (GEM—progression of patterns (POP) and VIM-POP)) [101, 102].
4. A new statistical model for progression analysis has been suggested by Warren, J.L. and colleagues. It is defined by clinician expert consensus and accounts for spatial correlation. It has been shown to be promising in progression detection and can be easily used in clinical practice [103].

FORUM Glaucoma Workplace

Zeiss Company has developed FORUM glaucoma workplace to enable the clinicians to analyze HFA data on their PC and view the results of Zeiss glaucoma tools (HFA and CIRRUS optical coherence tomography (OCT)) in a single report. This software can search and find the results of previous exams of the patient that are stored in FORUM and display them at once. So, the clinician can compare the exams with each other and see any changes if present. The FORUM server manages the database, searching and retrieving the wanted data. In this platform the data are displayed in an intuitive layout with plain and simple graphics. With a few clicks the user can interact with GPA. One can use drag and drop moves and change or tune the factors GPA uses for analysis. For example, the clinician can change the

baseline in GPA or view it using a dual baseline; he/she also can remove outliers from VFI plot or add notes wherever suitable.

FORUM glaucoma workplace offers combined reports in which it displays HFA and OCT data simultaneously.

Comprehensive reporting is another feature of this workplace. In the "visual field" page, any single perimetry exam is displayed. In the "review" page, all the threshold perimetries are presented together and the user can scroll down to view all of them. At last in "create reports" page, the clinician can create any kind of report he or she needs.

The software displays the reliability indices of visual fields and uses plain language alerts if they are unreliable. Also it shows the gaze tracker graph if available.

The RelEYE feature is a new feature that exists in HFA-3 models. This feature saves the patients' eye image during stimulus presentations so the user can see how the patient had fixated during the exam.

The FORUM glaucoma workplace is so flexible and each user can customize the program according to his or her own preferences (Fig. 3.5) [104].

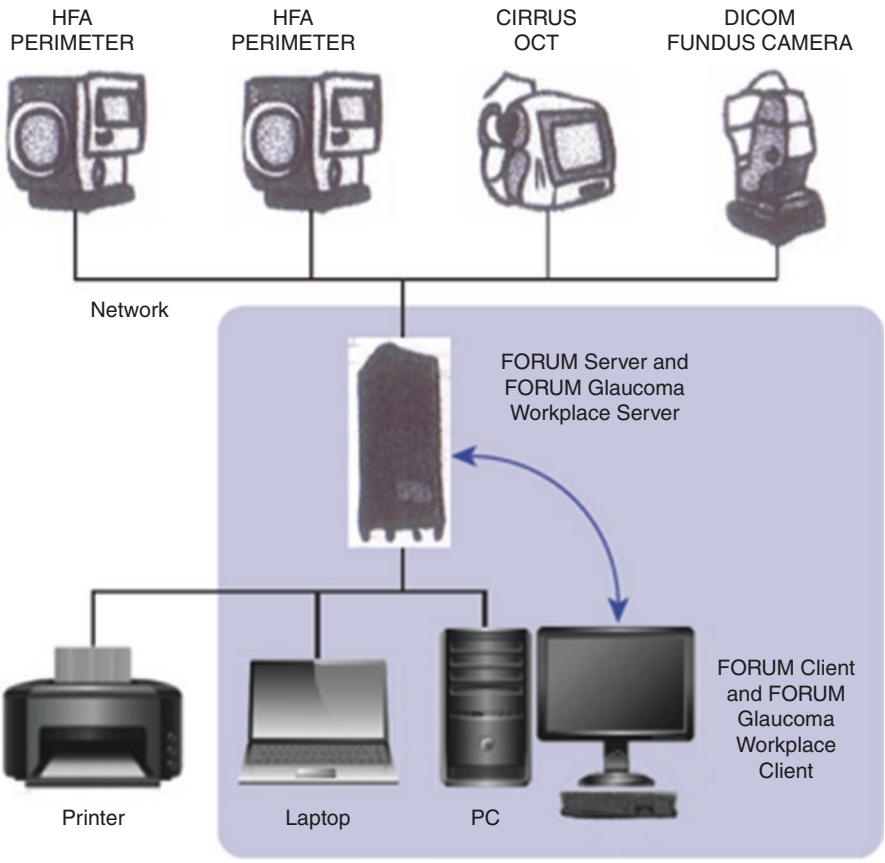

Fig. 3.5 Integrating structure and function with FORUM® glaucoma workplace

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What's New in Medical Management of Glaucoma

4

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This chapter reviews the current literature regarding existing medical therapies for glaucoma and those in pipeline.

Existing Drugs

Prostaglandin Analogs

Macular Edema in Early Postoperative Period of Cataract Surgery and Aggravation of Inflammation in Glaucoma Patients with Uveitis: Reality or a Myth?

Intraocular Inflammation

Earlier reports had suggested that latanoprost disrupted blood aqueous barrier (BAB) in pseudophakic or aphakic patients and resulted in intraocular inflammation. This was measured using a laser flare meter and higher mean anterior chamber flare values were noted [1]. In a multicenter clinical trial, on a large group of participants (latanoprost 3936 and usual care 1918 participants) with 5 years of follow-up, there was no difference for the ME and iritis development between the latanoprost group and usual care (antiglaucoma drops other than latanoprost) [2].

Macular Edema

Several case series have reported the disruption of BAB and increased rate of macular edema with the use of latanoprost. In a recently published study on PGAs, increased flare and central macular thickness were observed, but these changes were not clinically significant [3]. So, why is it logically not possible for latanoprost to

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cause increased intraocular inflammation or result in macular edema, despite being a vasoactive drug? A single drop of commercially available latanoprost 0.005% solution has approximately 1.5 μg of latanoprost (each ml contains 50 μg latanoprost). Laboratory studies show that only about 1% of a drop of 0.005% latanoprost (0.015 μg) penetrates the anterior chamber. One hour post instillation, the iris has the maximum drug concentration, followed by the anterior chamber and ciliary body. Elimination half-life of latanoprost from these tissues is 3–4 h; maximum effect is reached after 8–12 h. Drug does not reach the posterior segment [4]. In cases with a breach in the posterior capsule where the drug is likely to reach the posterior segment, it is much diluted from its anterior chamber concentration because of volumetric considerations, aqueous humor dynamics, and vitreous volume. This makes the potential effect on the retinal vessels very unlikely. ME resolution after discontinuing latanoprost may not be attributed to stopping the medication because there are reports of ME resolution even with continuing the latanoprost [5].

Then, who is to blame? Miyake et al. reported that based on four trials that they conducted, the ME caused by antiglaucoma eye drops was the result of the BAK used as a preservative [6]. It was thought that BAK enters the anterior chamber and results in intraocular inflammation; however, no scientific evidence shows BAK in the anterior chamber [7]. Therefore, according to the current literature, no causal relationship exists between flaring up of uveitis and presumed latanoprost-induced ME (even in high-risk eyes) [8].

Effect on Indigenous Conjunctival Flora

Most glaucoma patients need to instill topical antiglaucoma medications over a long period. Therefore, it is likely that the long-term administration may adversely affect the indigenous conjunctival flora. Till date not much has been reported about how PGAs affect the indigenous conjunctival flora. Ohtani S. et al. collected bacterial isolates from the conjunctival sacs of glaucoma patients, who were instilling PGAs for at least a year. Minimum inhibitory concentrations of gatifloxacin, moxifloxacin, levofloxacin, tobramycin, cefmenoxime, chloramphenicol, and erythromycin against the isolates were measured to determine the susceptibility. Authors reported a high positive culture rate in most cases (90.5%) and isolated about 79 bacterial strains. The isolated bacteria included 49% aerobic Gram-positive cocci, 33% facultative anaerobe *Propionibacterium acnes*, 5% coagulase-negative *Staphylococci*, 4% *Corynebacterium* spp., 4% Gram-negative bacteria, and 1% *Streptococcus* spp. The positive culture rates for patients using 0.005% latanoprost preserved with 0.02% BAK and 0.004% preservative-free travoprost were 88.9% and 92.6%, respectively, with no statistically significant difference in the isolated bacteria between the two groups. Methicillin-resistant *S. epidermidis* (MRSE) was significantly more frequently isolated in the BAK-preserved latanoprost group. The antimicrobial susceptibility rates of *S. epidermidis* were significantly lower in the latanoprost group for levofloxacin, gatifloxacin, moxifloxacin, and tobramycin. Therefore, the authors concluded that the indigenous flora might be affected by the long-term use of prostaglandin analogs. The higher incidence of MRSE in the latanoprost group must be considered during the prolonged course of therapy [9].

One would wonder why latanoprost, despite having BAK (which has antiseptic properties), is prone to increased MRSE. This can be explained by the fact that after the eye drops are instilled, the lacrimal fluid dilutes the BAK; therefore, its concentration continues to decrease. Just 5 min after the instillation, BAK decreases to 1/10 of its original concentration and continues to decrease thereafter [10]. It has been previously reported that when antiseptics are used at much lower than realistic concentrations, the likelihood of bacterial resistance increases [11].

Chronic PGA Use and Meibomian Gland Dysfunction (MGD)

As MGD is an inflammation-driven eyelid disorder, topical PGA use may potentially be involved in its pathogenesis. The possible association between MGD and topical PGA use has been suggested in a previous study by Cunniffe et al., in which the authors detected 19% of patients undergoing incision and curettage for the treatment of chalazion were on PGA drops [12]. A recent, prospective study graded the severity of MGD as defined by the *Tear Film and Ocular Surface Society International Workshop on Meibomian Gland Dysfunction* and evaluated the type of MGD associated with preserved PGA monotherapy use. The authors reported that PGA use is mostly associated with obstructive type of MGD and grades 2 and 3 (mild and moderate) [13]. It seems plausible that prolonged exposure of topical PGA medications to the eyelid margin may induce keratinization of the meibomian gland acini together with induction of hypertrichosis and periocular pigmentation, perhaps through a common molecular pathway [14].

Prostaglandin-Associated Periorbitopathy (PAP)

Factors Related to PAP

In 2004, prostaglandin analog-induced changes to the periorbital soft tissues were reported, and the entity, prostaglandin-associated periorbitopathy, was recognized. This entity includes deepening of the upper eyelid sulcus, upper eyelid ptosis, involution of dermatochalasis, inferior scleral show, mild enophthalmos, flattening of the lower eyelid bags, increased prominence of eyelid vessels, and tight orbits. Majority of reported prostaglandin-associated periorbitopathy cases have been seen with topical bimatoprost and travoprost. Latanoprost-induced periorbital soft tissue changes are milder with a slower onset than those seen with bimatoprost and travoprost as the antiadipogenic effect of latanoprost is the weakest of the prostaglandin analogs [15]. A recent study has also shown that with older age, bimatoprost and travoprost were more associated with PAP than latanoprost, whereas high BMI was found to be a protective factor. High BMI may be protective as more reserved orbital fat volume will affect the rate of adipogenesis reduction, making it more difficult to detect the appearance of PAP. Additionally, it is likely that timolol precipitated periorbital change when used with PGAs [16].

Clicking Eyelids

Recently, an audible blink or a clicking eyelid has been reported in patients on prolonged PGAs. The click occurs because of the formation and bursting of an air bubble.

It is hypothesized that the recessed position of the enophthalmic globe results in reduced area of contact of the lateral eyelid margin, thus generating a negative pressure, resulting in formation of a bubble. When the lids continue to move further apart and the surface tension cannot withstand the distance, then the bubble bursts [17, 18].

Alternative Clinical Uses of Prostaglandin Analogs

Prostaglandin F2alpha (PGF2α) analogs can induce the anagen phase in hair follicles and stimulate melanogenesis in the skin. These drugs are being used to target androgenic alopecia by lengthening the phase of anagen follicles and stimulating resting follicles into anagen and increase hair density. Bimatoprost 0.03% is being evaluated in clinical trials for the treatment of idiopathic or chemotherapy-induced eyelash hypotrichosis and alopecia areata [19]. The results are favorable in nonimmune-mediated apoptosis of anagen-phase hair follicles (chemotherapy-induced hypotrichosis) vis-à-vis the immune-mediated pathologies (alopecia universalis). Barring a few case reports, the use of PGF2α analogs in hypopigmentary skin conditions has not been adequately studied till date [20].

Timolol

Cardiac Safety of Ophthalmic Timolol

Plasma timolol levels are correlated with cardiovascular adverse effects in patients, since timolol is mainly metabolized by cytochrome P450 2D6 (CYP2D6) enzyme in the liver. Patients who lack the functional CYP2D6 or who are concomitantly using potent CYP2D6 inhibitor drugs (e.g., paroxetine or fluoxetine) or verapamil or other beta-blockers are at risk of developing cardiac adverse effects. Therefore it is prudent to get an ECG done prior to commencing treatment, and CYP2D6 genotyping must be considered in cases that are on CYP2D6 inhibitor drugs [21].

Newer Drugs

Currently prescribed antiglaucoma medications reduce IOP either by decreasing aqueous humor production or by increasing uveoscleral outflow. However, they fail to address the main physiological issue, the dysfunctional trabecular meshwork (TM). Prolonged compromised trabecular outflow (conventional pathway) may lead to dysfunction of Schlemm's canal endothelial (SCE) cells. Thus, IOP-lowering medications started for primary open angle glaucoma (POAG), which address the conventional pathway, may be beneficial in maintaining the function of this pathway.

Rho Kinase (ROCK) Inhibitors

The conventional outflow pathway is the major route of aqueous humor outflow in humans. The resistance to outflow is mainly generated in the juxtacanalicular region of the TM and the inner wall of SC and is modulated by the Rho-ROCK–signaling

pathway. Rho kinases are serine/threonine protein kinases expressed in the TM. ROCK inhibitors decrease actomyosin-driven cellular contraction and reduce production of fibrotic extracellular matrix proteins. Therefore it is believed that ROCK inhibition would decrease IOP and increase conventional outflow by altering permeability of SCE cells and TM cell morphology. IOP lowering through ROCK inhibition is a more physiological and natural approach than any other current therapy.

Ripasudil

Ripasudil (previously K-115) (Glanatec) (Kowa Company, Ltd., Nagoya, Aichi, Japan) is the first Rho kinase inhibitor approved for the treatment of glaucoma. Ripasudil is effective when administered both during the day and at night, with peak reductions of 6.4 mmHg and 7.3 mmHg, respectively (approximately 2 h post instillation). It produces stable reduction in IOP, both when used as monotherapy and in combination with PGAs and β-blockers.

Recently, approximately 3 mmHg additional reduction of IOP was observed when ripasudil was administered in twice-daily dosage, to patients undergoing maximal tolerated medical treatment [22]. The main adverse event seen with ripasudil is conjunctival hyperemia, which is seen in approximately 70% of patients using the drug for 8 weeks or more. Conjunctival hyperemia reaches the peak about 10 min after administration and disappears within 2 h. This symptom is considered to result from smooth muscle relaxation and subsequent dilatation of the blood vessels [23].

Netarsudil

Netarsudil (previously AR-13324) (Aerie Pharmaceuticals, Durham, North Carolina, USA) is both a novel Rho kinase inhibitor and norepinephrine transporter (NET) inhibitor. Proposed mechanisms of action for IOP lowering include decreasing aqueous production and improving outflow via the trabecular meshwork and the uveoscleral pathway and decreasing episcleral venous pressure. When its IOP-lowering effects were compared with latanoprost, this agent was less effective by approximately 1 mmHg [24].

Two large phase III trials, Rho Kinase Elevated IOP Treatment Trial 1 and 2 (ROCKET-1 and ROCKET-2), were conducted to compare the efficacy and safety of netarsudil 0.02% dosed once at bedtime to timolol maleate 0.5% dosed twice daily. ROCKET-2 trial had an additional treatment arm of netarsudil 0.02% dosed twice daily.

In both ROCKET-1 and ROCKET-2, netarsudil 0.02% dosed once at bedtime showed clinically as well as statistically significant reductions in mean IOP from baseline at all time points and met the criteria for noninferiority to timolol in patients with maximum baseline IOP < 25 mmHg. In ROCKET-2, though netarsudil 0.02% instilled twice daily met the criteria for noninferiority to timolol, it was not as well tolerated as the once-daily dosing [25]. Most frequent ocular adverse events were conjunctival hyperemia, conjunctival hemorrhage, and cornea verticillata.

Netarsudil has been shown to maintain similar efficacy across different baseline IOPs and this may be accounted by its distinct IOP-lowering mechanisms compared to other drug classes [26].

Latanoprostene Bunod (LBN)

LBN ophthalmic solution, 0.024%, is under review by the US Food and Drug Administration (FDA) for the reduction of IOP in patients with OAG or ocular hypertension (OHT). LBN is metabolized in the eye to latanoprost acid and butanediol mononitrate (BDMN) which is further metabolized to 1,4-butanediol and nitric oxide (NO). Latanoprost acid and NO have each been shown to lower IOP via independent mechanisms. NO relaxes TM and SC cells and enhances TM/SC permeability through activation of the soluble guanylyl cyclase/cyclic guanosine monophosphate (sGC-cGMP) signaling pathway, which triggers a myriad of downstream cellular effects notably including Rho kinase and overall Rho pathway inhibition and culminating in cytoskeletal relaxation. Thus, while both LBN and ROCK inhibitors mediate cytoskeletal relaxation of TM cells through Rho kinase inhibition, LBN activates the sGC-cGMP pathway upstream of Rho kinase and is thought to promote cell relaxation via multiple additional mechanisms. LBN 0.024% given once at bedtime has been shown to have a good IOP-lowering effect that appeared significantly better than either latanoprost 0.005% [27] or timolol 0.5% [28], with IOP lowering sustained over 1 year of treatment in European and North American subjects with OHT or OAG [29] and in Japanese subjects that were predominantly normotensive [30]. Sleep laboratory studies have shown that LBN instilled once a day provides consistent IOP reductions from baseline throughout the entire 24-h period and also improved ocular perfusion pressure [31].

Oligonucleotide-Based Compounds

Oligonucleotides can be designed to target specific genes or RNAs with the aim of altering gene expression or exert a direct interaction by binding to molecules. The main classes of oligonucleotides that are currently being developed as therapeutic tools include siRNAs, ASOs, aptamers, and microRNAs (miRNAs).

Short Interfering RNAs (siRNAs)

Bamosiran

Bamosiran (SYL040012) (Sylentis S.A., Tres Cantos, Madrid, Spain) is a naked siRNA which blocks the beta 2-adrenergic receptor (ADRB2) via specific gene silencing. This compound specifically targets ADRB2 (predominant receptor in iris–ciliary body) and thus influences aqueous humor production [32]. In contrast to traditional beta-blockers (which are absorbed in the systemic circulation), bamosiran acts only locally in the eye—as it is rapidly degraded when it reaches the systemic circulation, thus reducing the systemic adverse effects. Thus, bamosiran is relatively safe for glaucoma patients with risk of heart disease or other conditions where beta-blockers are contraindicated.

Interim results from a phase IIb trial have shown that bamosiran 1.125% achieved noninferiority to timolol twice daily only in the patients with baseline IOPs greater

than 25 mmHg. The trial also had excellent tolerability with less adverse events in the bamosiran group vis-a-vis the timolol group [33].

QPI-1007

QPI-1007 (Quark Pharmaceuticals) is a 19-bp siRNA targeting caspase-2 and is under trial as a neuroprotective drug for nonischemic optic neuropathy and other optic neuropathies, including glaucoma. It is given as an intravitreal injection. Caspase-2 is specifically activated during ganglion cell death leading to irreversible loss of vision. This protein has a unique feature of being both an initiator and an effector of apoptosis. Reducing caspase expression may thus potentially protect retinal ganglion cells from apoptosis [34].

Aptamers

Aptamers are RNA or DNA oligonucleotides that have the ability to bind proteins with both high affinity and specificity. Aptamers have not been widely tested for glaucoma. Pegaptanib, a FDA-approved RNA aptamer directed against VEGF-165, for the treatment of age-related macular degeneration (AMD), has been studied for the treatment of neovascular glaucoma (NVG) [35].

Antisense Oligonucleotides (ASOs)

ASOs are single-stranded RNA or DNA oligonucleotides, of approximately 15–25 bp, that mediate mRNA degradation by an RNase H-mediated mechanism. Aganirsen (GS-101) and ISTH0036 are ASOs in pipeline for treatment of glaucoma.

Aganirsen

Aganirsen is a 25-bp ASO that targets insulin receptor substrate-1 (IRS-1), which is over expressed in pathological angiogenesis. Unlike inhibiting VEGF-1, reducing IRS-1 has been demonstrated to target pathological vessels specifically, without inhibiting normal vessel growth.

This product holds four orphan drug designations in Europe, for the prevention of corneal graft rejection, due to corneal neovascularization, and treatment of NVG, ischemic central retinal vein occlusion, and retinopathy of prematurity.

ISTH0036

ISTH0036 is a fully modified phosphorothioate 14-bp oligodeoxynucleotide with a 3 + 3 LNA-gapmer pattern targeting TGF-β2. TGF-β2 is an antiproliferative and anti-inflammatory factor that is upregulated in the aqueous of POAG patients. Increase in TGF-β2 correlates with deposition of fibrillar extracellular matrix in the TM. These extracellular deposits in the TM impede aqueous outflow and consequently result in IOP increase.

ISTH0036 is currently being tested in a Phase I dose-finding clinical study in patients with advanced glaucoma undergoing trabeculectomy. In the first human trial, the compound was administered as a single intravitreal injection in the dose of 67.5 or 225 μg at the end of trabeculectomy [36].

ISTH0036 is likely to have a direct pathologic impact of elevated TGF-β2 levels on the optic nerve head.

Prostanoid Receptor Agonists

The prostanoid FP receptor, a receptor for PGF2α, is thought to be the target through which IOP is lowered by PGAs. Recently, there has been increased interest in other prostanoid receptors, such as Ep2 and Ep3, as targets for topical IOP lowering.

DE-117 (Santen Pharmaceutical, Ofukacho, Osaka, Japan) is an Ep2 agonist. In animal models, Ep2 agonists lower IOP by facilitating Schlemm's canal endothelial cell relaxation, increasing uveoscleral outflow, and have recently been shown to act on the trabecular meshwork by decreasing both cell contractility and collagen deposition. This is in contrast to latanoprost, which decreases collagen deposition but may increase TM contractility. Phase II trials for DE-117 showed similar safety and efficacy to latanoprost [37, 38]. Phase II and III trials are currently ongoing.

ONO-9054

ONO-9054 (Ono Pharmaceuticals, Chuo-ku, Osaka, Japan) is both an Ep3 agonist and a FP receptor agonist. Subhuman primate studies have suggested that this drug may decrease IOP more than both latanoprost and travoprost, in addition to maintaining the lower IOPs for a longer period of time [39]. Initial Phase I trials showed tolerability and a peak IOP lowering at 9 h, with a mean 28–29% reduction [40], which is consistent with morning or evening once-daily dosing [41]. A phase II study of this drug has recently been completed in the USA and results showed that ONO-9054 was more likely to have IOP reductions of 25–35% than latanoprost [42].

Adenosine Receptor Agonists

This novel class of drugs reduces IOP by increasing the aqueous outflow via the conventional pathway. Adenosine functions through interactions with four known adenosine receptor subtypes: A_1, A_{2A}, A_{2B}, and A_3. The mechanism of IOP reduction for adenosine receptor agonists is via the stimulation of the A_1 receptor that enhances the secretion of matrix metalloproteinase-2 (MMP-2), which promotes digestion of type IV collagen components of the extracellular matrix in TM. As levels of MMP-2 rise, increased extracellular matrix turnover in the TM removes protein from the conventional TM outflow pathway, thus lowering outflow resistance and IOP.

Trabodenoson (INO-8875)

Trabodenoson (INO-8875) is a highly selective A_1 adenosine receptor agonist that is being studied for its activity in lowering IOP in OAG and OHT. Myers et al. conducted a randomized, placebo-controlled dose-escalation phase II clinical trial for 144 subjects with POAG or OHT to assess the safety and efficacy of trabodenoson

compared to placebo for 28 days [43]. The study found that trabodenoson produced a dose-dependent reduction in IOP, with the 500 μg trabodenoson group achieving significantly greater IOP reductions than the placebo group. The 500 μg trabodenoson group had a mean decrease of 4.1 mmHg compared to 1.6 mmHg decrease for the placebo group. Additionally, trabodenoson demonstrated long duration of action, with persistent IOP reduction 24 h after the final 500 μg dose. The efficacy also increases with longer treatment time, given that IOP reduction at day 28 was significantly greater than at day 14. The most frequent drug-related adverse event was conjunctival and ocular hyperemia. Phase III trials are ongoing.

Role of Statins

Drug repurposing is a process of finding new uses for drugs outside the scope of their original indication. This results in reduced risk and costs as the drug candidates have either already been approved for clinical use or been through several stages of clinical development with known safety and pharmacokinetic profiles.

Recent evidence suggests that statins are capable of reducing the risk of cerebrovascular and cardiovascular events, independent of their effect on cholesterol levels. There has been growing evidence that suggests that statins may be useful in patients with diseases of the central nervous system including ischemic stroke, Alzheimer's disease, and multiple sclerosis. Protective role of statins in patients with other diseases of the central nervous system leads us to hypothesize that these agents may also be beneficial in preventing the development of OAG, as optic nerve and retinal nerve fiber layer are the primary structures which are damaged in glaucoma [44].

The pleiotropic properties of statins such as inhibition of isoprenylation of Rho GTPase and immunomodulation have been proposed to protect RGCs against glaucomatous damage [45, 46]. Effect of statins on glaucoma progression and IOP is uncertain. Short-term statin use is associated with a reduced incidence of glaucoma.

A recent study found that after accounting for baseline low-density lipoprotein levels, patients who took statins continuously for 2 years had a 21% reduced risk of glaucoma versus nonusers. There was no additional protective effect associated with taking the highest dosage of statins (80 mg) vis-a-vis a lower dosage (40 mg) or with other types compared with atorvastatin. When planning clinical trials to study the effect of statins on glaucoma, it is reasonable to use a generic statin like atorvastatin and a 40-mg or lower daily dosage [47]. Statin use was associated with a significant reduction in the risk of OAG in patients with hyperlipidemia.

Sustained-Release Devices

Adherence and persistence to topical glaucoma drop regimens are less than ideal. Significant resources are therefore being directed toward the development of sustained-release glaucoma therapeutics that can achieve 100% patient-independent

adherence. Sustained-release intraocular drug delivery may be appropriate for those elderly glaucoma patients who lack the hand steadiness and dexterity (such as patients with arthritis, Parkinson's disease) to squeeze the medication bottle and dispense a single drop in their eyes.

Topical Bimatoprost Ocular Insert

The topical bimatoprost ocular insert (ForSight Vision5, Inc., Menlo Park, CA, USA) is an ocular ring composed of bimatoprost incorporated within a silicone matrix and supported by an inner polypropylene structure. The insert is designed for placement between the upper and lower fornices, with sizing dependent on patient's intercanthal distance (Fig. 4.1). It is available in diameters ranging from 24 to 29 mm. The device continuously elutes bimatoprost over a 6-month period, although the rate of drug elution into the tear film is not constant over this time period. This results in a descending dose of bimatoprost elution, ranging from 35 mg/day on day of insertion to 6 mg/day at 6 months. The device needs to be replaced after 6 months [48].

Brandt and colleagues reported efficacy and safety outcome of the topical bimatoprost ocular (BIM) insert at 6 months. After an initial medication washout, OAG or OHT patients were randomized to receive either a placebo insert plus timolol 0.5% twice daily or the bimatoprost insert plus artificial tears twice daily. The mean IOP reduction from baseline across all time points was 3.2–6.4 mmHg for the bimatoprost group vis-a-vis 4.2–6.4 mmHg for the timolol group.

The study provided proof of concept that bimatoprost ocular insert resulted in clinically significant IOP reduction, even though it did not meet the definition of noninferiority to timolol at all time points. At the conclusion of this phase II study, participants were enrolled in a 13-month open-label extension (OLE) study in which used the BIM ring (13 mg) for a 7-month cycle followed by another 6-month cycle. The primary objective of this OLE was to meet the FDA's requirement for at least 1 year of exposure and safety data. The OLE cohort had a primary retention rate of 88.0% during the phase II study. The retention improved as patients became more experienced using the ring, as corresponding retention rates during cycles 1 and 2 of OLE improved to 97.3% and 94.7%, respectively [49]. Median IOP reduction of 4 mmHg during the 13 months of OLE follow-up was similar to the last 3 months of the preceding study. During the OLE period, there was no difference in efficacy between patients who had been in either arm of the preceding study.

Bimatoprost Intraocular Implant

Bimatoprost SR consists of bimatoprost in the biodegradable NOVADUR (Allergan plc, Dublin, Ireland) platform for drug delivery. The implant is designed to be placed intracamerally and provides slow release of bimatoprost over time.

Bimatoprost SR is currently being evaluated in patients with OAG in a 2-year, phase I/II study. Dose of bimatoprost SR 10-mg implant is similar to the dose in a single drop of bimatoprost 0.03% ophthalmic solution. Thus, total drug exposure is much less in eyes that received implant vis-a-vis eyes that received topical therapy. The 6-month study results show that bimatoprost SR was well tolerated and

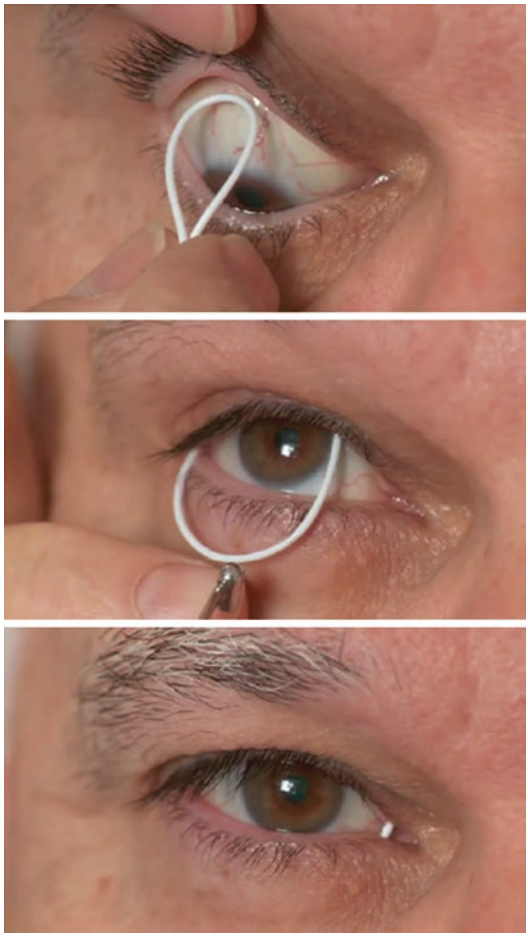

Fig. 4.1 Bimatoprost ring (Source: Getting in the ring. Glaucoma Today 2017; September/October: 44–46. With Permission from Dr. Brian Flowers)

effectively reduced IOP. Through month 4, >90% of study eyes remained in the IOP analysis did not require rescue or retreatment. Overall IOP reduction of all dose strengths of bimatoprost SR (6, 10, 15, or 20 mg) was comparable with topical bimatoprost. No serious ocular adverse events were noted and no implants had to be removed for safety reasons. Adverse events were similar across the bimatoprost SR dose strengths [50].

Latanoprost-Eluting Contact Lens

Soft contact lenses may be impregnated with an IOP-lowering agent, which via diffusion into the tear film, can then be absorbed by the cornea in a continuous fashion. Ciolino and colleagues recently reported on preclinical results using a novel latanoprost-eluting contact lens in glaucomatous monkeys. The contact lenses were produced in high- (149 micrograms latanoprost; CLHI) and low- (97 micrograms latanoprost; CLLO) dose variations [51]. The IOP-lowering efficacy of the

high- and low-dose latanoprost-eluting contact lenses was compared with topical latanoprost therapy in four eyes of four adult glaucomatous monkeys using a cross-over design with a 3-week washout period between the consecutive treatments. More studies are needed to reach maximally effective and well-tolerated optimal continuous-release dose. Contact lens drug delivery is a promising option for the future of glaucoma treatment.

Travoprost Intraocular Implants

ENV515

The travoprost extended-release implant (ENV515; Envisia Therapeutics, Morrisville, NC, USA) is a biodegradable device fabricated using novel particle replication in nonwetting template microparticle engineering technology.

The ongoing phase 2 trial is a 12-month safety and efficacy evaluation that enrolled five glaucoma patients at sites within the USA. The pre-washout baseline IOP for all patients in this cohort, treated with Lumigan (bimatoprost) or Xalatan (latanoprost) prior to enrollment, was 19.7 mmHg and a post-washout baseline IOP at 8 am of 26.1 mmHg [52]. Single low dose of ENV515 decreased the mean 8 am IOP by 6.7 ± 3.8 mmHg (26%) over 9 months. The mean 8 am IOP after a single low dose of ENV515 was 19.4 mmHg over the 9-month period. ENV515 was well tolerated and the most common adverse event was early-onset transient hyperemia, related to the dosing procedure. There were no serious adverse events, no changes in corneal thickness, and no changes in corneal endothelial cell counts.

iDose

iDose (Glaukos Corp., San Clemente CA, USA) is a travoprost implant designed for intracameral injection (Fig. 4.2). This implant is currently under investigation in a phase 2 clinical trial. The device is made of titanium and allows for continuous travoprost elution into the anterior chamber. When the device is depleted of active drug, removal and replacement with a new implant may be performed.

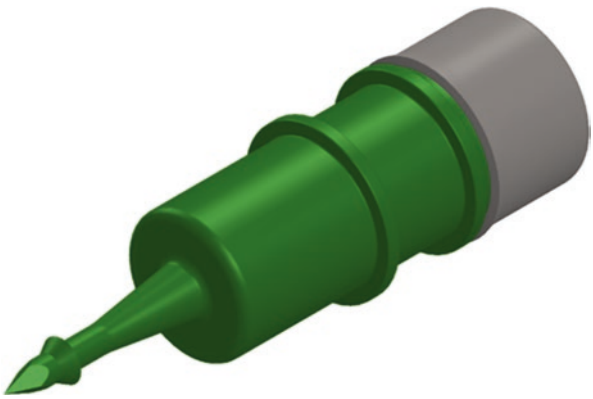

Fig. 4.2 iDose travoprost implant (With permission from Glaukos Corp.)

Prostaglandin Punctal Plugs

Travoprost Punctum Plug, OTX-TP

The travoprost punctum plug (OTX-TP, Ocular Therapeutix, Inc., Bedford, MA, USA) is composed of travoprost encapsulated in polylactic acid microparticles suspended within a polyethylene glycol resorbable hydrogel rod. Upon exposure to the tear film, the rod swells and occupies the space within the upper or lower canaliculus. Hydrolysis of the polylactic acid microparticles takes place over a 90-day period, resulting in sustained release of the travoprost drug into the tear film.

The presence of the color additive D&C Violet No. 2 helps to identify the retention and placement of OTX-TP. An initial feasibility trial of the OTX-TP demonstrated significant IOP reduction of up to 24% from baseline over a 1-month period, with good retention and low adverse events. The effect appeared to reduce by day 30 as the plug retention rate declined [53].

Latanoprost Punctal Plug, Latanoprost-PPDS

Another prostaglandin punctal plug device is the latanoprost punctal plug delivery system (Latanoprost-PPDS, Mati Therapeutics, Inc., Austin, TX, USA). The device consists of a core of latanoprost–polymer matrix surrounded by silicone (Fig. 4.3).

The L-shaped silicone plug is inserted using standard procedures at the slit lamp. It can be seen on eversion of lid. The trials studied two different delivery doses and placement variations in the upper and lower puncta, both separately and simultaneously. So far, multiple multicenter US clinical trials indicate that the lower punctum has better retention rates of up to 96% over a 12-week period [54]. Its use has been associated with approximately 20% IOP reduction from baseline. A phase 2 study investigating the safety and efficacy of Latanoprost-PPDS in comparison with timolol maleate ophthalmic gel-forming solution dosed once a morning is ongoing.

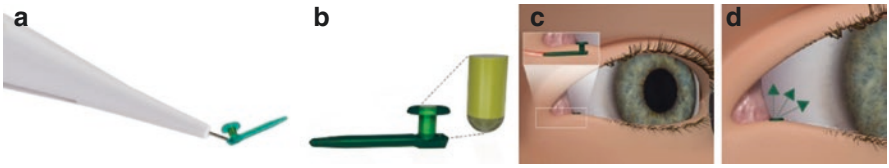

Fig. 4.3 (**a**) Evolute® punctal plug; (**b**) Drug core of the Evolute® punctal plug; (**c**) Secured placement in the punctum; (**d**) Targeted delivery: unidirectional release in the tear film (Source: With permission from Mati Therapeutics)

Injectables and Implants

Durasert

pSivida has developed a sustained-release, subconjunctival, bioerodible drug delivery implant for glaucoma (Durasert, Pfizer, New York, NY, USA). This implant is approximately 3–4 mm in length, 0.4 mm in diameter, and contains latanoprost in a tiny translucent cylindrical polymer tube, which is injected in subconjunctival space using a 27 gauge system. According to the company, the device is likely to work for 3–6 months and need not be removed afterwards. A Phase I/II clinical trial is underway to determine the safety and efficacy of the implant in subjects diagnosed with OHT [55].

Replenish

The "Ophthalmic MicroPump" is a "smart device," implanted in the sclera just like a drainage device, to dispense nanoliter-sized doses of drugs every hour, day, or month as needed before refills.

The MicroPump System is composed of four subsystems: (1) the Anterior MicroPump (AMP) for glaucoma, (2) the Posterior MicroPump (PMP) for retina, (3) the Eyelink, and (4) the Drug Refill System. The Eyelink is a wireless programmer/charger for bidirectional communication with the MicroPump implants, and the Drug Refill System is a separate console unit used to fill and refill the MicroPump implants with drug.

The MicroPump can be coupled with a closed-loop IOP-monitoring system that measures data every 5 s. The system stores the data, which the users can download when they charge the pump.

The Replenish device can last more than 5 years before needing replacement, much longer than current treatments [56].

Euclid Systems

Euclid Systems has partnered with Ora, Inc. for its two collagen-based systems to provide sustained release of latanoprost [57]. First one is an injectable, in situ gelling collagen solution, and second is a collagen wafer about 2 mm × 4 mm, that is implanted in the sclera. The wafer system has shown release of latanoprost for up to 180 days.

Even with so many unanswered questions, the clinical use of many of these sustained-release devices in the future is promising.

Subconjunctival Injection of Timolol

Despite having several effective drugs for glaucoma, the major challenge lies in their delivery. Timolol maleate is a water-soluble drug, which makes it difficult to develop a formulation that will deliver the molecule for extended periods of time. However, through a blend formulation, a microsphere delivery system that released timolol for over 90 days in vitro has been developed. Timolol microspheres have been fabricated using a double emulsion technique of a blend of 50/50 (w/w)

poly(lactic-*co*-glycolic acid) and poly(D,L-lactic acid). A single subconjunctival administration of these microspheres achieved delivery and IOP reduction in rabbits for up to 90 days without any local or systemic adverse effects [58].

Drugs for Ocular Surface Disease

Chronic use of topical hypotensive therapies in glaucoma patients leads to chronic inflammation of the ocular surface, which decreases the success rate of long-term glaucoma management. So, there is a need of drugs that can prevent or reverse this inflammatory damage.

Palmitoylethanolamide

Topical palmitoylethanolamide (PEA) (Defluxa[a]), an anti-inflammatory and analgesic agent, has been recently used to suppress the ocular surface inflammation associated with the use of hypotensive eye drops. It inhibits the expression of proinflammatory genes, thereby reducing cytokines and metalloproteases and also increases catabolism of eicasonoids. In a recent study, Defluxa instilled twice a day increased the Schirmer test and the tear film break-up time (T-BUT) and improved the conjunctival hyperemia by day 30, compared to baseline [59]. A decrease in inflammation also improves the lipid secretion by the meibomian and accessory glands.

Rebamipide

Prolonged use of topical antiglaucoma drugs results in decreased goblet cell density (resulting in a reduction in mucin on the ocular surface) and corneal epithelial disorders. Ocular surface is coated with two types of mucin: membranous mucin (present in the microvilli) and secretory mucin (present in the tear film). Electron microscopic studies have shown that corneal epithelial cells with microvilli appear as "light cells" and cells without microvilli appear as "dark cells."

Kawaguchi and coworkers conducted an in vivo rabbit study and found that topical rebamipide significantly reduced the number of dark cells in the corneal epithelium, that were increased as a result of topical glaucoma medications. Their study demonstrated that short-term use of topical antiglaucoma drugs induces corneal epithelial disorders at the cellular level, but simultaneous use of rebamipide may help protect as well as repair the ocular surface [60, 61].

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What's New in Laser Therapy for Glaucoma

5

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The mainstay of glaucoma treatment is lowering of IOP to slow or prevent further progression of optic neuropathy and visual field loss. This may be achieved by either medical, laser or surgical modalities.

Trabeculoplasty

Selective Laser Trabeculoplasty

Selective laser trabeculoplasty (SLT) is increasingly being used as both primary treatment modality and as an adjunct to medical and surgical therapy to lower IOP in OAG and OHT patients. We review the current perspectives on the role of SLT in clinical practice.

Newer Insights into Mechanism of Action

SLT has been shown to induce biological changes that help to modulate increased aqueous outflow through the trabecular meshwork (TM). An increase in pro-inflammatory cytokine expression, including interleukin-1-alpha (IL-1α), interleukin-1-beta (IL-1β), tumour necrosis factor-alpha (TNFα) and interleukin-8 (IL-8), has been shown by in vitro studies. These cytokines, in turn, increase stromelysin-1 expression [a matrix metalloproteinase (MMP-3)], which is implicated in TM extracellular matrix remodelling to increase aqueous outflow via the juxtacanalicular TM [1].

In vitro studies suggest that SLT and prostaglandin analogues may share a common pathway of action by inducing intercellular junction disassembly in Schlemm's canal (SC) and TM cells thus increasing aqueous permeability [2].

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Technique

Currently, there is no universally accepted treatment protocol for SLT. By convention, SLT is performed with a laser wavelength of 532 nm, spot size of 400 μm and pulse duration of 3 ns is fixed, but the clinician is able to adjust the extent of TM being treated (90°, 180°, 360°), the number of applications applied to the TM and the energy per application of laser.

Pulse Duration

It would be intriguing to know the impact of shorter pulse duration on the efficacy and safety of the treatment.

A recent study reported the clinical outcomes when SLT was performed using a pulse duration of 1 ns vis-a-vis the 3–5 ns (standard) pulse duration. The authors used a new SLT laser device, OptoSLT M DPSS (Optotek d.o.o., Slovenia), which comprises of a Q-switched 532 nm frequency-doubled Nd:YAG laser that emits short pulses with energy levels from 0.2 to 2.6 mJ. The new laser is a diode-pumped, solid-state laser unlike the standard 3–5 ns SLT devices which have flash lamp-pumped lasers.

Participants had a mean IOP reduction of 22% and 23% from baseline, 6 months after surgery in 1 ns and 3–5 ns SLT laser groups, respectively. The authors observed that the therapeutic laser energy required for each eye depends primarily on the pigmentation of the patient's TM rather than the duration of the laser beam. Higher energy levels were required in eyes with minor pigmentation to reach the therapeutic level and vice versa. This study highlighted the potential of SLT using a solid-state diode-pumped laser technology in treating OAG [3].

Number of Applications

Many studies comparing the extent of TM being treated (90°, 180° or 360°) have been carried out, but there was paucity of studies assessing the effectiveness of increasing the number of applications to the same extent of the TM.

A retrospective review has shown that IOP-lowering effect of SLT with 160 applications per 360° may be more effective than 120 applications per 360°, without any additional risk of transient IOP spikes [4]. Univariate analyses showed significant difference between IOP reduction between the two treatment groups, but when multivariate analyses accounted for the effect of clustering and other covariates such as age, baseline IOP, glaucoma subtype and changes to medication, no significant difference in success rates was noted. This disparity between univariate and multivariate analysis may be due to difference in baseline patient characteristics between the two treatment groups.

Site of Laser Application

The standard SLT procedure is performed using a gonioscopy lens which enables aiming of beam directly on the TM. Visualization of the angle with a gonioscopy lens requires sufficiently open angles, and the procedure requires training and experience. Additionally, the gonioscopy lens abuts the corneal surface, creating a potential risk of transmitting infections.

Geffen and co-workers thought of exploring the possibility of performing a transscleral procedure without using a gonioscopy lens to simplify and shorten the performance of SLT and to reduce the side effects related to gonioscopy and transmission of the laser beam through the cornea. The 532 nm Nd:YAG laser radiation used in SLT loses half its energy at the depth of 0.8 mm, so if the beam is applied directly to the overlying sclera, sufficient energy is likely to reach the TM. In their study Geffen et al. found that IOP reduction was similar in both perilimbal SLT group and conventional SLT group, throughout the study, with an average IOP reduction after 6 months of 23.4% in the former and 27.1% in the latter [5].

Additional studies including a greater number of participants, investigation of more treatment parameters, including using different energy levels, and variable treatment extents such as comparison between 180- versus 360-degree treatment are required to validate and expand current knowledge.

Same Day or Sequential SLT

There are limited data for comparing same-day bilateral SLT and sequential SLT therapy [6].

Sequential therapy is considered safer, as it allows for assessment of efficacy and side effects of SLT on one eye before treating the fellow eye.

In a prospective cohort study, POAG/NTG patients underwent bilateral SLT. The bilateral success rate was 42.9%, and there was a strong correlation between the two eyes, while 38.1% of eyes had bilateral "non-success", with a moderate correlation between the two eyes [7]. Nineteen percent had success in one eye and non-success in the fellow eye with an inverse correlation between the two eyes.

Therefore, in most cases, the success or "non-success" of one eye may predict the expected outcome of the fellow eye.

Repeatability

Most studies have shown that the IOP reduction is not significantly different between initial and repeat SLT at any time point [8].

Francis et al. reported that the reduction in IOP after either initial or repeat SLT was not affected by whether the patients had undergone Argon laser trabeculoplasty (ALT). This suggests that SLT may be used to treat patients who have had ALT in the past [9]. Additionally, repeat 360° SLT may be effective and safe after an initially successful 360° SLT has failed.

Indications and Outcome

Primary Angle-Closure Glaucoma

Recent studies have studied the efficacy and safety of SLT in cases where portions of the angle are open and amenable to treatment.

A retrospective case–control study compared the efficacy of SLT in eyes with primary angle closure (PAC) or primary angle-closure glaucoma (PACG) and POAG, with an average of 10 months and 11 months of follow-up, respectively [10]. The authors reported that, in patients with poorly controlled pre-SLT IOP, SLT

resulted in a mean IOP reduction of 38% following treatment in the PAC/PACG group. In PAC/PACG patients with controlled pre-SLT IOP with medication but having intolerance to drugs, SLT resulted in a reduction of 1.6 medications. The success rate of SLT in reducing IOP by at least 20% was 84.7% in the PAC/PACG group, and the clinical outcomes were comparable to those in the POAG group.

Narayanaswamy and colleagues evaluated SLT vis-a-vis topical prostaglandin analogues (PGA) in patients with PAC/PACG. They reported that although SLT was effective in treating PAC/PACG, its overall efficacy and safety profile was less favourable than that for PGA [11].

Pseudoexfoliation Glaucoma (PXFG)

Lindegger et al. found that 1 year after SLT, PXFG eyes showed superior IOP reduction compared to non-PXFG glaucomas [12].

Miraftabi and co-workers investigated SLT efficacy in PXFG versus POAG [13]. They found a statistically significant percentage reduction in IOP after SLT in the first 6 months in PXFG eyes vis-a-vis POAG (29% vs. 19%). SLT efficacy decreased in both PXFG and POAG at 12 months, with no significant difference in IOP reduction (16% vs. 16%). The chief drawback of this study was that the degree of angle pigmentation was not recorded, and therefore, the potential role of this variable could not be addressed.

Normal Tension Glaucoma

Studies have shown a beneficial IOP lowering in NTG, but the efficacy is lower than in POAG, PXFG and pigmentary glaucoma [14, 15].

Uveitic Glaucoma

SLT is considered as a relative contraindication because of the fear of triggering inflammation in uveitic eyes. Recently, a study reported outcome of SLT for eyes with fluocinolone acetonide intravitreal implant induced glaucoma. Patients in the study had received the steroid implant for a variety of non-infectious uveitis and panuveitis [16]. The authors concluded that SLT can be used only in selected uveitic eyes with well-controlled inflammation, IOP ranging between 20 and 40 mmHg and no advanced glaucomatous changes. They were not able to pinpoint any specific parameters that suggest which eyes are likely to respond favourably post-SLT. Therefore, SLT may be considered as an alternative to increasing anti-glaucoma medications or doing a glaucoma surgery in “quite” uveitic glaucoma.

As Primary Therapy in Low-Resource Countries

SLT has several attributes favourable for application in low-resource settings. Many glaucoma patients progress to blindness owing to limitations of health care resources in low-resource regions such as Africa. Additionally, it is a known fact that OAG is more common in people of African descent compared to those of European descent.

SLT provides IOP reduction similar to a PGA, with a favourable safety profile, is portable, has a fast learning curve and does not require glaucoma sub-specialty

training, requires no post-operative anti-inflammatory drugs and is more cost-effective than topical anti-glaucoma drops.

The West Indies Glaucoma Laser Study established the efficacy and safety profile of SLT in Afro-Caribbean subjects with POAG. Mean IOP reductions at 1 year post-treatment were approximately 30%, with a mean IOP of 14.5 mmHg. Nearly 80% of treated subjects maintained a minimum IOP reduction of 20% through the first year post-SLT. Side effects were generally mild and self-limited [17].

In another study, SLT resulted in clinically significant IOP reduction in South African glaucoma patients with or without prior anti-glaucoma medications or surgical therapy [18]. This study also enrolled socio-economically comparable individuals of Indian ancestry, although these patients also had good therapeutic response, but it was significantly less than the Black patients.

Iris Heterochromia

A recent case report achieved favourable outcome with a frequency-doubled Nd:YAG laser (SLT device) for changing the eye colour of a sectorial heterochromia case [19]. After two complete sessions, the colour difference disappeared and a solid eye colour was noted.

Efficacy and Safety

The efficacy of SLT in reducing IOP varies substantially among studies. In some studies, reported success ratio of SLT is moderately favourable (59.7–89%) [20], while some others have reported dismal outcomes [21].

This large variability in the success ratio suggests that the efficacy of SLT may be greatly influenced by myriad factors and underlines the importance of identifying the predictors for success of SLT to determine the optimal indication for the treatment.

Predictors of Success

Outflow Facility

Gulati and co-workers studied changes in aqueous humour dynamics 3 months after SLT and found that the IOP-lowering effects of SLT were mediated through an increase in outflow facility [22]. No meaningful effects on any of the other parameters of aqueous humour dynamics or the contralateral eye were detected. They noted that a higher baseline aqueous flow and a lower baseline outflow facility were found to be predictive of IOP response to SLT.

Pre-SLT IOP

A study was conducted by Hodge et al. to determine the efficacy and prognostic factors of SLT for cases taking maximally tolerated medical therapy [23]. Overall probability of success in controlling IOP below pre-SLT levels for 1 year was only 45.3% in this study. Diagnosis of POAG, lower pre-SLT IOP and lower number of pre-operative medication were significantly associated with treatment success.

Pre-operative IOP and types of glaucoma were significant in both univariate and multivariable models.

Several previous studies also found significant association between pre-operative IOP and success of SLT. However, the direction of correlation is inconsistent: higher IOP was associated with treatment success in most of previous studies, whereas higher IOP was associated with failure in this study [24]. A solitary study from Japan demonstrated correlation between lower IOP and success of SLT [25]. One possible reason for inconsistency in effects of pre-operative IOP among studies is racial difference.

SLT has good IOP-lowering capacity even in already maximally treated patients as long as the right patients are chosen. The best IOP-lowering effect has been seen in patients with mean diurnal pre-SLT IOPs over 18 mmHg. Between 14 and 18 mmHg, though the effect diminishes, it still remains clinically relevant. In the low teens, however, SLT should be performed with caution, as some patients may have a rise in IOP following SLT. Therefore, the success rate of SLT should not be judged in general but rather according to the level of pre-SLT IOP [26, 27].

Type of Glaucoma

Literature is sparse as regards the correlation between types of glaucoma and probability of success after SLT. Earlier reports on treatment outcomes of ALT showed favourable outcomes in PXFG and pigmentary glaucoma. This could be due to the fact that heavy angle pigmentation is advantageous for ALT. However, studies on SLT found no such effect of pigmentation on success of SLT [23, 25].

Effect of SLT on Quality of Life

Numerous studies have shown the efficacy of SLT in patients with POAG/OHT. SLT has great therapeutic potential when used as a primary or adjunctive treatment modality, but not much is reported about the health-related quality of life (HRQoL). LiGHT (Laser in Glaucoma and Ocular Hypertension Trial) is an ongoing multicentre randomised controlled trial that is comparing clinical outcome, HRQoL, safety and cost-effectiveness of SLT versus topical IOP-lowering medication in treatment-naive patients with newly diagnosed POAG/OHT [28].

Using routine clinical practices, LiGHT looks at eye-specific target IOP and permits use of any medication (except pilocarpine) and any treatment escalations, thus providing a realistic analysis of management instituted.

SLT significantly lowers the amount of anti-glaucoma medication needed and improves treatment-related QoL [29]. Patients are less dependent on care providers for eye drop instillation, have less objective signs (punctuate keratitis) and less subjective symptoms.

Adverse Effects

Recent case reports document three glaucoma patients with decreased visual acuity associated with corneal oedema and keratitis (endothelial, epithelial) shortly after SLT. Resolution of symptoms after starting treatment with oral antivirals and topical

steroids was variable. The origin of virus in such cases is unclear, but it is likely that it may enter the anterior chamber through the TM with increased secretion of viral particles from disruption of the TM and subsequent increased inflammatory response. In rabbits, viral shedding has been shown to elicit an endothelitis reaction, clinically similar to that found in humans [30].

More studies are needed to determine the risk factors and aetiology of post-SLT keratitis. But one must be aware of the potential risk of keratitis and commence treatment without wasting time, preventing scarring or endothelial cell loss [31].

Several case studies have reported transient changes in the cornea such as changes in corneal hysteresis, corneal thickness and endothelial cell function following SLT [32, 33]. Anterior chamber volume and macular thickness have also been shown to change transiently after SLT [34].

Pattern Scanning Laser Trabeculoplasty (PSLT)

A computer-guided pattern scanning laser with wavelength 577 nm has recently received FDA approval for use in trabeculoplasty. The earlier model had 532 nm (green) laser while the newer version has 577 nm laser. At the start of the treatment, titration is done to result in a barely visible effect on TM, after which the pulse energy is reduced by half to cause sub-visible effect on TM. The computerised algorithm has arc-shaped patterns that are automatically rotated after each application by the angle matching the angle of arc covered by a single pattern on TM (11.25°). This ensures that there is complete coverage of TM and consecutive patterns abut without significant gaps. Eight adjacent treatment segments corresponds to 180° of the TM, and 16 treatment segments equates to 360° [35].

PSLT has longer pulse duration than SLT: 5 ms versus 3 ns, smaller spot size: 100 μm versus 400 μm and slightly higher pulse energy: approximately 3 mJ compared to approximately 1 mJ. The 400 μm spot in SLT covers 16 times larger area than a 100 μm spot in PSLT, and therefore the total treated area with 100 spots in SLT is about 30% larger than with 1152 spots in PSLT.

Both SLT and PSLT have a similar safety profile, but patients are more comfortable with PSLT [36]. Similarly there is no statistically significant difference between efficacy of PSLT and ALT [37, 38].

Titanium-Sapphire Trabeculoplasty (TSLT)

TSLT uses a 790 nm laser, emitting near-infrared energy in pulses ranging from 5 to 10 ms. The lasing medium is a crystal of sapphire (Al_2O_3) that is doped with titanium ions and pumped with another laser with a wavelength of 514–532 nm, such as argon or frequency-doubled Nd:YAG lasers. This laser penetrates about 200 mm into the juxtacanalicular TM, inner wall of SC and even the proximal bed of collector channels. The TM tissue is preserved as energy is selectively absorbed by pigmented phagocytes.

The spot size is smaller than SLT or MLT at 200 mm. Fifty non-overlapping shots are applied to 180° of the pigmented TM. Treatment energy is started at 50 mJ and stepped down to 30 mJ (if necessary). The treatment endpoint is the formation of mini-bubbles or the visible burst of pigments from the TM.

In a study with 37 POAG patients, success was seen in 44% of TSLT patients and 61% of SLT patients at 1 year and in 22% of TSLT patients and 46% of SLT patients at 2 years ($p = 0.11$), with no complications [39].

Literature is sparse regarding clinical studies reporting the efficacy of TSLT, and the device is also not widely available. Large-scale randomised-controlled trials must be carried out before the long-term safety of TSLT can be determined.

Cyclophotocoagulation

Micropulse Cyclophotocoagulation (MPCPC)

MPCPC uses an 810 nm diode laser to deliver a series of repetitive, short pulses of laser energy separated by rest periods across the sclera. Off cycles allow for thermal dissipation and hence reduce collateral damage and inflammatory response. MicroPulse P3 glaucoma device (IRIDEX IQ810 Laser Systems) is applied at 2–2.5 W (total energy of 112–150 J) at a 31.3% duty cycle, with a duration of 90 s per hemisphere.

Emanuel and colleagues used MPCPC on 84 eyes with refractory glaucoma and reported IOP lowering from 27.7 ± 10.3 mmHg on an average of 3.3 ± 1 medications to 16.3 ± 9.5 mmHg (41.2% reduction) on an average of 1.9 ± 1.3 glaucoma medications at 1 month, with a final decrease to 11.1 ± 4.4 mmHg at 12 months post laser ($p < 0.001$). At 12 months, the requirement for glaucoma medications increased to 2.3 ± 1.5 [40]. MPCPC has shown favourable efficacy and complication profiles [41].

Ultrasound Cycloplasty (UCP)

UCP uses high-intensity focused ultrasound (HIFU) that triggers hyperthermia in focal areas in the ciliary body, thereby reducing aqueous production and IOP. The effect is independent of ciliary body pigmentation.

The EyeOP1 device (Eye Tech Care, France) for UCP is equipped with six miniaturised cylindrical piezoelectric elements with a positioning cone. The probe is available in three different sizes (11-, 12- and 13-mm ring diameters). Size of probe is determined using ultrasound biomicroscopy (UBM) or anterior segment optical coherence tomography (ASOCT). The treatment acts on six circular sectors of the ciliary body, with a 20-s interval between each shot.

Seventy-three Indian patients with OAG underwent UCP with two treatment protocols of ultrasound delivery depending on exposure time (8 and 10 s) with second-generation probe. Successful IOP control after a single procedure was 78.3% (79% and 78% in the 8 s and 10 s groups, respectively) at 12 months. Overall, the mean

IOP reduction achieved in responding patients was 41% [42]. Patients in the 10-s group had a higher incidence of anterior chamber reaction and scleral marks compared to 8-s group.

Giannaccare and colleagues reported results of UCP using both generations of probes (4 s/6 s [first generation]; 8 s [second generation]) in 49 eyes. One year post-UCP, mean IOP decreased from 27.7 ± 9.2 to 19.8 ± 6.9 mmHg ($p < 0.001$), and mean number of anti-glaucoma medications decreased from 3.2 and 0.5 to 2.3 and 0.2, respectively ($p < 0.05$). Significantly higher IOP reduction was achieved with second-generation probes. Complete success was achieved in 21 (42.9%), while failure was seen in 12 patients (24.5%) [43].

Though long-term results are awaited, it is a safe and efficacious option for short-term IOP reduction for both refractory and non-refractory cases.

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What's New in the Surgical Management of Glaucoma

6

Alice L. Williams and Marlene R. Moster

Introduction

Although trabeculectomies and tube shunts remain mainstays of glaucoma management, the last decade has seen an unprecedented expansion in the surgical armamentarium for glaucoma. Several minimally invasive glaucoma surgeries (MIGS) have been introduced into practice or are in pipeline. These devices provide moderate reduction in IOP and are indicated in patients with mild to moderate open-angle glaucoma (OAG), either as a stand-alone procedure or at the time of cataract extraction. In select patients, more robust IOP reduction may also be attained with the Xen gel stent (Allergan, Dublin, Ireland), InnFocus MicroShunt (InnFocus Inc, Miami, FL), and gonio-assisted transluminal trabeculotomy (GATT). These procedures show promise for patients with advanced glaucoma who may have traditionally needed a filtration procedure.

Because they target angle-based outflow pathways, most MIGS are indicated for use in the open-angle glaucomas. Although fewer surgical options are available for primary angle-closure glaucoma (PACG), several recent clinical trials have clarified the indications for stand-alone cataract extraction in these patients for whom the mechanism of angle closure is related to the anatomical size or position of their lens.

This chapter summarizes the indications for glaucoma surgery as dictated by the mechanism of the glaucoma, its severity, and the level of IOP control needed. The current literature is reviewed regarding the relative efficacy and safety profile of the various glaucoma surgeries, as well as patient factors that need to be considered when choosing a surgical approach.

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Trabecular Bypass Procedures

For patients with mild to moderate OAG and a visually significant cataract, a trabecular bypass stent can be considered at the time of cataract surgery. There are no long-term studies regarding the impact of trabecular bypass procedures on disease progression, but several MIGS procedures have proven evidence of modest IOP reduction with a favorable safety profile.

iStent

The iStent (Glaukos, Laguna Hills, CA) was approved by the FDA in 2012. It is approved for use at the time of cataract surgery in patients with mild to moderate OAG on one to three medications. It bypasses the trabecular meshwork (TM) to create a direct communication between the anterior chamber and Schlemm's canal (SC) and is therefore contraindicated in angle-closure glaucoma and neovascular glaucoma and in patients with elevated episcleral venous pressure [1, 2]. A recent meta-analysis of 37 studies including 2495 patients found iStent implantation with concurrent phacoemulsification to be superior to phacoemulsification alone in reducing IOP and dependence on antiglaucoma medications. Patients undergoing phacoemulsification experienced a 4% IOP reduction from baseline with a mean reduction of 1.01 medications, compared to an IOP reduction of 9% and 27% and a medication reduction of 1.33 and 1.1 with one and two iStents, respectively [3].

Kahook Dual Blade

The Kahook dual blade (KDB) (New World Medical, Rancho Cucamonga, CA) is a novel ab interno goniotomy device (Fig. 6.1). It is a single-use device that allows the surgeon to cleave the trabecular meshwork for approximately 120°.

The dual blade is designed in a way to achieve a more complete goniotomy. Its sharp tip is designed with a taper to allow for smooth entry of the blade through TM

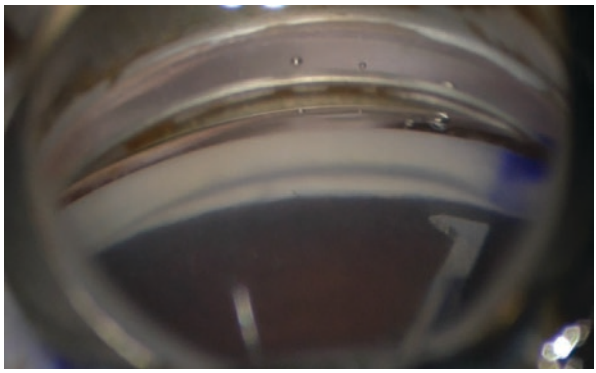

Fig. 6.1 Gonioscopic view of the Kahook dual blade

and into SC, and the heel fits within the SC and thus allows smooth advancement of the blade within the canal while preventing collateral damage during treatment. The ramp of the blade generates a gentle stretch of the TM as the blade is advanced. The dual blades create parallel incisions of the TM allowing excision of a strip of TM which achieves a near-complete removal of TM. Additionally, there are no implant-related risks.

Greenwood et al. studied 71 eyes with glaucoma that underwent goniotomy with the Kahook dual blade at the time of cataract surgery. The study subjects had a mean IOP reduction of 26% with a reduction of 0.7 medications. The most common adverse event observed was postoperative hyphema [4].

Satisfactory results have been seen in patients with secondary open-angle glaucoma such as pseudoexfoliation glaucoma and pigmentary glaucoma since the mechanism of elevated IOP in these patients is related to accumulation of extracellular material and pigment within the TM, respectively. The KDB goniotomy has also shown success in congenital glaucoma, in patients with uveitic and/or steroid-induced glaucoma [5]. However, given the relative novelty of this blade, most studies are limited to 12-month follow-up.

Hydrus Microstent

The Hydrus microstent (Ivantis Inc., Irvine, CA, USA) is a trabecular bypass stent intended for use in patients with mild to moderate OAG at the time of cataract surgery. It is made of nitinol and is 8 mm in length. Its curved shape facilitates scaffolding and dilation of SC for 3 clock hours ("intracanalicular scaffold") (Fig. 6.2).

Although not yet approved by the FDA, Phase 3 clinical trials are underway. A prospective randomized trial of 100 patients demonstrated that combined cataract and Hydrus surgery resulted in a 36% reduction in washed-out mean diurnal IOP vis-a-vis a 27% reduction for the cataract surgery group [6]. The Hydrus group also used 1.5 fewer medications at 2 years of follow-up, compared to one fewer medication for the control group. The only adverse event reported in the Hydrus group was

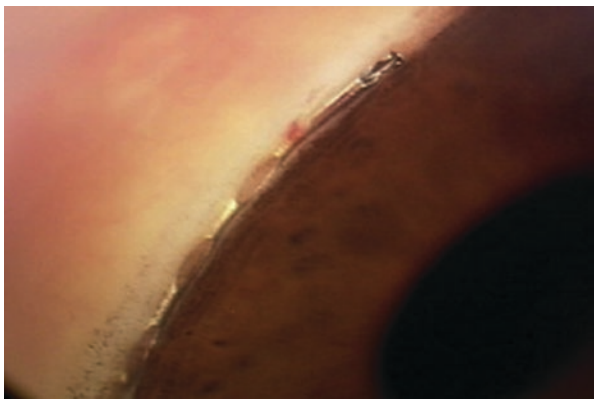

Fig. 6.2 Gonioscopic view of the Hydrus microstent after implantation in Schlemm's canal (From SooHoo JR, Seibold LK, Radcliffe NM, et al. Minimally invasive glaucoma surgery: current implants and future innovations. Can J Ophthalmol 2014;49:530; with permission)

the formation of focal PAS, which did not appear to affect the IOP outcomes. Recently, Fea et al. compared the efficacy of stand-alone Hydrus microstent implantation to selective laser trabeculoplasty in a cohort of 56 patients with uncontrolled POAG. Although both groups experienced significant reduction in IOP, only the Hydrus group experienced a reduction in number of medications, with 47% of patients remaining medication free at 12 months (vs. 4% in the SLT group) [7].

Gonio-Assisted Transluminal Trabeculotomy

For patients with OAG requiring significant IOP reductions, gonio-assisted transluminal trabeculotomy (GATT) may be tried. GATT is a form of ab interno trabeculotomy in which an illuminated fiber-optic microcatheter (iScience International, Menlo Park, CA) is advanced circumferentially through SC and then externalized to open the TM for a full 360° (Fig. 6.3). Grover et al. published the largest retrospective case series of 85 OAG patients who underwent GATT alone or in combination with cataract surgery. They found a 30% reduction in IOP with an average decrease of 0.9 medications at 1 year of follow-up for patients with POAG, while patients with secondary open-angle glaucoma experienced a 57% IOP reduction with a decrease of 1.9 medications [8]. Early reports indicate that GATT may also be more efficacious in younger patients with congenital or juvenile open-angle glaucoma (46% IOP reduction with a decrease of 1.8 medications) [9]. Thus in select patients for whom the TM is the primary site of outflow obstruction, GATT is a potentially efficacious primary procedure which still preserves the conjunctiva for incisional glaucoma surgery should it be required at a later date. GATT can also be performed after a failed trabeculectomy or glaucoma drainage device [10]. As with other procedures, which create an open pathway to the episcleral venous system, the main adverse event associated with GATT surgery is postoperative hyphema. This is usually self-limited but can rarely result in intractable IOP elevation necessitating incisional glaucoma surgery. Thus inability to stop anticoagulant medications and history of a bleeding diathesis are contraindications for GATT.

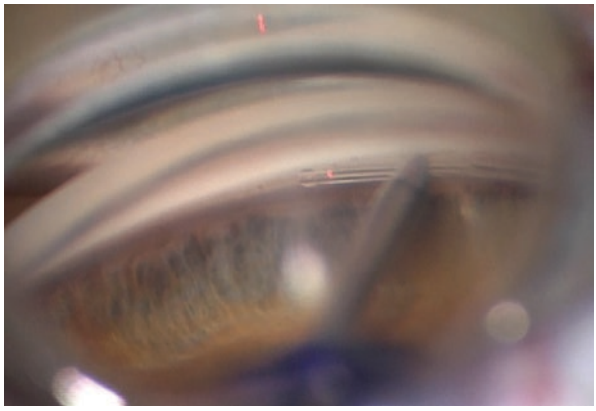

Fig. 6.3 Gonioscopic view of gonio-assisted transluminal trabeculotomy just prior to insertion of the illuminated fiber-optic microcatheter into Schlemm's canal

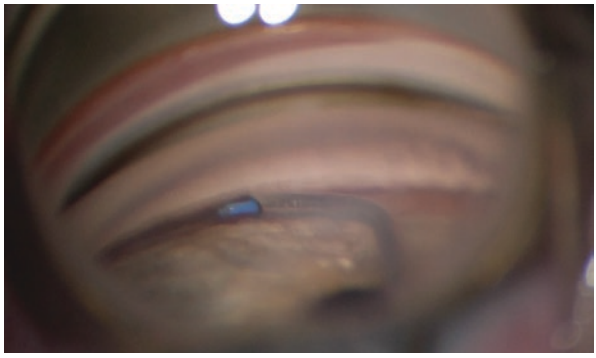

Fig. 6.4 Gonioscopic view of the TRAB360 just prior to insertion into Schlemm's canal (Courtesy of Jonathan S. Myers, MD, Wills Eye Hospital, Philadelphia, PA)

The disadvantages of GATT include its technical difficulty to perform, the expense of the fiber-optic probe, and the rare but significant postoperative IOP spikes. Modifications have been suggested to overcome these limitations.

Ab interno canaloplasty (ABiC) describes the procedure in which a microcatheter is passed through SC for 360°. Viscoelastic is injected to dilate the SC during its passage; however the catheter is not externalized, and so the TM remains intact. No clinical study has yet been published regarding this procedure; however it is expected to have a reduced incidence of hyphema as compared to GATT [11]. Grover and Fellman have also described a simple modification of the GATT procedure in which a thermally blunted 4-0 or 5-0 nylon suture is used to cannulate SC, thus obviating the need for the fiber-optic probe [12].

Finally, the TRAB360 (Sight Sciences, Menlo Park, CA, USA) is a single-use device, which allows completion of a 360-degree goniotomy (Fig. 6.4) through a clear corneal incision, just like cataract surgery. With the exception of viscodilation, this is theoretically equivalent to the GATT, although no studies have yet been performed to confirm its effect.

Supraciliary Procedures

The CyPass microstent (Transcend Medical, Inc., Menlo Park, CA) has been approved by the FDA for implantation at the time of cataract surgery in patients with mild to moderate OAG. It is a fenestrated microstent that is inserted into the supraciliary space after creation of a small cyclodialysis cleft (Fig. 6.5).

In a prospective randomized clinical trial of 505 POAG patients, combined cataract and CyPass surgery resulted in a 30% IOP reduction and 1.2 fewer medications. These results were superior to the control group, which experienced a 22% IOP reduction with 0.6 fewer medications from cataract surgery alone. In this study, main adverse events associated with CyPass implantation were transient hypotony, which in three patients (1%) was associated with signs of maculopathy but no visual acuity loss and transient IOP rise >10 mmHg in 16 patients (4.3%) [1, 13].

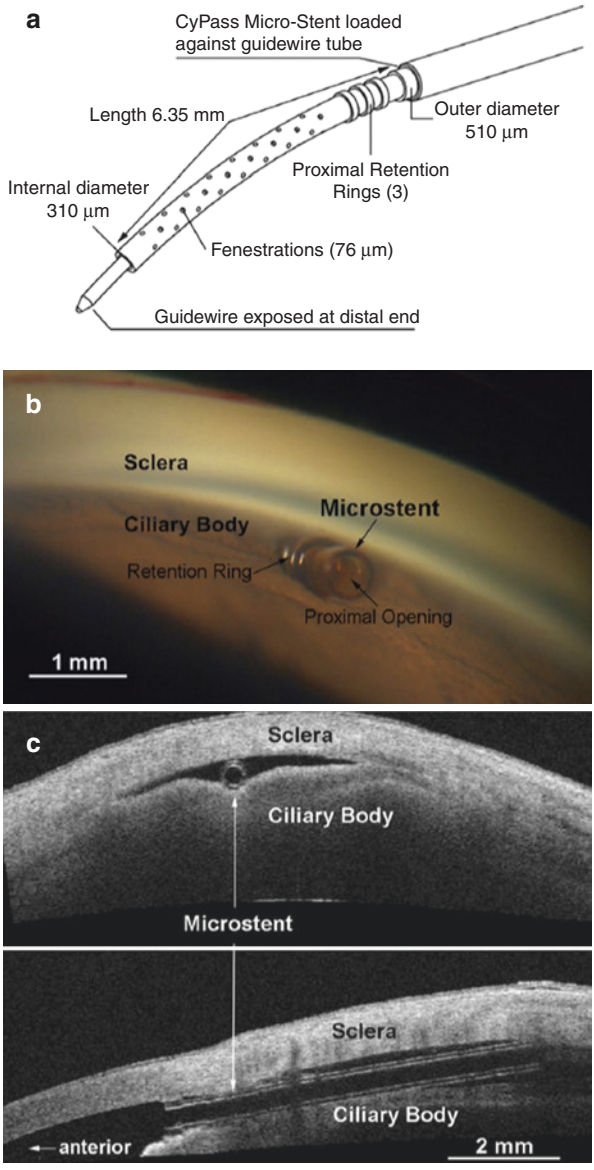

Fig. 6.5 CyPass microstent. (**a**) Illustration of the CyPass microstent threaded on the guidewire of the applier. (**b**) Gonioscopic view of the CyPass microstent and (**c**) positioning on ocular coherence tomography (From Vold S, Ahmed IIK, Craven ER, et al. Two-Year COMPASS Trial Results: Supraciliary Microstenting with Phacoemulsification in Patients with Open-Angle Glaucoma and Cataracts. Ophthalmology 2016;123:2103–2112; with permission)

A retrospective study has shown that that IOP-lowering effect of CyPass may be more pronounced for patients with a baseline IOP ≥ 21 mmHg [14]. Although no direct comparisons have been made, the CyPass thus appears to have similar efficacy to the trabectome.

The iStent G3 Supra (Glaukos, Laguna Hills, CA) is a similar suprachoroidal stent, made of a biocompatible polymer with a titanium sleeve. It is a 4-mm-long curved stent with a lumen of 0.165 mm. It is currently being studied for use with

concurrent cataract surgery in a multicenter randomized controlled trial in the USA. The iStent Supra has received CE Mark approval in Europe.

Subconjunctival Filtration Procedures

For patients with advanced glaucoma or those requiring more aggressive IOP control typically obtained with trabeculectomy or tube shunt, new approaches to filtration via the subconjunctival space are available or in development.

Xen Gel Stent

The Xen gel stent is a collagen implant that is inserted ab interno through the scleral spur into the subconjunctival space (Fig. 6.6). A prospective multicenter clinical trial of 65 glaucoma patients whose IOP was uncontrolled on maximum tolerated medical therapy demonstrated a 64% reduction in IOP with 1.8 fewer medications at 12 months. The most common complications were subconjunctival fibrosis requiring bleb needling (32%) and transient hypotony (IOP < 6 mmHg not requiring surgical intervention, 24%). Only four patients (6%) had persistent loss of ≥2 lines of BCVA [15]. Implantation of the stent at the time of cataract surgery has also been studied, with similar outcomes [16]. One retrospective study has compared the efficacy and safety of the Xen gel stent to trabeculectomy in 354 eyes (293 patients) with uncontrolled glaucoma and no prior incisional surgery. Outcomes were similar between the two groups, with no significant difference in failure rates or visually significant complications. The investigators identified preoperative IOP > 21 mmHg, nonwhite race, and preoperative BCVA better than 0.4 logMAR as factors that trended toward better outcomes with the Xen gel stent [17].

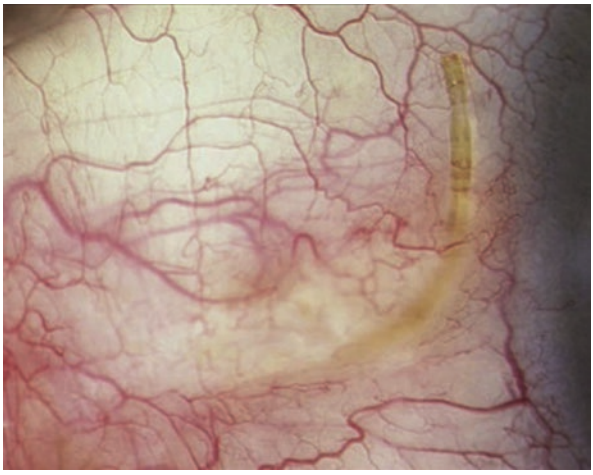

Fig. 6.6 The Xen gel stent in the subconjunctival space (From Lewis RA. Ab interno approach to the subconjunctival space using a collagen glaucoma stent. J Cataract Refract Surg 2014;40:1305; with permission)

InnFocus MicroShunt

The InnFocus MicroShunt is an aqueous drainage device made of an ultra-stable synthetic polymer of poly(styrene-block-isobutylene-block-styrene) or SIBS. It has been approved in Europe since 2012 but is yet to get US FDA approval. It is implanted through an ab externo modified filtering procedure. It drains aqueous fluid 3 mm posterior to the limbus to a subconjunctival flap created with adjunctive mitomycin C.

A cohort of 14 patients, nine of whom underwent InnFocus placement in combination with cataract surgery, were followed for 3 years. These patients had 55% reduction of IOP from a baseline of 23.8 mmHg with the use of 1.5 fewer topical medications. This translated to a 95% qualified success rate using the relatively stringent criteria of an IOP $\leq$ 14 mmHg and IOP reduction $\geq$20%. Serious adverse events that included hypotony (13%) and transient choroidal effusion (8.7%) have been noted [18]. Although these rates are similar to those reported in studies of the Ex-Press shunt and trabeculectomy, all cases of hypotony in this cohort resolved spontaneously. There were also no cases of shunt erosion, bleb leak, or infection. Prospective randomized trials comparing the InnFocus MicroShunt to trabeculectomy in patients with refractory glaucoma are now underway. If these results are confirmed in these appropriately powered prospective trials, the InnFocus MicroShunt may provide another avenue for the treatment of advanced glaucoma in conjunction with cataract surgery.

Special Considerations for Angle-Closure Glaucoma

Stand-Alone Cataract Extraction for Angle-Closure Glaucoma

Patients with primary angle-closure glaucoma (PACG) derive a significant IOP-lowering benefit from cataract extraction. A meta-analysis of patients with angle closure demonstrated a 30% reduction in IOP and a 58% reduction in number of medications after stand-alone cataract extraction through 16 months of follow-up [19]. Several recent prospective trials have helped to clarify which of these patients may do well with cataract surgery alone.

Tham et al. in a study of 72 patients with medically controlled PACG (IOP $\leq$ 21 mmHg on 1–3 medications) found that phacoemulsification alone was equivalent to combined phacotrabeculectomy in IOP control at 2 years of follow-up [20]. The patients in the combined surgery group required 0.8 fewer medications, however, at the cost of significantly more postoperative complications. There were no differences in visual acuity or progression of optic nerve cupping or visual field defects between the two groups. Only one patient in the phacoemulsification group required a trabeculectomy through 2 years of follow-up.

MIGS for Angle-Closure Glaucoma

Thus in patients with mild to moderate angle-closure glaucoma, stand-alone phacoemulsification results in significant reductions in IOP [21]. These patients may derive further benefit with an acceptable safety profile from a concurrent MIGS procedure. In aiming to bypass the trabecular meshwork, most MIGS discussed previously are best suited for patients with OAG. Because it targets aqueous production at the ciliary body, however, endoscopic cyclophotocoagulation (ECP) can theoretically be effective for any type of glaucoma. It may be particularly well suited for patients with chronic PACG because it causes the ciliary body to rotate posteriorly with a resultant deepening of the anterior chamber angle [22]. Multiple retrospective studies have found that combined phaco-ECP consistently lowers IOP with a safety profile that is similar to that of cataract surgery alone [23–26]. Recently, one prospective nonrandomized study confirmed this finding. In a study of 80 eyes with medically controlled OAG, Francis et al. found that mean reduction in IOP was modest but statistically superior in the phaco-ECP group as compared to the phacoemulsification group alone (1.1 mmHg and 0.8 mmHg at 2 years, respectively) [27]. The combined phaco-ECP patients also used statistically fewer glaucoma medications, while visual acuity and complication rates were similar between the two groups. Thus, ECP is an appropriate adjunct for patients with mild-moderate glaucoma who require phacoemulsification surgery for a visually significant cataract. It is best avoided in patients at increased risk for postoperative inflammation or macular edema, given its pro-inflammatory side effects.

Advanced Angle-Closure Glaucoma

Although the aforementioned studies provide important insights into the effects of stand-alone cataract extraction on IOP control in PACG, it is important to note that they predominately included patients with mild to moderate disease, and were not designed to assess its long-term impact on glaucomatous progression. Guidance regarding patients with more severe disease is found in another prospective trial by Tham et al. [28]. They randomized a group of medically uncontrolled PACG patients (IOP > 21 mmHg on maximally tolerated medications) to either phacoemulsification alone or phacotrabeculectomy. This cohort represented the full spectrum of disease severity, with mean MD of −17.1 dB (range, −2.1 to −32.1 dB). The phacotrabeculectomy group had consistently superior IOP control by a margin of 2 mmHg and used an average of 1.25 fewer topical medications. Also, at 2 years of follow-up, only 25.9% of patients in the phacoemulsification group required no medications, while 70.8% of patients in the combined surgery group met this goal. Four eyes (14.8%) in the phacoemulsification group subsequently required trabeculectomy. Although the phacotrabeculectomy group endured more complications during the postoperative period, this did not result in any significant differences in visual acuity between the two groups.

Thus, for patients with advanced or medically uncontrolled glaucoma, combined cataract and glaucoma surgery provides superior IOP control with the use of fewer topical medications. A concurrent trabeculectomy may also decrease the likelihood of a perioperative spike in IOP, which is an important consideration in patients with very advanced disease. Finally, results from these studies indicate that patients with any severity of chronic angle closure are more likely to require a subsequent trabeculectomy if their IOP is uncontrolled.

Single-Pass Four-Throw (SFT) Pupilloplasty for Angle Closure

Angle crowding is an associated feature with ACG, and in long standing cases, it causes formation of peripheral anterior synechiae (PAS), and the extent of PAS correlates with the level of IOP.

Surgical pupilloplasty has recently been attempted to break PAS [29]. The procedure involves taking a significant area of iris tissue into the loop/knot of pupilloplasty in order to relive traction exerted to break the PAS. In cases with more than 270° synechiae, it is recommended to do a 6-point traction that translates into making three passes with SFT for achieving pupillary knots. In cases with <270° of PAS, a 4-point traction is sufficient. This procedure has also been used for the management of secondary ACG due to trauma [30]. Post-SFT pharmacological pupil mydriasis can be achieved that can aid in adequate fundus examination to monitor glaucoma, unlike surgical pupilloplasty.

Phacoemulsification with Intraocular Implantation of Lens, Endocyclophotocoagulation, and Endoscopic Goniosynechialysis (PIECES)

This new technique combining phacoemulsification with intraocular lens (IOL) implantation (PI), endocyclophotocoagulation (EC), and endoscopic GSL (ES) has been suggested to control IOP in extensive (>270°) synechial angle-closure glaucoma [31]. This approach addresses both the inflow and outflow of the aqueous humor simultaneously. It minimizes the need for glaucoma medications and drainage surgery. Conjunctiva is also preserved, so future drainage surgery can still be done, if needed.

New Drainage Devices

New Susanna Glaucoma Drainage Device (SGDD)

The new SGDD is a nonvalved silicone device with a plate having area of 200 mm^2 and two extensions measuring 4 × 1 mm. The anterior portion is fixed at 6 mm from limbus, allowing the plate to be located at 10 mm, decreasing the possibility of extrusion.

The new SGDD plate is better than its older version that had a larger area of 350 mm^2 and an elliptical form and thus was difficult to implant in many cases. New SGDD is thinner (0.5 mm) than Ahmed (1.9 mm) and Baerveldt (0.84 mm) and also has a thinner tube [32].

The initial study with 58 patients reported a qualified success rates for neovascular glaucoma group and failed trabeculectomy group to be 73% and 86%, respectively. Significant complications noted were two cases of conjunctival erosion and two cases of late hypotony [33].

Future Directions

Randomized controlled trials will be necessary to directly compare the aforementioned procedures to each other and to trabeculectomy in the setting of advanced or uncontrolled glaucoma.

Prospective trials are also needed to identify the specific demographic and clinical factors, which may be indicative of success in each type of surgery. For example, the patency of downstream collector channels has been suggested as one factor that may determine the efficacy of canal-based surgeries. The presence of an episcleral venous fluid wave may indicate that this system is intact, but at the time, there is no way to assess this factor preoperatively [33, 34].

In the future, improved diagnostic approaches may allow surgeons to predict which patients will benefit from procedures that target SC and the supraciliary space or subconjunctival filtering procedures.

Finally, there is very limited data at this time on cost-effectiveness and quality-of-life measures for these procedures. Stand-alone cataract surgery has well-defined positive effects on performance-based measures and quality of life [35]. Its cost-effectiveness is also well established, including for surgery on the second eye [36]. Studies regarding the cost-effectiveness of MIGS are limited, but two analyses performed in Canada and the UK indicate that the cost of the iStent may be superior to topical ocular medication in long-term follow-up of greater than 5 years. Modest cost-effectiveness for trabectome and ECP has also been established in comparison to medical therapy [37, 38]. Additional research is needed to compare the cost-effectiveness and quality-of-life impact of the various MIGS and to delineate these effects from the already well-known benefits of cataract extraction.

Conclusions

Several new minimally invasive surgical procedures are now available for use in mild to moderate POAG at the time of cataract extraction. As reviewed here, the iStent, Hydrus, CyPass, and ECP have demonstrated evidence of modest improvements in IOP control. Although this benefit is largely reflected in a lower medication burden for these patients, the favorable safety profile of these interventions

makes them an attractive adjunct to cataract surgery. Given the many barriers to long-term compliance with topical medications, it can be argued that any intervention that decreases this medication burden is likely to be beneficial. Formal economic and quality-of-life analyses are necessary to confirm the validity of this approach, but the few studies, which have been conducted so far in this regard, are promising. Since these procedures involve minimal tissue manipulation, they theoretically should not change the success rate of subsequent filtering surgery. This has been confirmed in one cohort study involving patients who underwent a trabeculectomy following trabectome surgery [39]. Several other devices including the Kahook dual blade and Hydrus trabecular bypass stent await further study or FDA approval but are also likely to be useful for the treatment of mild to moderate POAG at the time of cataract surgery. Although a superficial analysis of the available literature indicates that the CyPass and Hydrus stents may be more effective than the other MIGS, direct comparisons in randomized controlled trials are necessary to fully explore these differences. It may be too that individual demographic and clinical factors will predispose certain patients to success with a particular procedure.

Due to their modest efficacy, these MIGS are not appropriate for patients with advanced or medically uncontrolled glaucoma. GATT, the Xen gel stent, and the InnFocus MicroShunt do show promise for these patients. Each of these procedures has the benefit of sparing at least the majority of the conjunctiva for future incisional surgery, and so far each seems to have a relatively favorable safety profile. However, it is important to bear in mind that both the Xen and InnFocus stents still involve the formation of a conjunctival bleb and require the use of mitomycin C. Given the limited results published on each of these surgeries to this point, additional study with larger patient populations is necessary to capture the full range of complications that may occur with these devices. Randomized controlled trials are also necessary to compare these procedures to the current gold standard surgical approaches to refractory glaucoma.

An abundance of research in the past decade has also clarified the importance of the native lens in the regulation of intraocular pressure and the pathogenesis of angle-closure glaucoma. This research as well as improvements in cataract surgical technique has paved the way for a paradigm shift in the management of concurrent cataract and PACG. Patients with mild to moderate PACG may achieve sufficient IOP control with cataract surgery alone, although they may derive additional benefit from combination with ECP. Finally, for patients with advanced PACG, combined cataract extraction with trabeculectomy has also been shown to provide superior IOP control with a lower medication burden than stand-alone cataract surgery and is still the preferred approach.

In conclusion, there have never been more avenues for surgical management and thus greater opportunity to individualize care for patients with glaucoma. In the years to come, additional prospective trials will more fully characterize the long-term efficacy, safety profiles, and cost-effectiveness of these procedures.

Acknowledgement *Disclosure Statement*: The authors have no relevant financial disclosures.

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What's New in Optical Coherence Tomography Angiography for Glaucoma

7

Gábor Holló

Why to Add Optical Coherence Tomography Angiography to the Investigation Armamentarium of Glaucoma?

The primary pathological process in glaucoma is the accelerated apoptosis of the retinal ganglion cells. The loss of the ganglion cell axons (the retinal nerve fibers) can be directly measured with the optical coherence tomography (OCT) retinal nerve fiber layer thickness (RNFLT) parameters while the loss of the retinal ganglion cell bodies with the OCT inner macular retinal thickness parameters. However, capillary and precapillary dysregulation is considered as an important risk factor for the development and progression of open-angle glaucoma, and the vascular changes may precede or predict the onset of neural tissue loss. OCT angiography is a novel noninvasive method developed for the detailed analysis of capillary perfusion in the various retinal layers and areas, respectively [1]. When evaluated in combination with the structural OCT measurements, it can detect early alterations, separate glaucoma eyes from normal eyes, and may potentially provide new information on early glaucomatous progression. Several methods of ocular blood flow measurements have been established and investigated for glaucoma in the last decades [2]. However, due to their limitations, their use remains minimal in clinical glaucoma care. The most important difference between information provided by the earlier blood flow measurement methods and OCT angiography is that the latter provides segmented measurement data for various retinal layers and areas, separately, while the former methods provide results for the whole eye, whole optic nerve head, retina, or large retinal areas, respectively. The segmented and localized information offered by OCT angiography can be coupled with the spatially corresponding localized structural and functional alterations and their longitudinal changes in glaucoma.

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Technical Aspects of OCT Angiography

The common clinical goals of OCT angiography are achieved with somewhat different technologies in the different OCT angiography systems [1]. This is not unexpected since the various OCT angiography systems arrive from different manufacturers. Table 7.1 summarizes the most important technical characteristics of the five OCT angiography systems currently used or examined for clinical application in glaucoma. It is important to emphasize that all OCT angiography systems are subjects of continuous technical development; therefore their clinical applicability may further improve in the future; and the corresponding parameters are not convertible between the different systems. In this chapter, images obtained with the RTvue XR/AngioVue OCT angiography system (Optovue Inc., Fremont, CA, USA) are shown, since till now most clinical information has been obtained with this instrument. The AngioVue instrument obtains amplitude decorrelation angiography images, in which the moving red blood cells generate information on perfusion [1, 3]. The current A-scan rate is 70,000 scans per second, the light source is centered on 840 nm, and a bandwidth of 50 nm is used. Motion correction is applied to minimize motion artifacts arising from microsaccades and fixation changes. The OCT angiography information is displayed as the maximum of the decorrelation values when viewed perpendicularly through the thickness. For optic nerve head and peripapillary retina assessment, six peripapillary sectors based on the Garway–Heath map and four retinal layers for en face imaging are generated automatically by the software (Figs. 7.1, 7.2, and 7.3). The corresponding en face vessel density and retinal layers from the vitreous to the choroid are (a) the optic nerve head layer (the innermost layer), (b) the vitreous–retina border, (c) the layer of the radial peripapillary capillaries (paired with the retinal nerve fiber layer on the structural retinal image), and (d) the retina–choroid border. For glaucoma investigations, in the peripapillary area, the radial peripapillary capillaries layer is the primary layer of

Table 7.1 Comparison of the most important characteristics of the currently available optical coherence tomography (OCT) angiography systems [1]

Instrument	AngioVue OCTA	AngioPlex OCTA	Spectralis OCTA	Angioscan RS-3000 OCTA	Swept Source OCT Angio
Manufacturer	Optovue Inc., Fremont, CA, USA	Carl Zeiss Meditec, Inc., Dublin, CA, USA	Heidelberg Engineering, Heidelberg, Germany	Nidek, Inc., Gamagori, Aichi, Japan	Topcon Corporation, Tokyo, Japan
Scanning speed	70,000 scans/s	68,000 scans/s	85,000 scans/s	53,000 scans/s	100,000 scans/s
Algorithm	SSADA algorithm	OMAG algorithm	Probabilistic mathematical model	Full-spectrum amplitude difference	Full-spectrum amplitude ratio analysis
Automated segmentation	Yes	Yes	Yes	No	No

SSADA split-spectrum amplitude-decorrelation angiography, *OMAG* optical microangiography

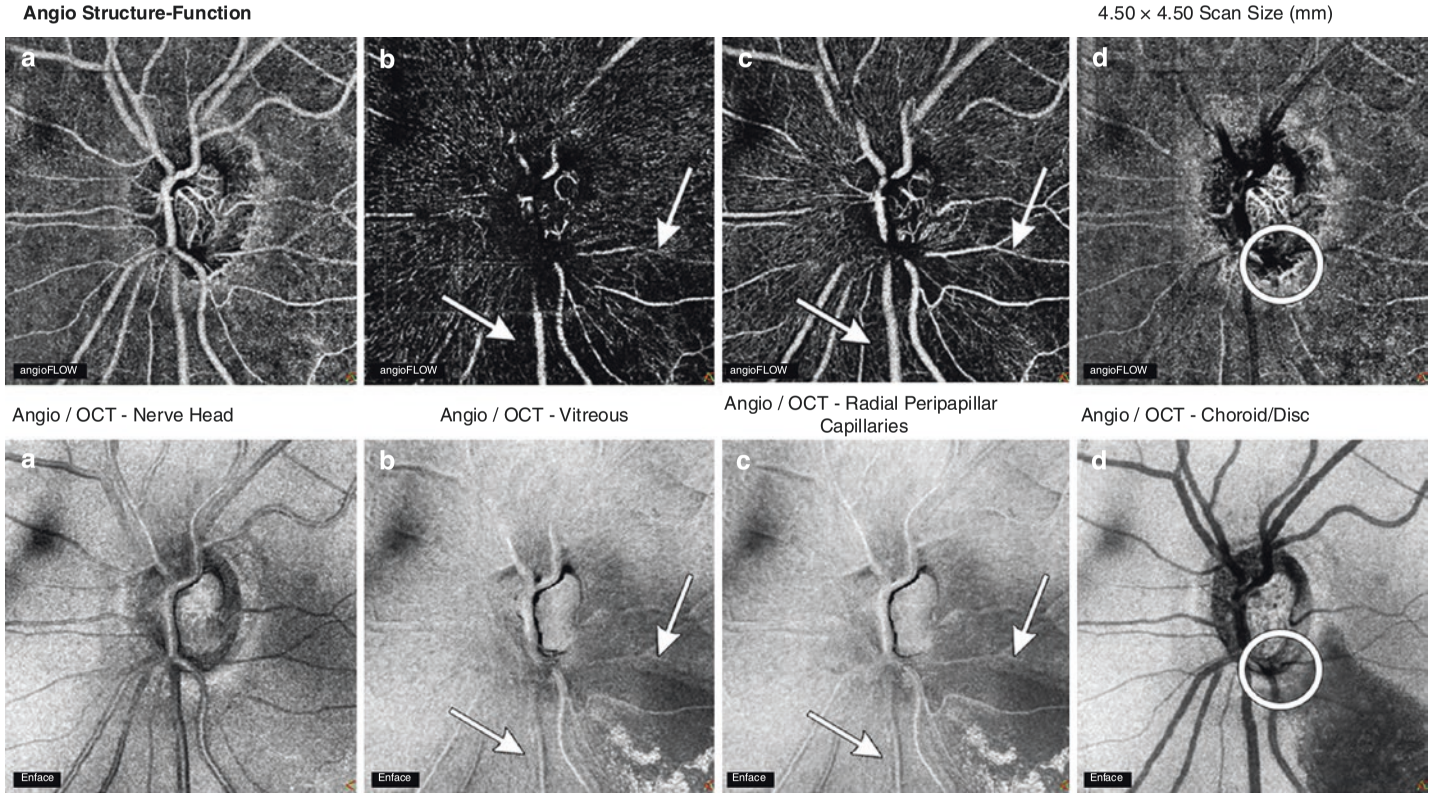

Fig. 7.1 Corresponding peripapillary en face vessel density and structural images of a glaucoma eye (angio structure-function overview presentation). Optic nerve head layer, (**a**); vitreous–retina border, (**b**); the layer of the radial peripapillary capillaries, (**c**); and the retina–choroid border, (**d**). The explanation of the layers is given in the text. The wide retinal nerve fiber bundle damage is indicated with arrows and the suspected lamina cribrosa defect with an ellipse

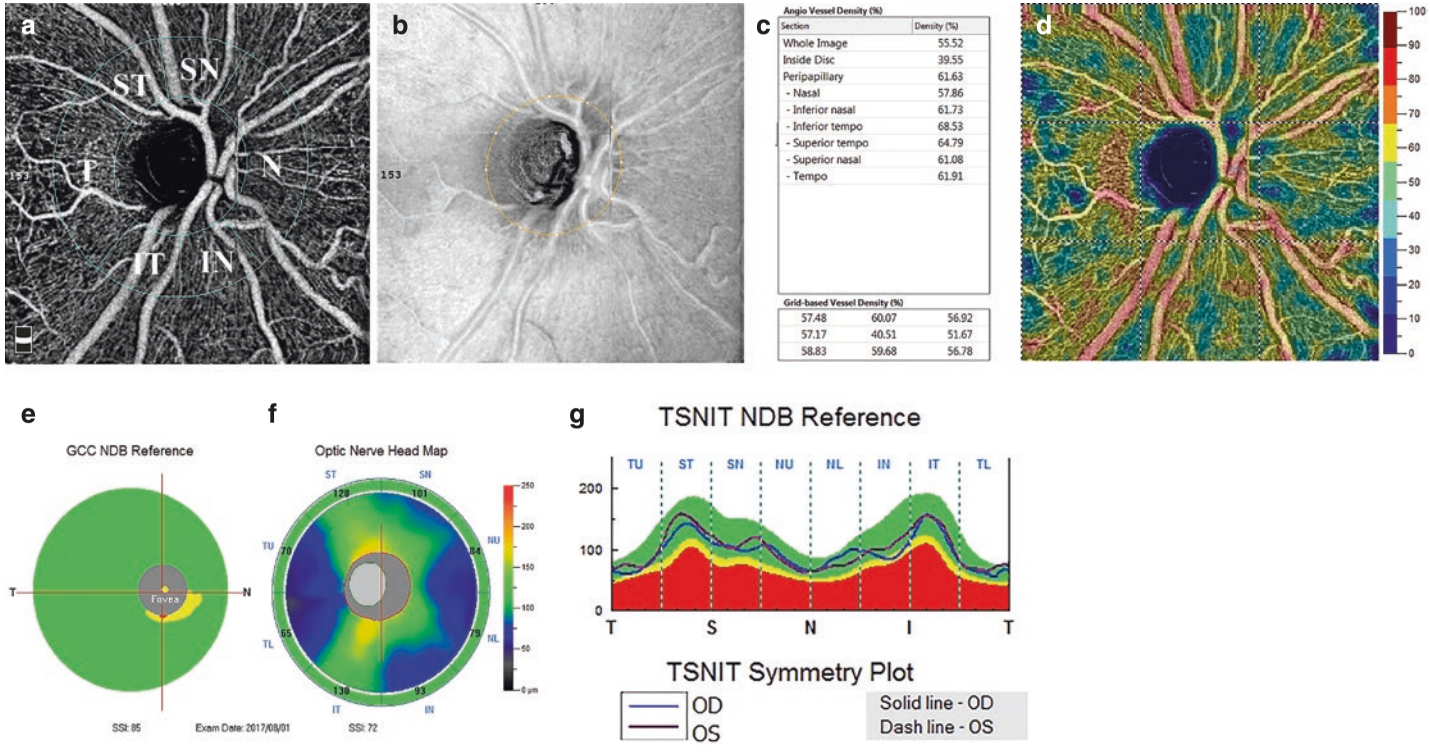

Fig. 7.2 Montage of an optical coherence tomography angiography (OCT angiography) vessel density report for the radial peripapillary capillaries layer and the corresponding retinal nerve fiber layer thickness (RNFLT) and macular inner retinal thickness (GCC) maps of a healthy eye (AngioVue OCT angiography). The explanation of the findings is given in the text. Peripapillary vessel density sectors, (**a**); en face retinal nerve fiber layer image, (**b**); vessel density and flow density measurement report, (**c**); color-coded perfusion map, (**d**); ganglion cell complex map, (**e**); retinal nerve fiber layer map, (**f**); and retinal nerve fiber layer thickness symmetry plot (**g**)

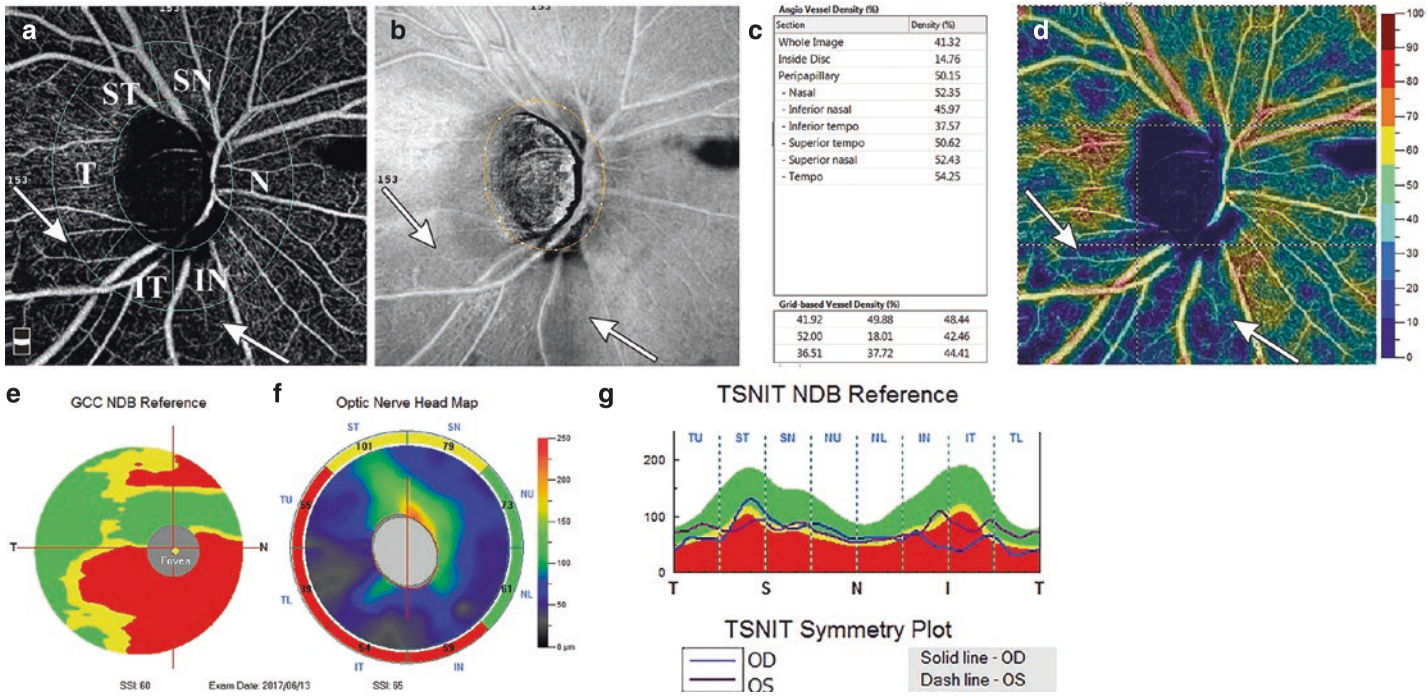

Fig. 7.3 (**a**–**g**) Montage of an optical coherence tomography angiography (OCT angiography) vessel density report and the corresponding retinal nerve fiber layer thickness (RNFLT) and macular inner retinal thickness (GCC) maps of an eye with advanced primary open-angle glaucoma. The montage follows the structure of Fig. 7.2. The most severe retinal nerve fiber defect is indicated with arrows on the vessel density image (**a**), the en face retinal nerve fiber layer image (**b**), and the color-coded perfusion map (**d**). The detailed explanation is given in the text

interest since it represents perfusion in the retinal nerve fiber layer. For the assessment of the peripapillary retina in glaucoma, the 4.5 mm × 4.5 mm scan size is used. The inner elliptical contour (which defines the optic nerve head) is obtained by automatically fitting an ellipse to the disc margin based on the OCT en face image. The peripapillary area is defined as the area between the inner and outer ellipses. The ring width between the inner and outer elliptical contour lines is 0.75 mm. No pupil dilation is needed for optimal image quality (signal strength index, SSI > 50). When the macula is studied for glaucoma, the 3 mm × 3 mm macula scan is used, and the superficial and deep vascular plexus are investigated separately (Fig. 7.4). For quantitative analysis, in the peripapillary area, vessel density (expressed in % of vessels in the measured area within a well-defined retinal layer) and flow index (the maximum decorrelation value of the whole en face angiogram) are used. In the macula, flow density and the extent of the foveal avascular zone (FAZ) can be measured with the instrument's software.

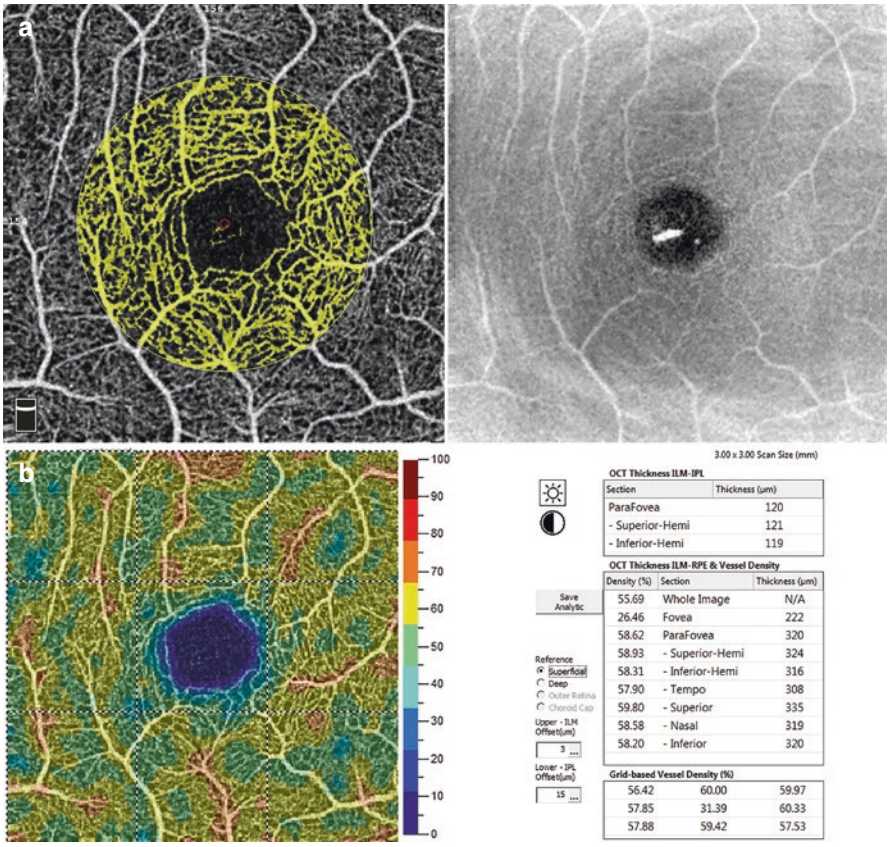

Fig. 7.4 Macular optical coherence tomography angiography (macular OCT angiography) report for the superficial vascular plexus of a healthy eye. One report shows the flow with colored outlining and the corresponding en face structural image (**a**), and the other report shows color-coded perfusion map and the vessel density measurement results (**b**)

Understanding the OCT Angiography Report

In order to understand and correctly interpret the OCT angiography report, it is mandatory to analyze the spatially corresponding structural OCT images and thickness parameters, the locations of the structural abnormalities, and the visual field alterations. Figure 7.1 shows how a retinal nerve fiber bundle defect appears on the corresponding en face structural and OCT angiography images.

Figure 7.2 shows a montage made using the OCT angiography report for the radial peripapillary capillaries layer and the corresponding RNFLT and inner macular retinal thickness (GCC) maps of a healthy eye of a 51-year-old male subject. The peripapillary vessel density measurement area (Fig. 7.2a) is subdivided into six sectors: the superotemporal (ST), temporal (T), inferotemporal (IT), inferonasal (IN), nasal (N), and superonasal, SN sectors. The corresponding en face structural image (Fig. 7.2b) shows homogeneous normal reflectivity of the retinal nerve fibers. Vessel density (Fig. 7.2c) is 61.63% for the total peripapillary area, and the sector vessel density values range between 57.86% (nasal) and 68.53% (inferotemporal). These values are typical for healthy eyes in the radial peripapillary capillaries layer. On the color-coded vessel density map (Fig. 7.2d), the vessels (including both the capillaries and the main retinal vessels) are indicated with yellow and red colors ("normal perfusion"). The GCC and RNFLT maps show normal thickness values (Fig. 7.2e, f), and the right and left eye's RNFLT plots are symmetric.

Figure 7.3 is a montage structurally similar to Fig. 7.2. But it shows a primary open-angle glaucoma eye of a 63-year-old patient with severe diffuse glaucomatous structural and perfusion damage. The en face structural image (Fig. 7.3b) shows diffuse retinal nerve fiber loss and a wide inferior and inferotemporal and a less extensive superotemporal retinal nerve fiber bundle defect. The global peripapillary vessel density (Fig. 7.3c) is 50.15% (abnormally low). In the inferotemporal peripapillary sector, the vessel density is 37.57%. On the color-coded vessel density map (Fig. 7.3d), bluish colors indicate decreased ("abnormal") perfusion. Both the GCC and RNFLT maps indicate severe structural damage (Fig. 7.3e, f). This case clearly shows that the more severe the axon loss, the more reduced the perfusion in the peripapillary retina. Since the glaucomatous retinal nerve fiber loss builds up from many localized damages, it is important to note that OCT angiography is able to show reduced perfusion in the area of narrow nerve fiber bundle defects (Fig. 7.5). In several cases, it shows reduced perfusion even before the corresponding sector RNFLT value decreases to the outside normal limit cutoff value (red color-code) [4, 5]. It has also been shown that the location and the severity of decreased vessel density in the radial peripapillary capillaries layer spatially correspond to the glaucomatous lamina cribrosa defect [6] (Fig. 7.1).

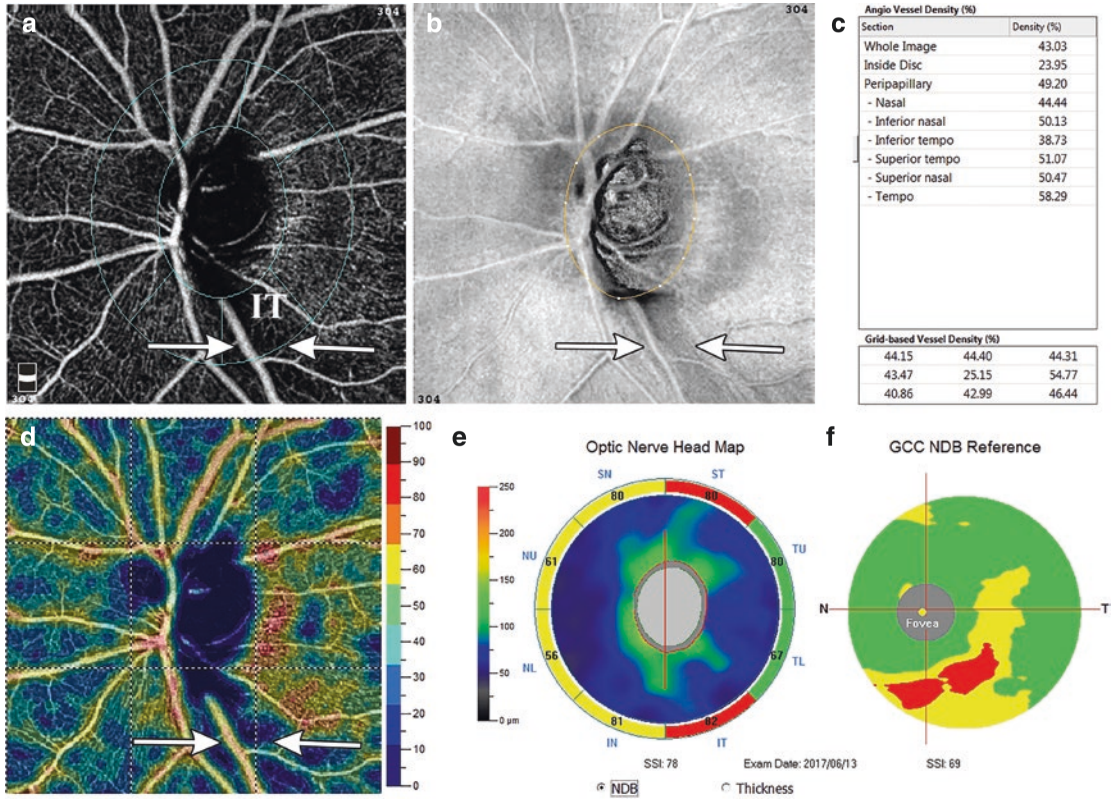

Fig. 7.5 (**a**–**f**) Montage of an optical coherence tomography angiography (OCT angiography) vessel density report and the corresponding retinal nerve fiber layer thickness (RNFLT) and macular inner retinal thickness (GCC) maps of a primary open-angle glaucoma eye with a narrow inferotemporal (IT) retinal nerve fiber bundle damage and a spatially corresponding decrease of vessel density (arrows). The detailed explanation is given in the text

Measurement Reproducibility, Artifacts, and Differential Diagnosis

Both peripapillary and macular OCT angiography measurements have favorable short- and long-term reproducibility in glaucoma eyes [4, 7]. Reproducibility of peripapillary vessel density measurement is not influenced by RNFLT [4]. The clinical significance of this result is that OCT angiography offers good reproducibility on both healthy eyes with high RNFLT and advanced glaucoma eyes with low RNFLT. However, it is important to note that OCT angiography is influenced by measurement artifacts [8], and the favorable reproducibility figures reflect only image series with optimal image quality and no artifacts. Image quality must always be evaluated after image acquisition. Images with low-quality score (for the AngioVue system SSI less than 50), motion artifacts, lid-related shadows, and shadows caused by vitreous floaters must be deleted. Vitreous floaters are of particular importance since their effects are variable; therefore they decrease the measurement reproducibility and may falsely imitate glaucomatous progression during follow-up. Figure 7.6 shows an OCT angiography report on a glaucoma eye with a wide inferotemporal retinal nerve fiber loss (arrows) and a superotemporal nerve fiber bundle shape shadow caused by a vitreous floater (asterisk). It is also essential to emphasize that the OCT angiography report is not disease specific; thus a proper clinical examination of the eye and the retina is mandatory prior to the evaluation of OCT angiography findings [8]. Figure 7.7 shows four color-coded OCT angiography vessel density maps which belong to four different eyes. The eyes have different optic nerve head diseases which all cause serious capillary perfusion damage of similar appearance on OCT angiography.

Relationship of Vessel Density, Glaucoma Severity, and Visual Field Damage

It has been show that peripapillary vessel density correlates with glaucoma severity expressed in RNFLT decrease or visual filed damage [9–12]. Thus, peripapillary vessel density reflects the disease stage. For research purposes and future clinical application, it is important that peripapillary vessel density has a strong relationship with visual field sensitivity and damage [9, 10, 12]. It is even more interesting that the relationship between the spatially corresponding sector vessel density and visual field cluster mean defect values is strong [9, 13, 14]. The relationship between the temporal peripapillary sector vessel density and the paracentral visual field mean defect is also significant [15]. Since in glaucoma RNFLT is most stable in this area (the papillomacular bundle area), the correlation between temporal peripapillary angioflow vessel density and paracentral visual field mean defect may potentially support the detection of glaucomatous progression in the papillomacular area. Several investigations showed that in primary open-angle glaucoma, the relationship between sector vessel density and visual field damage is strongest for the inferotemporal sector [9, 13, 16, 17]. The relationship in this sector may even be stronger for vessel density than RNFLT [9].

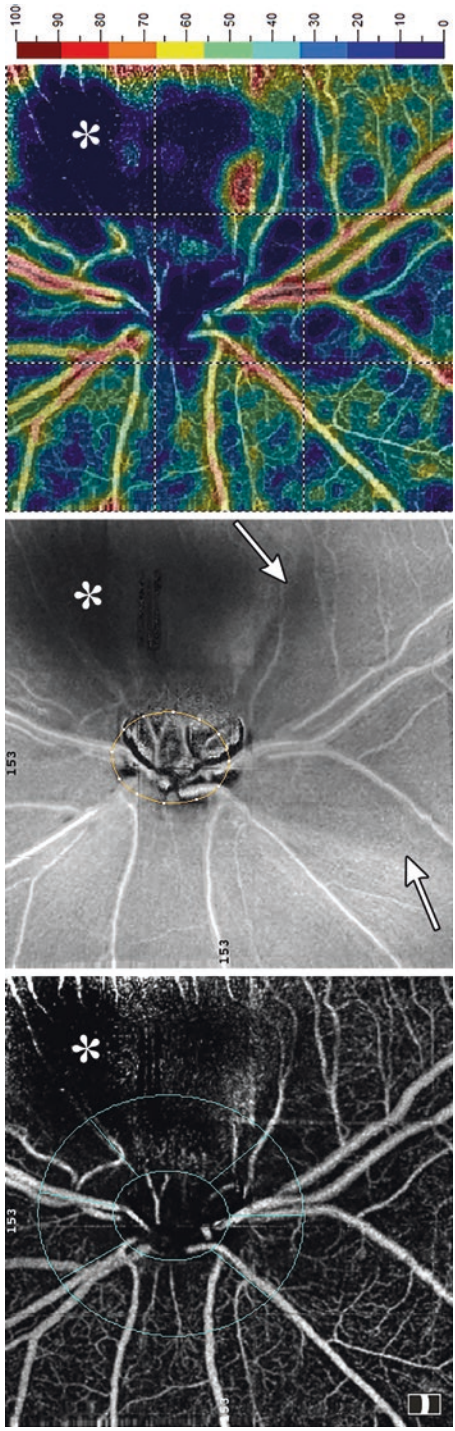

Fig. 7.6 Optical coherence tomography angiography (OCT angiography) report for the radial peripapillary capillaries layer of an open-angle glaucoma eye with a true retinal nerve fiber bundle defect (arrows) and a nerve fiber bundle shape shadow caused by a vitreous floater (asterisk)

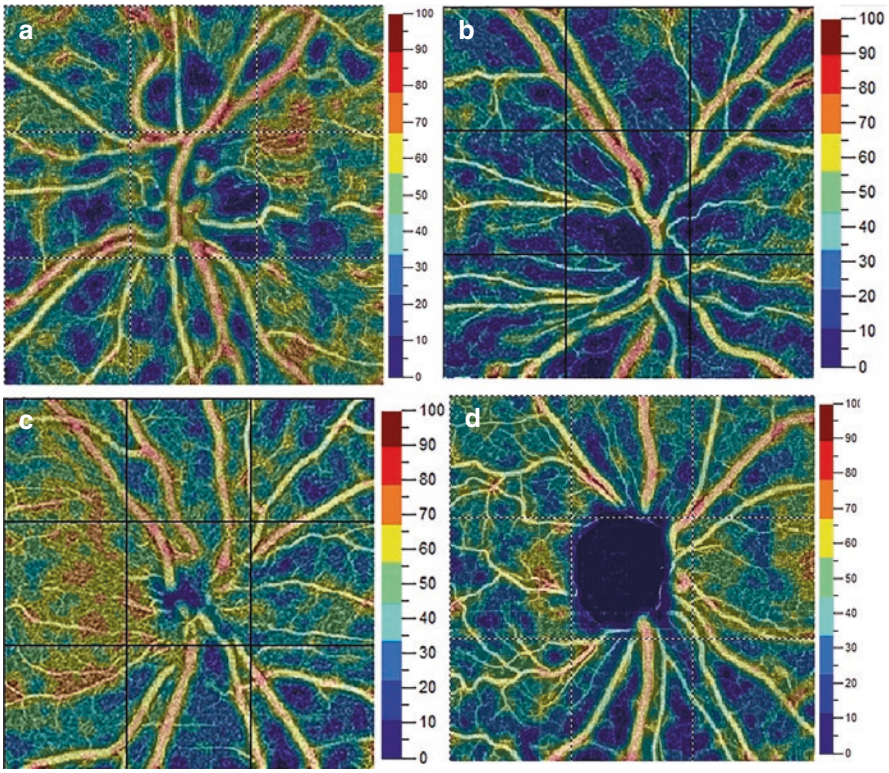

Fig. 7.7 Comparison of four color-coded vessel density maps of the radial peripapillary capillaries layer obtained on four eyes with different diseases. All four diseases caused retinal nerve fiber layer and perfusion damage in the peripapillary retina. Mild, nonischemic retinal vein occlusion (**a**), optic nerve atrophy due to an earlier nonarteritic anterior ischemic optic neuritis (**b**), optic nerve head drusen compressing the retinal nerve fibers (**c**), and severe juvenile open-angle glaucoma (**d**)

Diagnostic Accuracy

Several cross-sectional investigations analyzed the diagnostic accuracy of the various peripapillary and macular OCT angiography parameters for separation of perimetric glaucoma eyes from normal eyes and preperimetric glaucoma eyes form normal eyes [18–23]. In general, 360-degree peripapillary angioflow density performed best for separation, and in various studies, its accuracy was similar to that of peripapillary RNFLT. However, depending on the study population (severity of glaucoma) and the image quality (SSI values), the studies did show differences. The accuracy of separation of preperimetric open-angle glaucoma eyes from normal eyes varied across the investigations [24, 25]. In contrast, for separation of angle-closure glaucoma and healthy eyes, the OCT angiography parameters were inferior to the structural OCT parameters [26]. This difference between primary open-angle

glaucoma and primary angle-closure glaucoma may reflect the difference of the pathomechanisms of the diseases: the vascular involvement in the former and the absence of vascular involvement in the latter.

Influence of Intraocular Pressure on Peripapillary Vessel Density

The influence of medical and surgical intraocular pressure reduction on the actual peripapillary and macular perfusion values was only recently clarified. In a prospective case series, a detailed ophthalmological examination and peripapillary OCT angiography vessel density measurement were made on systemically healthy, young, treatment-naive, and newly diagnosed ocular hypertensive and early open-angle glaucoma patients [27]. OCT angiography was made first time when the untreated intraocular pressure was high (35–42 mmHg). Then it was repeated some weeks later when the intraocular pressure was medically reduced by at least 50% to 18 mmHg or less. In the second visit, a considerable improvement of vessel density was seen (Fig. 7.8) and measured in all cases [27]. In another study, the area of decreased peripapillary vessel density was measured before and 3 months after a successful filtration surgery in primary open-angle glaucoma eyes [28]. A significant improvement (defined with an at least 30% decrease of the area of reduced vessel density) was found in 19 of the 31 patients. These results show that large intraocular pressure reduction can be associated with considerable improvement of capillary perfusion in the retinal nerve fiber layer. However, the clinical significance of the results remains to be specified. Currently we do not know if (1) a relatively small intraocular pressure reduction causes any improvement of capillary perfusion and (2) pressure reduction in advanced glaucoma results in a measurable perfusion change. Since the actual intraocular pressure does have an effect on the measured vessel density values, in long-term OCT angiography investigations, the influence of the actual intraocular pressure on the measured vessel density value needs to be considered.

OCT Angiography for the Assessment of Glaucomatous Progression

Currently the information on the applicability of OCT angiography for the detection of glaucomatous progression is limited. Till now one case report and one prospective 2-year study were published on this important field. In the case report, an early primary open-angle glaucoma eye with uncontrolled intraocular pressure was followed for 1.5 years [29]. The patient did not accept treatment intensification. Similar, statistically significant progression rates were seen for peripapillary RNFLT, GCC, and peripapillary vessel density, and the visual field also converted from normal to mild glaucomatous. In the prospective 2-year study, 53 healthy, ocular hypertensive, and primary open-angle glaucoma eyes with optimal image

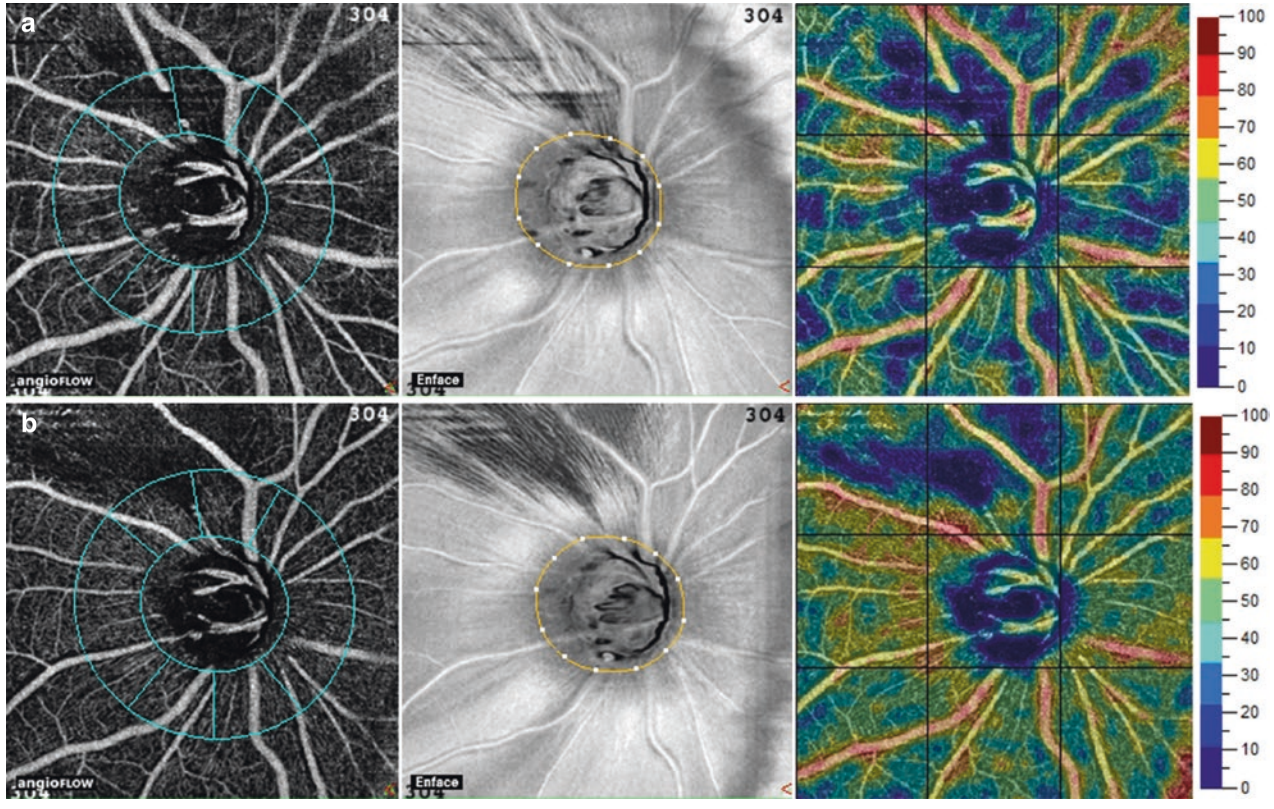

Fig. 7.8 Influence of large intraocular pressure reduction on peripapillary vessel density. Color-coded vessel density map of an early open-angle glaucoma eye of a 37-year-old patient. The untreated intraocular pressure is 37 mmHg (**a**), and some weeks later, it is reduced to 15 mmHg on topical medication (**b**). The increase of vessel density is shown by the color changes

quality during the total follow-up period were investigated [30]. The RNFLT and peripapillary vessel density images were obtained immediately after each other, without changing the patients' position. A statistically significant RNFLT progression was found for 16 eyes, but no eyes progressed for peripapillary vessel density. In addition, the measurement variability was greater for vessel density measurements than RNFLT measurements. In fact, this result is not unexpected since peripapillary perfusion (in contrast to the structural OCT parameters) is known to be influenced by systemic hypoxia and hypercapnia, and it is probably also influenced by the actual blood pressure and systemic medication. Unfortunately, in routine glaucoma practice, the systemic perfusion parameters cannot be optimally considered. A potential susceptibility of OCT angiography to the systemic vascular effects may reduce its applicability for glaucoma follow-up investigations. Further studies on larger populations are necessary to determine the role of OCT angiography for long-term glaucoma care.

Future of OCT Angiography for Glaucoma

OCT angiography is a rapidly evolving imaging method. The technology is under continuous development; therefore the current instruments and software versions cannot be considered as final. The manufacturers need to introduce vessel removing algorithms to neutralize the influence of the main retinal vessels on the measurement results. To measure glaucomatous progression, change-analysis software options are required. These unmet needs illustrate that OCT angiography will remain a hot and clinically important topic for ophthalmologists treating glaucoma in the upcoming years.

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What's New in Alternative Therapies for Glaucoma

8

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Although the focus of glaucoma treatment has been centered on lowering the intraocular pressure (IOP), there is increasing interest in the role of IOP-independent risk factors and alternative therapies. The interest in alternative treatments has been driven by the subset of patients who continue to progress despite rigorous IOP control. As a result, considerable attention has been directed toward the effects of blood flow, neuroprotection, and oxidative stress on glaucoma progression. There has also been increasing interest of alternative medicine use among patients with up to 14% of patients reporting current or prior use of complementary or alternative glaucoma treatment [1]. While many alternative medical therapies have been used for hundreds of years, we will describe what is new in the literature regarding complementary and alternative glaucoma treatments.

Ginkgo biloba

Ginkgo biloba has been used in traditional Chinese medicine for centuries and has been studied in the treatment of numerous medical conditions including glaucoma. It is now available as an extract, most commonly EGb 761. The medicinal components of the standardized extract include flavonoids and terpenoids. The flavonoids have antioxidant properties, and the terpenoids affect blood flow [2]. Within the eye, there is evidence that the extract increases blood flow [3], improves retinal ganglion cell survival [4], and has antioxidant effects [5] which may play a role in IOP-independent treatment of glaucoma. In healthy nonglaucomatous eyes, *Ginkgo biloba* extract has been shown to increase blood flow within the ophthalmic artery, and in normal-tension glaucoma, it has been shown to increase peripapillary blood flow [3, 6].

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The effects of *Ginkgo biloba* on functional glaucomatous changes such as visual fields have also been studied. Currently all studies regarding *Ginkgo biloba* extract and visual field outcomes include only normal-tension glaucoma patients, and the results have been conflicting. Studies have shown visual field improvement, slowed visual field progression, as well as no change with ginkgo extract use [7–9]. Some have attributed visual field improvement or slowed progression to the effect of *Ginkgo biloba* on enhanced cognition [10].

While *Ginkgo biloba* extract is generally well tolerated, there are concerns regarding its use and risks of bleeding. Case reports of spontaneous hyphema and intracranial bleeding with *Ginkgo biloba* use have been reported [11, 12]. Meta-analyses performed, however, have not shown a statistically significant difference in side effects compared to placebo [13].

Natural Substances

Natural substances such as wine, tea, coffee, and chocolate also contain flavonoids and its antioxidant properties [14]. A large long-term prospective study of flavonoid intake and glaucoma incidence found no statistically significant association between the two [15]. A subset analysis, however, did find daily tea consumption was associated with an 18% decreased risk of primary open-angle glaucoma. Alcohol has been shown to lower IOP in both glaucomatous and healthy eyes, but the results of alcohol's protective effect on glaucoma have been inconsistent with many studies reporting no protective benefit [16]. An association between acute ingestion of caffeinated coffee and elevated IOP has been shown, but Kang et al. did not find an increased risk of glaucoma with caffeine ingestion [17, 18]. Pasquale et al., however, demonstrated a positive association between coffee consumption and risks of pseudoexfoliation [19]. Dark chocolate also has high levels of polyphenol compounds and flavonoids, and its consumption has been shown to increase retinal vessel diameter in normal but not in glaucoma subjects [20]. There have been no reports of chocolate and its potential benefits in treating or preventing glaucoma. Despite the potential neuroprotective effects of these natural compounds and their ability to affect IOP, the results are variable, and there is no evidence that they play a definitive role in the treatment of glaucoma.

Vitamins

Vitamins are also associated with antioxidant properties, and theories of glaucomatous damage from free radicals have been proposed [14]. Despite the promising neuroprotective and vasoregulatory effects of vitamins, large cohort studies including the Nurses' Health Study and Health Professionals Follow-up studies have not found an association between vitamin intake and open-angle glaucoma [21]. A recent systematic review and meta-analysis of the effect of vitamins on glaucoma revealed that serum levels of vitamins show no clear relation with open-angle glaucoma [22].

Foods high in vitamins, however, such as dark leafy green vegetables as well as dietary intake of vitamins A and C were likely protective [22]. In addition, lower intake of niacin was associated with increased risk of glaucoma in the Korean National Health and Nutrition Examination Survey [23]. Overall, the data on vitamins and their protective effects on glaucoma progression have been variable and conflicting.

Citicoline

Citicoline has been used as an injectable nootropic drug aiding in the treatment of memory and cognitive impairment [24]. Its neuroprotective properties have also been studied in the eye. In an animal model, citicoline was found to rescue retinal ganglion cells in optic nerves with partial crush injury [25]. The neuroprotective effects are thought to be related to increased expression of the apoptotic regulating protein Bcl-2 [25]. The functional effects of citicoline in glaucoma patients have also been studied. Short- and long-term treatments with intramuscular injections of citicoline have been associated with improvement of VEP and ERG studies in primary open-angle glaucoma patients [26, 27]. An oral form of citicoline has recently been announced as a food supplement. The effects of intramuscular versus oral administration of citicoline have also been examined and were found to be similar [28]. A study by Ottobelli et al. demonstrated that the rate of Humphrey visual field progression decreased from 1.1 dB/year to −0.15 dB/year in patients treated with oral citocoline [29]. Topical citicoline eye drops have also been developed. A randomized clinical trial found that there was a positive trend in perimetric parameters in patients treated with topical citicoline in addition to hypotensive agents versus hypotensive agents alone; however it was not statistically significant [30]. While the neuroprotective effects of citicoline in glaucoma are promising, large clinical trials have yet to support its benefits.

Marijuana

Over 400 compounds are present in marijuana or cannabis, but the main chemical thought to be responsible for its medicinal effects is delta-9-tetrahydrocannabinol. Although the availability and topic of marijuana have become increasingly popular in the United States, it is argued that little has changed about our knowledge of marijuana and its effects on glaucoma [31]. Inhaled marijuana can substantially reduce IOP in patients with glaucoma, up to 25% reduction in select patients, but the duration of action is short about 3–4 h [32]. The short duration would require frequent dosing for sustained therapeutic effect with the risk of potential psychotropic and neurologic side effects [32–34]. Oral and intravenous administration of synthetic cannabinoids has been found to be as effective as inhaled cannabis but similarly has short duration [35–37]. Concerns of tolerance have also been raised, with the possibility that increasingly larger doses may be necessary to have the same effect [38, 39].

The mechanism of marijuana's IOP-lowering effects is poorly understood, but theories of decreased aqueous production and blood pressure-lowering effects have been proposed [40, 41]. The blood pressure-lowering effects of marijuana have been criticized as potentially harmful to patients with glaucoma by reducing optic nerve blood flow [34].

At this time, marijuana is not recommended as a safe and effective treatment for glaucoma patients by the American Glaucoma Society or the American Academy of Ophthalmology [31, 42].

Acupuncture

Acupuncture is a traditional Chinese healing method rooted in the belief that the flow of vital energy called Chi determines health, while blockage of Chi causes illness. Stimulating designated acupuncture points restores flow and health to the individual. The mechanism of how acupuncture affects the body is not clearly understood.

There have been case series reporting IOP-lowering effects of acupuncture. A randomized controlled trial of auricular acupressure reported significantly lower IOP of about 2.5 mmHg that returned to baseline after acupressure treatments stopped for 4 weeks [43]. These results, however, are contrasted by a recent randomized, prospective comparative study and Cochrane review, which did not show a sustained effect of acupuncture on IOP, visual acuity, visual field indices, and optic nerve or retinal nerve fiber layer measurements [44, 45]. To date, there is no clear evidence that acupuncture plays a significant role in the treatment of glaucoma.

Meditation

The effects of meditation and stress reduction in the treatment of glaucoma have been of interest to both patients and physicians. A study of self-relaxation techniques has shown to significantly reduce IOP over 1 year, but the sample size was small, had no control group, and was not randomized [46]. In contrast, a later study by the same group suggests that relaxation techniques do not affect IOP in patients with open-angle glaucoma given mental stressors [47]. While meditation may improve the quality of life of patients with glaucoma, there has yet to be any substantial evidence that meditation reduces IOP or slows glaucoma progression.

Exercise

There is considerable evidence that aerobic and dynamic exercise can lower IOP though the exact mechanism is not well understood. The amount and duration of IOP reduction reported is variable, likely due to the diversity of exercises studied [48]. Individuals with high myopia have been found to have greater exercise-induced IOP-lowering effects [49]. Habitual exercisers have also been shown to have

slowing of visual field progression in open-angle glaucoma. Secondary glaucoma, on the other hand, such as pigmentary glaucoma is associated with temporary exercise-induced IOP spikes due to pigment release during activity [48].

There are a series of exercises that may be associated with increased IOP and potential for glaucoma progression. Exercises with head-down postures such as during yoga activities have been associated with temporary increased IOP [50]. Valsalva from isometric exercises such a weight lifting have also been associated with transient increased IOP [51, 52]. However, other studies have reported decreased IOP after isometric exercise [53]. The increased IOP after isometric exercises are so transient they are unlikely to cause progressive vision loss in glaucoma patients. Despite evidence of transient increased IOP with certain exercises, there is no substantial evidence that supports these exercises cause glaucomatous progression. On the other hand, swimming is a common aerobic exercise, but the direct physical contact from swimming goggles has been associated with increased IOP and may be associated with glaucoma progression [54, 55].

Transcorneal Electrical Stimulation

There is evidence that retinal ganglion cell dysfunction may precede cellular death and apoptosis in primary open-angle glaucoma and neuroprotective efforts may prevent cellular death or allow for neuronal regeneration [56]. Electrical stimulation has been found to have neuroprotective effects on neural tissues including in the visual system [57]. A device placed on the cornea delivers electrical current to the retina and neuronal fibers in a noninvasive manner. It is thought that axonal regeneration may be enhanced by electrical stimulation by inducing expression of growth and regeneration-related genes [58]. After optic nerve transection, Morimoto et al. showed that transcorneal electrical stimulation improves survival of retinal ganglion cells by upregulating IGF-1, an endogenous neurotrophic factor [57]. Transcorneal electrical stimulation has shown some visual benefits in ocular diseases including nonarteritic ischemic optic neuropathy, retinal artery occlusion, traumatic optic neuropathy, and retinitis pigmentosa [59–61]. There is now interest in the potential use of transcorneal electrical stimulation's neuroprotective effects and glaucoma treatment. A recent study by Ota et al. showed that there is a positive relationship between the number of transcorneal electrical stimulation treatments and visual field mean deviation, which may suggest improvement of retinal ganglion cell function [62]. While this was a small study consisting of five eyes only, additional larger prospective studies will be necessary to determine if transcorneal electrical stimulation will play a role in the treatment of glaucoma.

Conclusion

The exact mechanism of the disease, glaucoma and its progressive optic neuropathy is still not fully understood. IOP has been demonstrated to be a major risk factor and more importantly a modifiable risk factor, yet there is growing interest

among patients and physicians to discover other modifiable risks and protective factors. Studies have begun to evaluate alternative substances and practices from newly discovered alternative treatments to traditional compounds that have been used for hundreds of years. While there is no definitive evidence that alternative and complementary treatments have a beneficial neuroprotective role in the treatment of glaucoma, there is some suggestive evidence warranting further clinical trials.

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What's the Future of Glaucoma Diagnosis and Neuroprotection

9

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Introduction

Glaucoma diagnosis is one of the most elusive and challenging situation in ophthalmology. In everyday practice, accurate glaucoma diagnosis is vital as several patients having early disease may be missed on diagnosis and a lot of those on antiglaucoma medications may not be suffering from the disease. In the past, tonometry and subjective clinical evaluation of optic nerve head and fundus photography were employed for diagnosis but had a wide variability among observers. Visual field analysis is a beneficial test, but the results depend on patient cooperation. The visual fields are often repeated several times to ensure a reproducible defect that can confirm the glaucoma diagnosis. To circumvent these issues, several modalities are currently being used to diagnose and monitor progression of glaucoma. From the use of advanced computer-based imaging technology, tablet-based perimeters, novel biomarkers, to genetic markers, glaucoma diagnostics, today is one of the most exciting areas to work in. In this chapter we look at the future of glaucoma diagnosis and how cutting-edge research is improving our accuracy in detecting glaucomatous change.

Imaging in Glaucoma

Which Is Better: HRT vs. GDx vs. OCT

Imaging devices are being increasingly used for assessing structure for early glaucoma detection. A meta-analysis evaluated the diagnostic odds ratio values for Heidelberg retinal tomograph-3 (HRT3), scanning laser polarimetry (GDx), and optical coherence tomography (OCT) to be 13.9, 18.6, and 29.5 respectively [1].

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This establishes the extensive role of OCT in the future of glaucoma diagnosis and management. With development of better machines with faster acquisition rate, higher resolution, and sophisticated software for layer/texture segmentation, imaging in glaucoma has potential to change the way we diagnose and manage the disease.

Which Is Better: Average RNFL vs. Macular GCC vs. Macular GCIPL vs. Total Macular Thickness

The diagnostic accuracy of commercially available OCT devices like Heidelberg Spectralis, Optovue RTVue, Topcon 3D-OCT, and Zeiss Stratus/Cirrus was compared in another metanalysis [2]. The area under the receiver operating characteristic curve (AUROC) of glaucoma diagnosis for average RNFL, macula ganglion cell complex (GCC), and macula ganglion cell inner plexiform layer (GCIPL) and for total macular thickness were 0.897, 0.885, 0.858, and 0.795, respectively. These results show that the use of RNFL and segmented macular region (GCIPL, GCC) scans for glaucoma diagnosis were similar but higher than total macular thickness indicating extensive role of ganglion cell analysis in early detection of glaucoma [2, 3]. Using software to characterize and quantify optical properties of RNFL with thickness analysis offers additional untapped knowledge in OCT scans that can be developed into indices for glaucoma detection [4].

Computing Algorithms

With the ability to accurately image the optic disk area, identification of anatomical landmarks like the Bruch's membrane and lamina cribrosa has also become possible. Advanced computing algorithms like the San Diego Automated Layer Segmentation Algorithm (SALSA) can be utilized for automatically segmenting OCT images into layers [5, 6]. These algorithms allow us to measure parameters like beta zone parapapillary atrophy (PPA) that have potential to become clinical endpoints for glaucoma detection [7]. Another approach that is being studied is to aggregate several individual parameters from the same test into a single composite parameter to boost the diagnostic accuracy, sensitivity, and specificity [8].

OCT Angiography

OCT angiography (OCTA) can provide a quantitative assessment of the microcirculation of the retina and choroid in a fast, reliable, and noninvasive way. OCTA has a high repeatability and reproducibility and can differentiate normal eyes from glaucoma eyes. OCTA has also been shown to be more strongly correlated with visual function, and in advanced disease stage, it reaches a floor effect at a later period than the conventional OCT [9]. The OCTA parameters like peripapillary flow index and vessel density have been found comparable or better than that of the peripapillary OCT-RNFL values but are yet to gain momentum in defining and diagnosing

glaucoma. Using OCTA in glaucomatous eyes, reduction in peripapillary retinal perfusion can be identified as focal defects and quantified using peripapillary flow index and vessel density parameters. OCTA data is thus helping to improve our understanding about the pathogenesis and progression and has utility in fine-tuning management of glaucoma [9–11].

Electrophysiology

Electrophysiological measures of vision function have the potential to highlight the pathophysiological processes and sequence of glaucomatous damage as well as to offer a potential complementary measure of function that might be more sensitive than visual field analysis. Pattern electroretinography (PERG) N95 and photopic negative response (PhNR) amplitudes have been shown to be significantly reduced in suspect and early glaucoma eyes [12].

New visual evoked potentials (VEP) testing modalities:

- ***Short-duration transient VEP (SDtVEP)***: SDtVEP has much shorter test duration than standard VEP due to synchronized signal acquisition in combination with a post-processing technique that results in less subjectivity in waveform assessment. The presence of an SDtVEP latency deficit is associated with long-term VF progression [13].
- ***Isolated check VEP (iCVEP)***: This technique is designed to detect the transmission function of the magnocellular pathway, which is mainly contributed by retinal ganglion cells (RGCs). Combining GCIPL analysis on OCT which detects structural changes in macular RGCs with iCVEP which identifies the functional abnormalities of macular RGCs offers an interesting alternative for early detection of glaucoma [14].

Further research is however required before electrophysiological tests can be effectively utilized for the diagnosis and management of glaucoma.

Future of Perimetry

Perimetry is still the gold standard for diagnosis of glaucomatous visual field loss. Currently researchers are focusing on devising methods for accurate and repeatable visual field loss assessment with cheap and portable devices [15].

- Tablet and virtual reality goggle-based perimetry has been clinically validated and seems to offer a good alternative for population-based screening applications [15, 16].
- "Pediatric perimeter" that quantifies visual field extent (VFE) for infants has recently been developed [17].
- Teleglaucoma is one such field that can build on these developments and effectively address challenges of delivering glaucoma care remotely [18].

Biomarkers

- ***Proteomic markers***: The term "proteomics" refers to characterization of a proteome. This includes study of protein expression, structure, modifications, functions, and interactions. Mass spectrometry-based analytical approaches have helped to discover clinically relevant glaucoma-related molecular biomarkers.

  For POAG, proteomic markers such as crystallins, heat shock protein 60 (HSP 60) and HSP 90, myotrophin, apolipoprotein B and apolipoprotein E, endothelial leukocyte adhesion molecule-1, myoblast determination protein 1, myogenin, vasodilator-stimulated phosphoprotein, ankyrin-2, and transthyretin have been identified as potential biomarkers [19]. Though the discovery of biomarkers is interesting, in order to translate this data into new treatment strategies, more work is needed for testing of these identified molecules and to better understand their role in glaucoma pathogenesis.
- ***Autoimmune involvement***: There is evidence that autoantibodies against alpha-fodrin, HSP70, or myelin basic protein (MBP) are upregulated, and antibodies against αB-crystallin or vimentin are downregulated in glaucoma. These antibodies thus are being investigated as biomarkers for diagnosis and assessment of severity and progression of glaucoma [19]. There is also evidence that autoantibodies are accumulated in the retinae of glaucoma patients; this indicates disturbance in the local immune homeostasis during pathogenesis of the disease.
- ***Antibody profiles***: Targeted antigen microarray for antibody profiles have also been used to differentiate POAG from non-glaucomatous controls. This technique has been shown to have a sensitivity and specificity of over 93% for glaucoma identification [20].
- ***Markers of oxidative stress***: Oxidative stress and reactive oxygen species (ROS) have been implicated in glaucoma pathogenesis. These molecules may be acting directly or indirectly as mediators, second messengers, or modulators of protein expression leading to retinal cell death. Thus molecular markers of oxidative stress like malondialdehyde and antioxidants like superoxide dismutase, glutathione peroxidase, and vitamins C and E are being evaluated for their role in early diagnosis of glaucoma [21].

Genetic Markers

Juvenile-Onset OAG and POAG

The genetic transmission of glaucoma occurs usually in monogenic form in juvenile-onset OAG. Adult POAG however has a complex inheritance pattern. It has however been estimated that 72% of all POAG cases have an inherited component [22]. The myocilin (MYOC, 1q32), WDR36 (5q22.3), optineurin (OPTN, 10p25), and NTF4 (19q13.3) are the principal genes that are implicated in glaucoma pathogenesis and inheritance [23]. In most cases, however, in spite of clear familial clustering, POAG does not follow a Mendelian pattern of inheritance, and mutations in these few genes account for less than 10% of POAG overall [24]. Techniques of genetic analysis like GWAS (genome wide association studies) are however constantly expanding our knowledge about the genetic basis of glaucoma [25].

Exfoliation Glaucoma

Recently using GWAS, single nucleotide polymorphism (SNP) are being used to determine association with glaucoma. After the initial LOXL1 locus discovery, researchers have identified additional loci at CACNA1A, POMP, TMEM136, AGPAT1, RBMS3, and SEMA6A [26].

The cost of GWAS has significantly reduced in recent years, and this has resulted in affordable technologies that can measure all common independently inherited genetic variations across the whole genome in individuals. Risk factors like young age of onset, high maximum IOP, and significant family history in patients provide evidence of the utility of genetic screening. Identification of these genes and subtle variations can help in development of genetic risk scores for glaucoma detection and possibilities of gene-based personalized treatment strategies [26, 27].

Neuroprotection

Glaucoma destroys neurons through oxidative stress, impairment in axonal transport, inflammation, and excitotoxicity. The concept of "neuroprotection" aims to reduce or halt this damage to retinal ganglion cells (RGCs). The pathophysiologic pathways under investigation include NMDA inhibitors, neurotrophins, anti-apoptotic pathways, bioenergetics, TNF-alpha, immune and inflammatory modulation, and stem cell replacement therapy [28]. By targeting these pathways, survival mechanisms in retinal vasculature, RGCs, and glial cells, like astrocytes or Muller cells, can be significantly augmented.

Table 9.1 enlists agents that are currently being investigated as neuroprotective agents. However no agent has been shown to provide reliable and repeatable evidence of benefit in a randomized controlled trial in human subjects. Additionally, there is no gold standard agent for potential agent comparison; however the search for alternate treatment modalities continues [28, 29].

Table 9.1 Possible neuroprotective agents [29]

Acetylcholine receptor agonists
Adenosine receptor antagonists
Alpha 2 receptor agonists
Antioxidants
Beta receptor antagonists
Calcium channel blockers
Carbonic anhydrase inhibitors
Citicoline
Excitotoxicity inhibitors
Gene therapy
Immunomodulators
Melatonin
Memantine
Minocycline
Neurotrophins
Nitric oxide synthase inhibitors
Prostaglandin analogues
Quercetin
Rho-associated kinase inhibitors
Stem cells

It needs to be considered that there is significant overlap between glaucoma and other disorders of the CNS, such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis; thus development of neuroprotection strategies for these diseases can be extended to glaucoma as well.

Rejected Neuroprotective Agents

Memantine

It is a NMDA receptor antagonist with moderate affinity to the target. It was postulated that memantine can deal with excessively increased extracellular glutamate levels in glaucoma. The molecule has been shown to protect RGCs in different animal models of glaucoma [30]. However the phase III randomized clinical trial conducted to test the efficacy of memantine as a neuroprotective agent in glaucoma found no significant effect in preserving visual function [28]. Animal models with moderately high IOP have however shown enhanced RGC survival with memantine treatment. Furthermore, although memantine reduces the rate of RGC loss based on ERG measurements early during the study, this beneficial effect cannot be observed if the injury was allowed to progress too long [31]. These observations suggest limited utility of memantine as a neuroprotective agent in glaucoma patients.

Brimonidine

Brimonidine tartrate is a highly selective alpha 2-adrenergic agonist. RGC survival after various types of injury in animal models has been shown in brimonidine-treated eyes [28]. This has prompted further investigation into the molecule's potential neuroprotective effects. Although the exact mechanism remains unclear, it has been postulated that brimonidine promotes RGC survival by inhibition of NMDA receptor function and presynaptic modulation of glutamate release [32]. The low-pressure glaucoma treatment study compared brimonidine tartrate 0.2% to timolol maleate 0.5% in preserving visual function in patients with glaucoma. Patients on brimonidine showed less progression of visual field loss as compared to those on timolol after 4 years of follow-up [33]. However this study suffered from a high rate of attrition and potential selection and reporting bias [34]. Thus no definitive conclusions can be drawn, and further research is needed to assess the role of brimonidine as a neuroprotective agent in glaucoma.

Future: Stem Cells and Genetic Engineering

Stem cells and gene-based therapeutics are also being explored for glaucoma management and possible cure [35]. The development of stem cell therapies for glaucoma have focused on the replacement trabecular meshwork (TM) cells and RGCs. Induced pluripotent stem cells also demonstrate a lot of promise. Animal studies have shown that stem cell transplant to the TM reduces IOP, promotes cell recovery, and enhances aqueous outflow [36]. Moreover, genome editing techniques, such as

CRISPR/Cas9, have additionally opened avenues like genomic surgery for ocular diseases [37]. The Cas9 endonuclease is directed by a guide RNA (gRNA) to cleave a 23-bp DNA sequence which can even be user customised. This allows unprecedented precision in genome editing that can be adapted for inherited ocular diseases.

Conclusion

The recent concept of RGC "coma" offers a whole new perspective to glaucoma diagnosis and management [38]. If we can accurately detect these RGC cells that can regain function with treatment, this may change the way we treat glaucoma today. Neuroimaging techniques like voxel-based morphometry and diffusion tensor imaging have shown trans-synaptic degeneration in glaucoma patients that suggests a neurodegenerative component in the disease. These novel findings require an unconventional treatment approach with potential use of neuroprotective drugs [39]. However with the body of evidence currently available to us, SD-OCT emerges as the new gold standard of glaucoma diagnosis and may soon replace conventional visual field testing. With the advent of newer hypothesis and concepts every day, we are closer to finding the "holy grail" in our quest to simplify glaucoma management.

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