ISSUE 2
2016

glaucoma now

A CONTINUING MEDICAL EDUCATION PUBLICATION

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LEARNING OBJECTIVES

- **Special Focus:**
A comprehensive overview of glaucoma alongside of other ageing diseases such as cataract and AMD, coverage of epidemiology findings, discussion on what this means for management
- **What's New:**
A review of changes attributable to glaucoma versus changes due to ageing in general, a focused discussion on neurodegenerative effects
- **Clinical Issues:**
A discussion on the diagnosis of glaucoma and detection of progression in the presence of concomitant diseases using visual field and disc assessments
- **Practical Tips:**
A comprehensive summary on currently available data for the use of ginkgo biloba in glaucoma

TARGET AUDIENCE

This educational activity is aimed at general ophthalmologists, glaucoma specialists and ophthalmology residents.

Main topic:

GLAUCOMA AND THE AGEING EYE

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A newsletter is sent out to participants registered to the program.

Glaucoma Now is published and administered by the editorial board and supported by an unrestricted grant from Alcon Laboratories Inc., Pfizer Inc and Santen Oy

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Special Focus:

Glaucoma and the Ageing Eye

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Core Concepts

- Glaucoma is the leading cause of irreversible and preventable visual disability worldwide (accounting for 12% of global blindness)
- The surgical management of the patient with cataract and glaucoma is dictated by the severity of the glaucoma, pre-operative intraocular pressure (IOP) control, and individual patient factors
- In patients with well-controlled IOP and early to moderate disease, cataract surgery alone could be considered, as this may reduce IOP by 2-4 mmHg (mostly not sustainable over longer term).
- In patients with uncontrolled moderate to severe glaucoma on maximal tolerable medical therapy, staged surgery where trabeculectomy is completed first may be reasonable, or combined cataract and trabeculectomy could be considered. However, visual recovery and post-operative course are usually longer.
- In patients with mild to moderate glaucoma and a desire to decrease medications or improve IOP control, a combined MIGS and cataract surgery may be appropriate. However, long-term outcomes data is not yet available.
- Multifocal lenses should be not be placed in patients with glaucoma and used with caution in glaucoma suspects.
- Femtosecond laser-assisted cataract surgery may be safe to use in glaucoma but should not be used in patients with a filtering bleb.
- Intra-vitreal injection of anti-vascular endothelial growth factors can cause sustained IOP rises and patients should be monitored closely and treated accordingly.

1) Epidemiology of the Ageing Eye

In the last 30 years much progress has been made to understand the epidemiology, risk factors, natural history, and treatment of age-related eye diseases such as glaucoma, cataract, and age-related macular degeneration (AMD). Glaucoma is the leading cause of irreversible and preventable visual disability worldwide, accounting for 12% of global blindness, with age as a major risk factor.[1,2] In the United States, prevalence of glaucoma is 1-2% in persons of European ancestry, 4% in African-Americans, and 2-5% in Mexican-Americans.[2] When national data is pooled, the overall prevalence of glaucoma is 1.86% in patients over 40 years of age.[3] The epidemiologic data worldwide offers a glimpse of the heterogeneity of glaucoma frequency across different populations as well as within populations. For example, prevalence estimates vary from 1% in Nigeria to 7-9% in African-Caribbeans, whose ancestry is mainly from West Africa.[2] Figure 1 shows open-angle prevalence estimates in persons aged 40 and over. The leading cause of reversible blindness worldwide, age-related cataract affects more than 20 million people.[4]

2) Management of coexisting glaucoma and cataract

As the population ages, the coexistence of cataract and glaucoma is common. When visually significant cataract is present with glaucoma, the clinician faces several management options. Here we consider the management of primary open-angle glaucoma (POAG) in the context of coexisting cataract. Options include cataract surgery alone with a monofocal or multifocal intraocular lens, femtosecond-assisted cataract surgery, trabeculectomy, combined cataract and trabeculectomy, or combined cataract and minimally invasive glaucoma surgery (MIGS). To limit the scope of this discussion, we will not consider the option of tube shunt surgery alone or combined cataract and tube shunt surgery. Which surgical algorithm to consider often is dictated by the severity of the glaucoma, pre-operative intraocular pressure (IOP) control, and individual patient factors. A comparative overview is presented in Table 1.

Cataract surgery with multifocal lens (MF-IOL) implantation in eyes with glaucoma

In recent years there has been increased interest in MF-IOLs for patients. While these increase the chance for spectacle independence there may be more glare, halos and decreased contrast sensitivity. Additionally, MF-IOLs require accurate centration, which may be difficult in glaucoma patients that inherently have zonular instability. At times, these MF-IOLs also require „touch up“ laser refractive corneal surgery after implantation which confounds IOP measurements thereafter. Eyes with glaucoma and ocular hypertension with a multifocal lens have been reported to show similar outcomes with those with a monofocal lens, except for better near vision acuity in the multifocal arm of the study.[5] Despite this, given the lack of larger studies, and the known issues associated with multifocal lenses, it is our opinion that monofocal lenses are preferable in patients with glaucoma and glaucoma suspects of at least moderate risk.

Femtosecond-assisted cataract surgery (FACS) and glaucoma

The use of FACS has increased recently and may offer specific benefits in glaucoma where zonular support is weakened and laser-assisted lens disassembly may decrease the need for in the bag cataract manipulation. However, for stabilization, the femtosecond laser requires the eye to be docked under suction for seconds to minutes. In one study looking at the one of the commercially available laser systems, the docking process was found to increase the baseline IOP in glaucoma patients by a mean of 14 mm Hg.[6] Given that this is only a relatively transient and moderate rise in IOP, the femtosecond docking procedure is likely to be safe. This technology is still relatively nascent and future issues with FACS may arise. The docking system also provides unique issues with glaucoma patients who have had prior filtering surgeries. The docking system creates a ring of suction along the conjunctiva just outside the limbus and theoretically could alter or even damage trabeculectomy blebs, and as such is considered to be a contraindication to FACS.

Cataract surgery alone

For POAG patients with well-controlled IOP and early to moderate disease, it may be reasonable to perform cataract surgery alone. However, if there is a surgical indication to lower IOP, such as inadequate IOP control or poor adherence or intolerance to medications, cataract surgery alone may not reduce IOP sufficiently over time. While there have been numerous studies examining IOP reduction after cataract extraction in glaucoma patients, the magnitude and duration of the effect needs further study.[7,8] In a Cochrane meta-analysis of 5000 patients with various types of glaucoma and cataract undergoing cataract and/or incisional glaucoma surgery, an estimated 2-4 mmHg IOP reduction was achieved by cataract surgery alone, but sustained long-term IOP reduction was reported only for patients who underwent combined surgery.[9] The magnitude of IOP reduction was related to a higher preoperative IOP, the presence of pseudoexfoliation, and pre-operative shallow anterior chamber depth.[10,11] Therefore, in the treated POAG patient, the effect of cataract surgery alone on IOP may be small (1-2 mmHg of IOP reduction). It is also unclear whether the effect is sustained in POAG patients, with IOP trending towards baseline over time.[7,8,11] Therefore, if IOP control may be questionable, cataract surgery alone may be insufficient to achieve long-term IOP reduction.

Trabeculectomy alone

In patients with uncontrolled moderate to severe glaucoma on maximal tolerable medications, trabeculectomy alone may be reasonable. After lowering IOP, cataract surgery can be performed. Prior to small incision and clear corneal phacoemulsification techniques, cataract extraction frequently caused bleb failure; patients then required additional medications or glaucoma surgery. Even with improved phacoemulsification techniques, cataract surgery can adversely affect a well-functioning bleb by stimulating fibrosis, either through post-operative inflammation or conjunctival manipulation during the cataract surgery.[12-15] Trabeculectomy alone was thought to achieve better outcomes than combined procedures, but with improved surgical technique, small-incision cataract surgery and the use of antimetabolites, combined cataract surgery and trabeculectomy may be a more appropriate choice for a patient with cataract and uncontrolled moderate to severe glaucoma.

Combined cataract surgery and trabeculectomy

In patients with uncontrolled glaucoma and visually significant cataract, combined cataract surgery and trabeculectomy should be considered.

There is no definitive consensus as

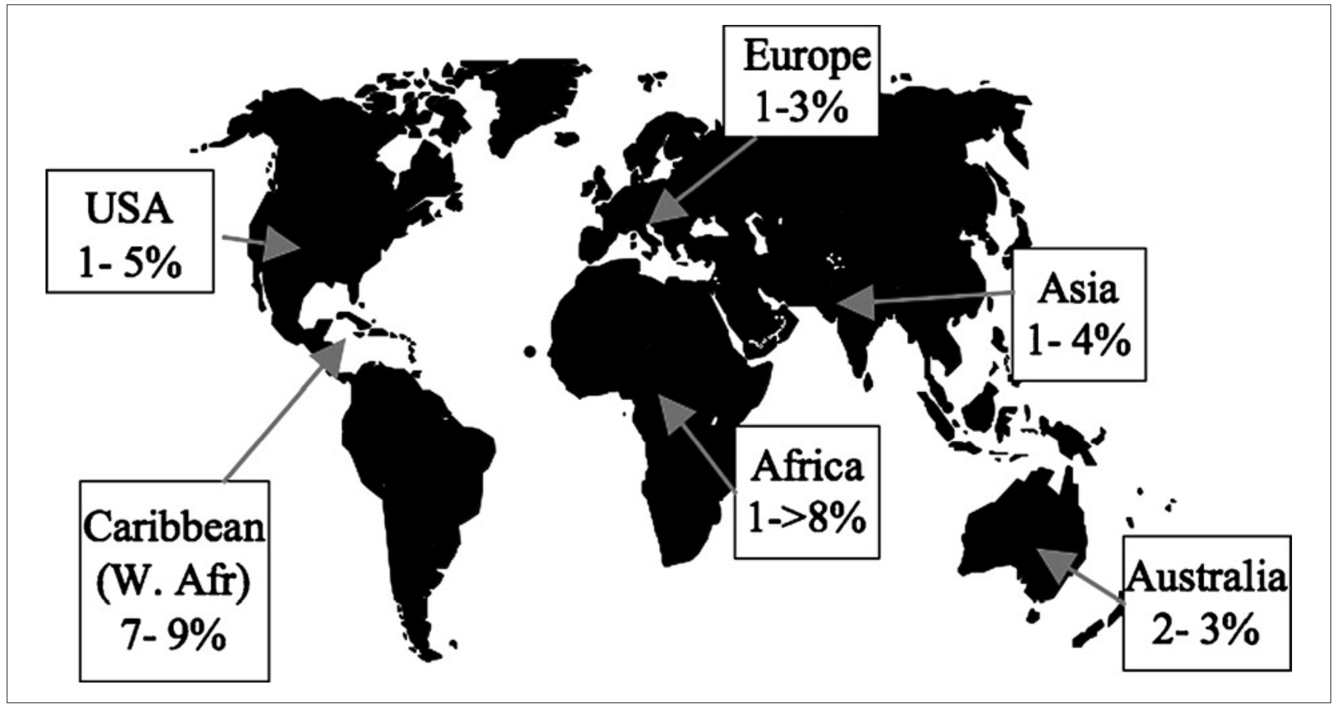

Figure 1. Worldwide open-angle glaucoma prevalence estimates for persons ages 40 years and older.

to whether trabeculectomy followed by cataract surgery versus combined surgery achieves better outcomes. A meta-analysis that examined combined versus staged procedures concluded that there was insufficient evidence in the literature as to which type of procedure resulted in better outcomes.[16]

When comparing trabeculectomy alone vs combined surgery, trabeculectomy alone results in better IOP control than combined surgery.[9] However, some recent evidence suggests the two procedures have similar IOP lowering effects. In one study in which intraoperative mitomycin C was used, the combined surgery and trabeculectomy alone groups achieved similar post-operative mean IOPs at 2 years.[17]

Although it is still controversial as to whether combined surgery is less successful than trabeculectomy alone, compared with cataract surgery alone, it offers some advantages. Combined surgery may avoid visually devastating postoperative IOP spikes in patients with advanced glaucoma undergoing cataract surgery and often eliminates or decreases reliance on glaucoma medications. Combined surgery also removes a cataract that often times worsens after glaucoma surgery. In addition, cataract surgery performed after a successful trabeculectomy may compromise a well-functioning bleb, as discussed above. Alternatively, in the patient with a cataract and an IOP above target, another option is to proceed with cataract surgery first and then a trabeculectomy afterwards if the IOP continues to be uncontrolled. This option should only be considered in patients where the IOP is not optimized but still is within a reasonable range where rapid glaucomatous damage is not a concern. In summary, when contemplating combined surgery, the clinician should consider the longer visual rehabilitation for patients undergoing combined surgery, as well as the severity of the glaucoma, the visual potential after cataract removal and the desired target IOP.

Newer glaucoma techniques for combined cataract and glaucoma surgery

With the advent of newer technologies, there has been significant interest in MIGS that can be paired with standard cataract surgery. Some of these techniques, such as *ab interno* trabeculotomy (e.g. Trabectome, Kahook dual blade, and Gonioscopy-assisted transluminal trabeculotomy) and trabecular meshwork bypass stents (e.g. iStent and Hydrus microstent) are designed to improve outflow by bypassing the trabecular meshwork. Alternatively, other devices attempt to access the suprachoroidal space (e.g. Cypass microstent, SOLX Gold shunt, and iStent supra). Yet other approaches that have been paired with cataract surgery are endoscopic cyclophotocoagulation (ECP), and pseudo MIGS procedures such as canaloplasty, and ab-interno approaches to access the subconjunctival space (Xen glaucoma implant). Although discussion on the specifics behind each of these emerging technologies is beyond the scope of this article, in general, MIGS procedures are known for their modest lowering of IOP and better safety profile when compared with traditional filtration glaucoma surgery.

3) Management of coexisting glaucoma, age related macular degeneration (AMD). and diabetic macular edema (DME)

As the population ages the incidence of glaucoma concurrent with AMD and DME increases. Oftentimes, the mainstay of therapy for exudative AMD and DME are intravitreal injections of anti-vascular endothelial growth factors (anti-VEGF) which have been found in multiple studies to be associated with sustained and delayed elevations in IOP. The underlying mechanism for this increase is not clear and may be due to blockage of outflow pathways by the drug itself, its delivery vehicle, or mediated by an inflammatory process. A recent review article collated all the known studies together and found that the incidence of sustained IOP rises in patients receiving injections for macular degeneration was 3.45% to 11.6%.[18] Several studies have looked at underlying risk factors including diagnosis of glaucoma, number of injections, interval between injections, injection medications, and lens status. The association of these risk factors with sustained elevated IOPs were inconsistent between studies and no definitive correlation was found. Ultimately, patients who are receiving injections of intravitreal anti-VEGF agents like those receiving steroid injections, need to be monitored closely both for spikes as well as sustained elevations in IOP as they can occur at any point during the treatment period.[18]

	Cataract Surgery	Cataract Surgery + MIGS	Trabeculetomy Alone	Cataract Surgery + Trabeculectomy
Visual Rehabilitation	Immediate to weeks	Days to weeks	Days to months; accelerates cataract progression	Days to months
Length of Post-operative course	Shortest	Short	Longer	Longer
IOP reduction	Modest reduction	Variable; often modest reduction	Larger reduction	Intermediate reduction
Post-operative glaucoma medications	Often necessary	Variable; often necessary but likely less agents	Usually not necessary	Usually not necessary
Complications	Lowest risk	Low risk	Higher risk	Higher risk

Table 1. *Comparison of cataract surgery alone, combined cataract surgery with MIGS, Trabeculectomy alone, and combined cataract surgery with trabeculectomy in the management of coexisting cataract and glaucoma.*

4) Conclusions

Age-related ophthalmic conditions such as cataracts, DME, and AMD commonly occur in elderly patients with glaucoma. In particular, cataracts and glaucoma are a management challenge for the ophthalmologist since there are no uniform recommendations. In a patient with severe glaucoma and an aggressively low target IOP, trabeculectomy alone or trabeculectomy with cataract surgery may be indicated. For patients with relatively well-controlled mild to moderate glaucoma, a desire for quick visual rehabilitation and with no aversion to glaucoma medications, cataract surgery alone, or with MIGS may be reasonable. We recommend against using MF-IOLs in patients with glaucoma and with caution in patients who are glaucoma suspects. FACS may be beneficial for patients with poor zonular support but we recommend against its use in patients with a filtering bleb. Patients with DME and AMD require close follow up to identify and to treat post injection spikes or sustained elevations in IOP. As with all treatments, consideration of the patient's individual situation is paramount for optimal outcomes.

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What's New

Diagnostic Challenges in ageing and dementia:

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Core Concepts

- The rate of retinal ganglion cell loss in normal ageing has been quantified in longitudinal studies.
- The effects of ageing on the optic nerve head (ONH) and retinal thickness are minimal and may not be of clinical significance when assessing glaucoma.
- Automated perimetry compares the results of a test with an age-matched normal group of individuals. Nevertheless the influence of age in retinal sensitivity is minor.
- Current optical coherence tomography (OCT) devices can measure macular as well as circumpapillary retinal nerve fibre layer (RNFL) thicknesses and combine anatomical and functional data, which may be useful in diagnosing and monitoring glaucoma.
- RNFL thinning in Alzheimer's disease (AD) and cognitive impairment is significantly greater than in normal age-matched controls and this potentially could have an impact on clinical decision making in glaucoma.

1) Introduction

As the leading cause of irreversible blindness glaucoma affects 64.3 million people worldwide and this is expected to increase to 111.8 million by 2040.[1] The age-dependent increase in open angle glaucoma (OAG) prevalence has been shown to be non-linear and estimated prevalence is highest among those over 80 years across all major ethnic groups (Figure 1).[2]

Retinal ganglion cell (RGC) loss resulting from glaucomatous changes is typically detected at the level of the optic nerve head (ONH) and retinal nerve fibre layer (RNFL) and is associated with visual field loss. Ageing may also be associated with some degree of RGC loss. Despite technological advances, distinguishing the normal changes of ageing from the pathologic changes of glaucoma theoretically may pose a challenge: there could be a degree of ambiguity when differentiating normal age-related change from abnormal findings due to disease.

Once glaucoma is diagnosed patients undergo monitoring to detect disease progression. However, separating progressive changes of glaucoma from the sequelae of normal ageing can be difficult. Quantifying the scale of age-related loss of RGCs helps to identify true glaucomatous loss.

The rate of RGC loss associated with normal ageing has been estimated to be 7209 RGCs per year.[3] Considering that the average number of RGCs is about 1.5 million the effects of age-related changes can be assumed to be minor. Similarly the cup/disc diameter ratio has been reported to increase only by about 0.1 between the ages of 30 and 70 years.[4] Thus the small age-related changes could perhaps be ignored in clinical practice.

Structural changes may precede functional deficits in the development of glaucoma and may become apparent with current imaging technologies.[5] Visual field testing relies on patient co-operation and technician skill and is subjective. For these reasons imaging devices, which objectively evaluate the anatomy of the retina and ONH, are now used widely to complement glaucoma assessment.

Optical coherence tomography (OCT) is currently the most commonly used non-invasive imaging technology for ocular posterior pole analysis. Recent advances in spectral domain OCT (SD-OCT) technology have enabled quicker capture of higher resolution images and have improved the segmentation of retinal layers for measurement of both the circumpapillary RNFL (cRNFL) and the macular RNFL.

2) Circumpapillary RNFL and ageing

Commercially available SD-OCT units compare global and sectoral cRNFL measurements with age adjusted normative databases and produce outputs which typically categorize each test as either within normal limits (green), borderline (yellow) or outside normal limits (red) (Figure 2).[6, 7]

However, age-related structural changes are apparent on the RNFL, which potentially could make assessment of glaucoma progression by OCT more difficult. Cross-sectional and longitudinal studies have quantified the loss of RNFL due to age, ranging from -0.14 to -0.56 μm per year.[8] Thus age-induced changes in RNFL are small, not clinically significant and structural changes observed in glaucoma patients may not be attributable to ageing.

3) Macular thickness and ageing

As OCT devices can quantify the retinal thickness at the macula, such macula evaluation may be useful to diagnose or monitor glaucoma as loss of RGCs would be associated with a decrease in macular thickness. For example, the posterior pole asymmetry

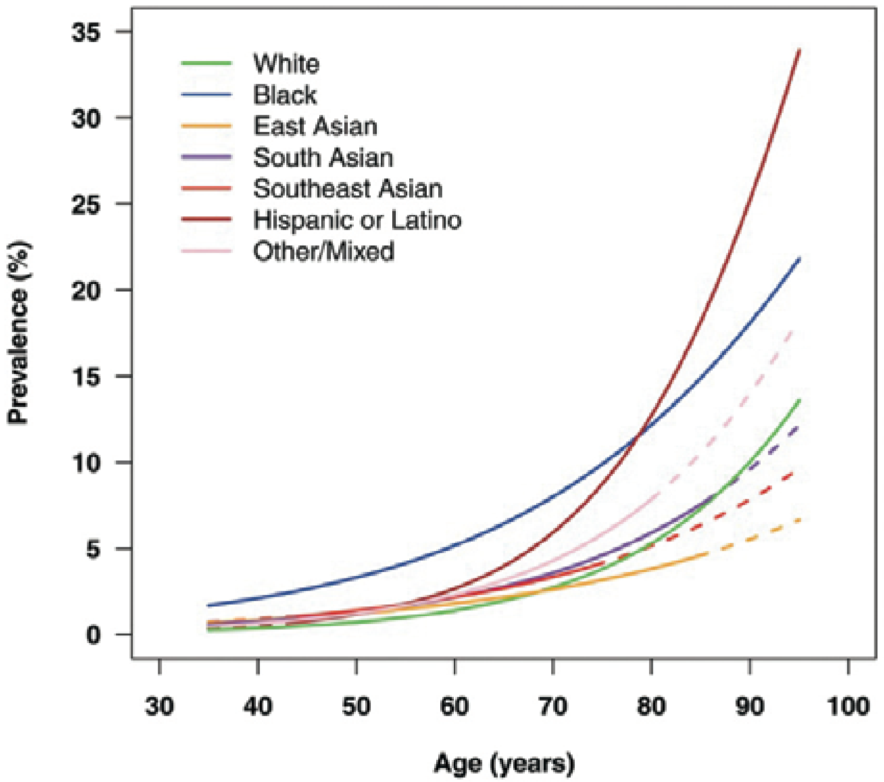

Figure 1. Estimated prevalence (%) of primary open angle glaucoma with age for men and women combined by ethnicity. (Adapted from Kapetanakis et al.[2])

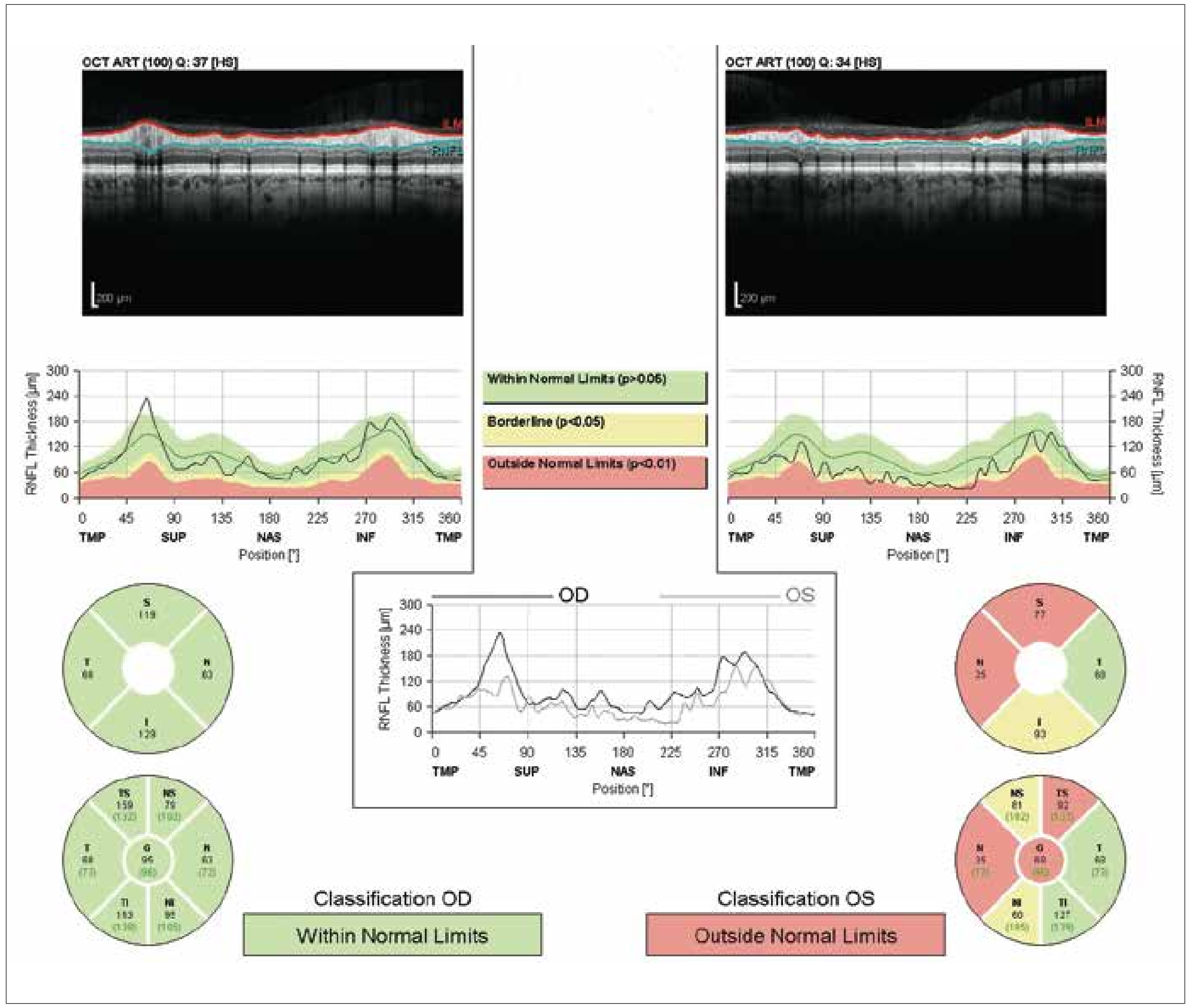

Figure 2. Section of OCT scan report demonstrating the measured RNFL thicknesses for both eyes compared with the normative database.

analysis (PPAA) protocol in the Spectralis HRA + OCT combines mapping of the retinal thickness at the posterior pole with asymmetry analysis between the eyes and between the hemispheres of each eye. The asymmetry parameters allow the use of the fellow eye or the fellow hemisphere for comparison; given variations between individuals, this might be advantageous over the use of normative databases.

The macula thickness map is displayed as a colour-coded 8 x 8 grid centred on the foveal pit. The scan covers a larger area than the Early Treatment Diabetic Retinopathy Study (ETDRS) grid and more closely corresponds to the 24-2 visual field (Figure 3). There is also a grey scale map which displays 64 3˚ x 3˚ square regions. White squares represent differences between eyes or hemispheres of 0 μm while black squares represent differences of ≥30 μm. PPAA structural asymmetry parameters have comparable sensitivity and specificity to cRNFL measurements to identify localised RNFL defects and early OAG.[9, 10]

Changes in PPAA associated with ageing have been reported. Indeed age is associated with a statistically significant mean inter-ocular retinal thickness asymmetry using the PPAA (0.04 μm per year), but these changes are not clinically significant.[11] Studies using other devices report macular ganglion cell complex (GCC) layer loss ranging from -0.1 to -0.32 μm per year but this small change is unlikely to influence the interpretation of glaucoma-related changes.[8]

4) Glaucoma, ageing and function

Visual field loss is measured with perimetry to detect disease and to monitor for progression. In normal ageing the rate of mean sensitivity loss is limited, estimated to be between -0.43 dB[12] and -0.70 dB per decade[13] in young adults and up to -1.02 dB per decade after 53.4 years (using a bilinear model).[12] For frequency doubling technology (FDT) perimetry the estimated loss resulting from ageing is approximately 0.6 dB per decade between 15 and 60 years and greater after 70 years.[14] As most automated perimeters report age-adjusted thresholds, they account for the normal and small age-related sensitivity decline.

5) Linking structure and function

Structural and functional tests complement each other when detecting different stages of glaucoma. However, despite the availability of modern technologies in clinical practice, incorporating the information provided by a combination of tests can be confusing. In order to simplify the use of the information from different tests, attempts have been made to develop indices which combine structural and functional measurements.[15] For example, the Heidelberg Edge Perimeter (HEP) can combine optic disc measurements from Heidelberg Retinal Tomography (HRT) and flicker defined form (FDF) perimetry. FDF mean deviation has been shown to be significantly correlated with HRT measurements such as cup/disc ratio and RNFL.[16] HRT uses algorithms such as the Moorfields Regression Analysis (MRA) or Glaucoma Probability Score (GPS) to decide whether the ONH is within normal limits. The MRA algorithm is based on data derived from measurements from 112 healthy eyes but currently no corrections for age-related changes are considered. However a recent study using HRT suggested that a reference database of healthy eyes could be used to help clinicians distinguish age-related neuroretinal rim area loss from rim area loss resulting from glaucoma.[17]

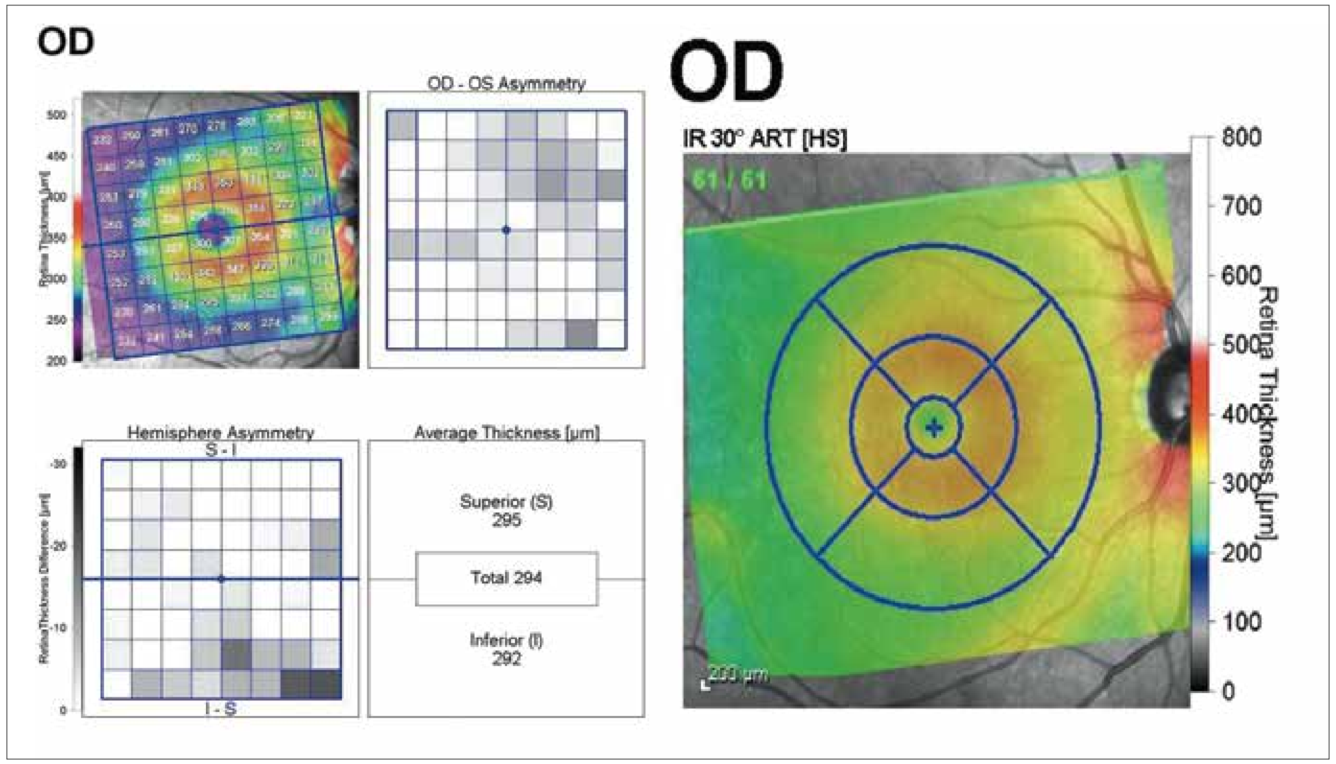

Figure 3. *Spectralis HRA + OCT Posterior pole asymmetry analysis (left); the Early Treatment Diabetic Retinopathy Study (ETDRS) macular grid (right).*

6) Glaucoma and neurodegenerative disorders

Dementia is the most common of neurodegenerative disorders that leads to cognitive decline and it becomes increasingly prevalent with age, akin to glaucoma. The epidemiological evidence for an association between dementia and glaucoma is conflicting although they may share common pathophysiological mechanisms.[18]

Recently, RNFL thinning in patients with Alzheimer's disease (AD) and mild cognitive impairment has been reported. Two meta-analyses found statistically significant reductions in mean global RNFL in AD [Weighted mean difference (WMD) -12.44 μm and -15.95 μm][19, 20] and in mild cognitive impairment (WMD -8.23 μm and -13.39 μm) [19, 20] when compared with healthy controls. The magnitude of these RNFL deficits may potentially impact diagnosis and clinical decision making in glaucoma patients with concomitant AD or mild cognitive impairment in whom visual field testing may not be reliable or possible.

7) Conclusion

Several studies on imaging and functional diagnostic technologies have quantified age-related changes but highlighted that such changes are small and thus unlikely to influence clinical decision making. In contrast the RNFL loss in people with AD and cognitive impairment, although modest, may be potentially significant and may be important considerations when we use technology to detect glaucoma and disease progression

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Clinical Issues:

Diagnosis of glaucoma in the ageing eye

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Core Concepts

- An examination of the neuroretinal rim and surrounding retinal nerve fibre layer is necessary to detect glaucomatous optic neuropathy.
- Glaucoma often affects the superior and inferior poles of the disc.
- Presence of disc haemorrhage and/or retinal nerve fibre layer defects is very suggestive of glaucoma.
- Reproducible visual field changes may be the first sign of glaucoma.
- Quantification of progressive disc/RNFL changes may be aided by analysis of serial confocal scanning laser ophthalmoscopy or OCT images.
- Pointwise analysis for VF progression is more helpful than use of global indices.
- Using glaucoma change software is more reliable than clinical judgement alone in estimating visual field progression.

1 Introduction

'Glaucoma' encompasses a group of conditions defined by characteristic, progressive changes in the optic nerve head (disc) and visual field. Diagnosis depends on the ability to identify pathological features in the disc and visual field reliably whereas detection of progression depends on the ability to identify change in these features reliably. Ageing changes and age-related comorbidities hamper these tasks. An appreciation of the effects of normal ageing and of age-related pathology other than glaucoma on the visual field and disc appearance enables the relative contribution of glaucoma to these clinical signs and investigations to be deduced. Quantification of progressive disc/RNFL changes may be aided by analysis of serial confocal scanning laser ophthalmoscopy or OCT images.

2 Diagnosis

2.1 Disc

Glaucomatous optic neuropathy is characterised by a loss of neuroretinal rim tissue at the optic disc. An examination of the contour of the neuroretinal rim is necessary to detect this. Particularly in the presence of other age-related change such as cataract, this is best performed by stereoscopic evaluation of the disc through a dilated pupil with a direct or indirect fundus lens at the slit lamp.[1] Glaucomatous change may be differentiated from normal age-related narrowing of the neuroretinal rim because glaucoma often affects the superior and inferior poles of the disc preferentially.[1] The presence of disc haemorrhage and/or retinal nerve fibre layer defect(s) is very suggestive of glaucoma since their prevalence in the general population is low.[1] Cup/disc ratio has a wide normal range; it also depends on age, disc size and intraocular pressure. [2]

2.2 Field

As most automated perimeters report age-adjusted thresholds, they account for normal age-related sensitivity decline: for example the Total Deviation plot of the Humphrey Field Analyzer (Carl Zeiss Meditec AG, Jena, Germany). Glaucomatous defects can be distinguished from those caused by other pathology by a thorough history and examination to detect co-morbidity along with noting the characteristic patterns of glaucomatous loss, such as paracentral scotoma, nasal step and arcuate scotoma. Some perimetric algorithms, such as the Pattern Deviation plot of the Humphrey Field Analyzer, highlight these focal changes and diminish the importance of diffuse depression of the hill of vision, which may be caused by other age-related pathology such as cataract. Repeat the field test if results are uncertain. Reproducible visual field changes may be the first signs of glaucoma rather than detectable change in the optic disc.[3]

3 Progression

3.1 Disc

Judging progressive disc changes by serial clinical examinations or serial photographs is difficult and unreliable. Salient features are progressive narrowing of the neuroretinal rim, violation of the Inferior Superior Nasal Temporal (ISNT) rule where it was previously obeyed, increase in zone beta-peripapillary atrophy , increase in number or width of retinal nerve fibre layer (RNFL) defects and presence of optic disc haemorrhages. For the last, consider differential diagnoses such as diabetic retinopathy and posterior vitreous detachment. Quantification of progressive disc/RNFL changes may be aided by analysis of serial confocal scanning laser ophthalmoscopy or ocular coherent tomography images. Some models of both modalities of imaging device now offer automated trend analysis of neuroretinal rim thickness and RNFL thickness respectively.

3.2 Field

To distinguish the effects of progressive glaucoma on the visual field from those of coexisting pathology, consider the characteristic patterns of glaucomatous loss as described in 2.2 above. It is more useful to analyse visual field progression on a pointwise basis rather than with global indices since the latter is relatively insensitive to focal areas of change. Using glaucoma change software is more reliable than clinical judgement alone.[4] Two examples of such software are the Humphrey Field Analyzer Guided Progression Analysis (figure 1) and the PROGRESSOR software (figure 2). Of these, the PROGRESSOR software gives a pointwise estimate of rate of progression and the Guided Progression Analysis (GPA) gives an estimate of rate of progression of the Visual Field Index (VFI), a global index. Rate of progression has been recognised as a measure of primary importance in glaucoma management.[1] A regimen of at least six visual field tests over the first two years in cases of manifest glaucoma has been recommended in order not to miss high rates of progressive visual field loss.[1,5]

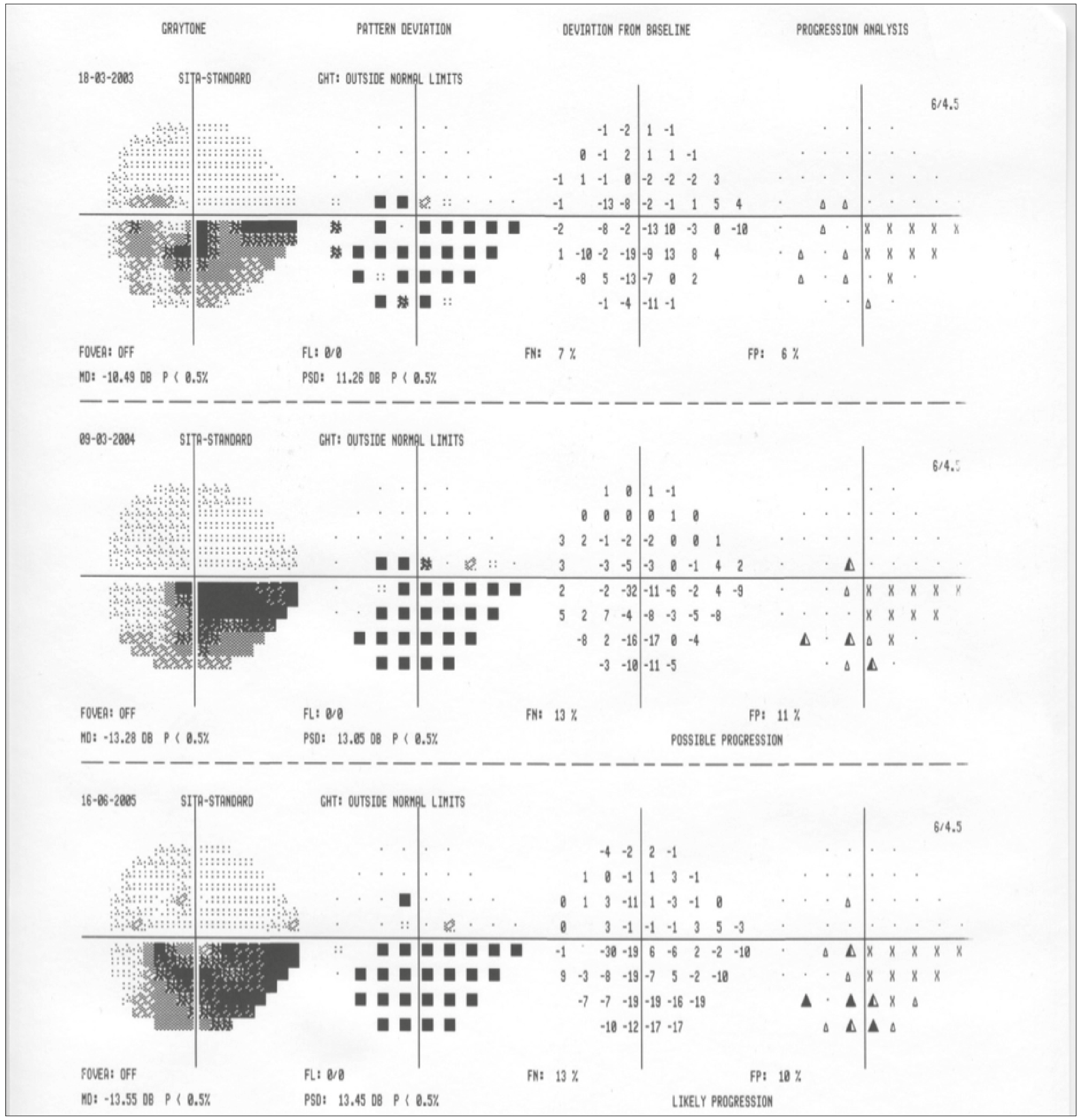


Figure 1. An example of the follow-up analysis printout of the Glaucoma Change Probability Map of the Humphrey Field Analyzer Guided Progression Analysis (GPA). The printout shows the analysis for three tests descending in chronological order. The progression analysis is shown as the rightmost graph for each test. Points showing deterioration ($p < 0.05$) compared to baseline are shown as empty triangles. Points in which this behaviour is maintained in two consecutive tests are shown as half-filled triangles. Points in which this behaviour is maintained in three consecutive tests are shown as filled triangles.

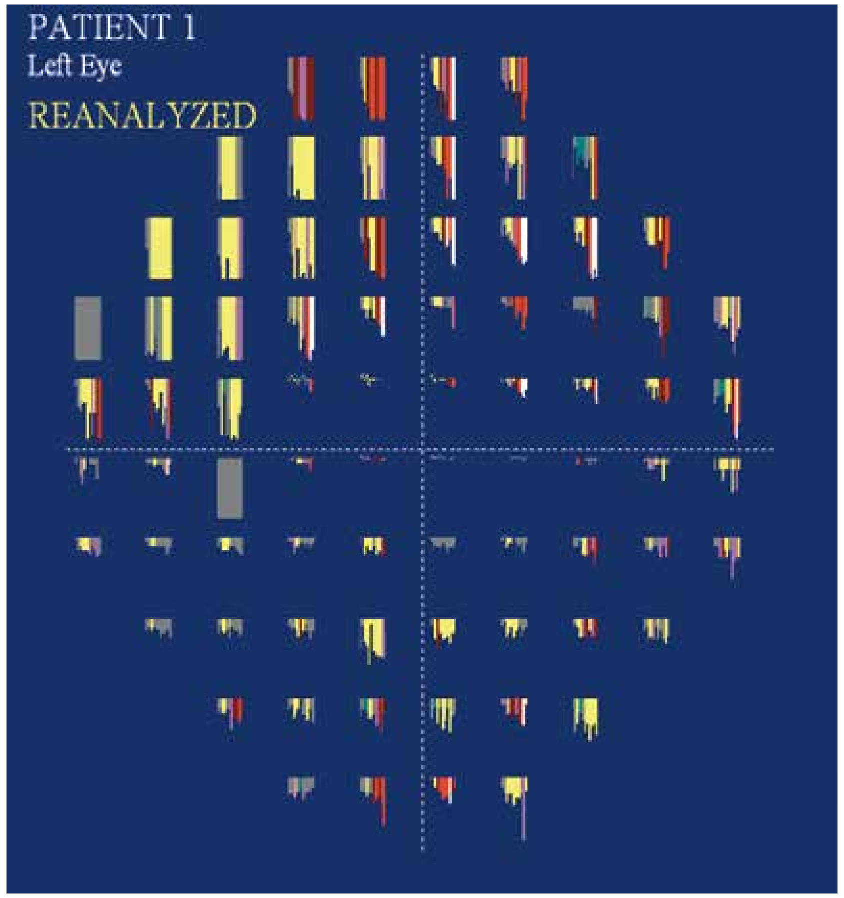
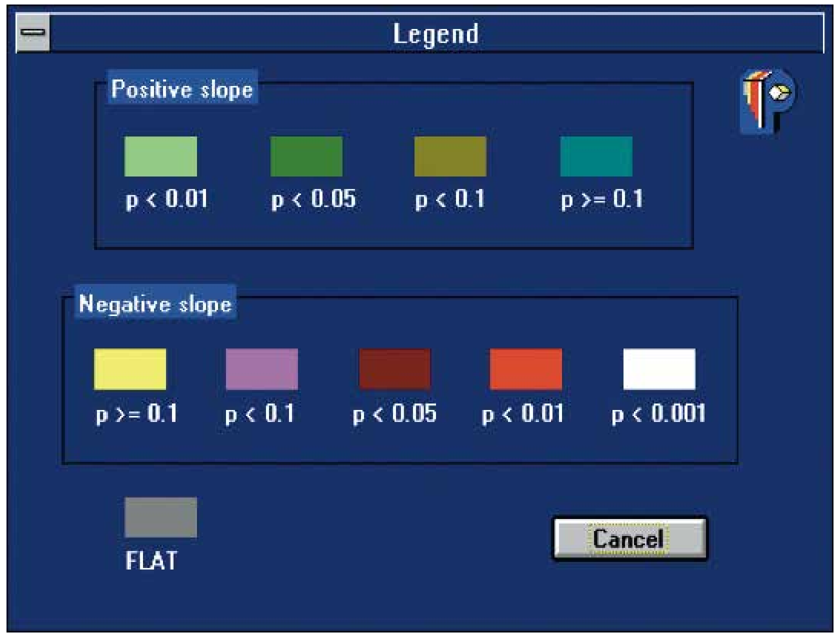


Figure 2. An example of the PROGRESSOR cumulative graphical display. Each test location is represented by a bar graph. Each bar in the graph represents the result of one test for that location. Longer bars correspond to worse sensitivity and the slope of the regression line is colour coded for significance according to the Legend. Thus, in this example, many points in the superior nasal field have bars which are progressively lengthening over time and have significant negative slopes. This behaviour represents visual field progression. Its arcuate distribution suggests that the cause is glaucoma.



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Practical Tips:

Use of Ginkgo biloba Extract in Glaucoma

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Core concepts

- Ginkgo biloba extract (GBE) contains multiple flavonoids and terpenoids and has been investigated in many studies for various conditions, with a growing body of evidence supporting its beneficial effects.
- GBE can target several underlying mechanisms in glaucoma.
- Oxidative stress has been identified as an important factor in glaucomatous damage. GBE has significant antioxidant properties and has been shown to be protective against oxidative stress in culture and animal models.
- Reperfusion injury due to disturbance of microcirculation plays a key role in glaucoma. GBE has been shown to improve ocular and peripheral circulation.
- GBE affects the trabecular meshwork, suppressing raised IOP and improving trabecular meshwork cellularity following steroid use in experimental models.
- GBE appears to be a safe treatment option with few reported adverse effects.
- Positive effects of GBE seen in experimental models and the theoretical impact on the underlying mechanisms make it a good candidate for an alternative glaucoma treatment.

1) Introduction

Treatments for glaucoma have historically been aimed at reducing intraocular pressure (IOP). However additional risk factors in the pathophysiology of glaucoma have been identified, and there is a need for other forms of therapy. Certain complementary, or non-pharmaceutical, treatments are possible candidates for this, one being *Ginkgo biloba* extract (GBE). *Ginkgo biloba* is the oldest known species of tree, dating back to the Permian era, and it has been used for medicinal purposes for around 5000 years.[1] It contains multiple flavonoids and terpenoids with a variety of actions. GBE has been investigated in many studies of various disorders. A growing body of evidence supports its potential benefits in diabetic retinopathy[2], coronary artery disease[3,4], and in Alzheimer's disease, in which it improved cognition, functional measures and quality of life[5,6]. GBE has neuroprotective effects, demonstrated for example in retinal ganglion cells following optic nerve crush models in rats[7]. When applied to glaucoma, GBE can target several underlying mechanisms.

2) GBE effects

Oxidative stress from reactive oxygen species has been identified as an important factor in glaucomatous damage, with mitochondrial damage being particularly important.[8] Mitochondrial abnormalities have been shown in patients with glaucoma, including decreased respiratory activity and damage to mitochondrial DNA.[9] GBE has significant antioxidant properties due to its free radical scavenging activity, and has been shown to be protective against oxidative stress in culture and animal models.[10] Unlike some other antioxidant substances (Vitamin C, Vitamin E), GBE is able to penetrate to the inner membrane of the mitochondria, making it an effective antioxidant at the mitochondrial level.[11]

Disturbance of microcirculation leads to reperfusion injury and plays a key role in glaucoma.[12] GBE increases cerebral blood flow, as demonstrated on MRI.[13] It also increases peripheral blood flow and has been used to treat Raynaud's disease,[14] which is a risk factor for normal-tension glaucoma. GBE has beneficial effects on ocular blood flow, increasing end diastolic flow in the ophthalmic artery in healthy individuals.[15] and Park et al[16] found that GBE increased mean blood flow, velocity and velocity of peripapillary vasculature compared to placebo in patients with normal tension glaucoma. Endothelial dysfunction with alterations in systemic NO and ET-1 may be involved in the vascular dysfunction seen in glaucoma.[17, 18] GBE can improve peripheral and ocular circulation by affecting the NO-pathway and endothelial dependant vasodilatation.[19] However not all studies have found an effect with GBE. Wimpissinger et al[20] investigated the effect of EGb761 in healthy volunteers, and in this case no change in ocular blood flow was found. It must be noted however that this study used only a single dose on EGb 761.

GBE also has an effect on the trabecular meshwork. Jia et al[21] demonstrated this effect in animal models and in human cell tissue culture. GBE significantly suppressed raised IOP in rabbits that had been given steroids. On examination of the trabecular meshwork after enucleation, there was a reduction in the accumulation of extracellular materials associated with steroid use, and there was better trabecular meshwork cellularity. When human trabecular meshwork cells were cultured and treated with GBE, they also showed a reduction in the adverse effects associated with steroid use.

In addition to its benefits, GBE appears to be a safe treatment option with few adverse effects. There have only been rare reports of headaches, gastro-intestinal and mild allergic skin reactions.[22] And while there had been some case reports of excessive bleeding, subsequent systematic review concluded that a link between taking GBE and bleeding was unlikely.[23]

3) Clinical data

The beneficial effects of GBE seen in animal and tissue culture models are being explored in the clinical setting. Quaranta et al[24] performed a prospective, randomised, double-masked trial of GBE in patients with normal tension glaucoma. A 40mg oral dose of GBE three times a day for 4 weeks showed an improvement in pre-existing visual field damage. Lee et al[25] investigated the long-term progression of visual field defects in patients with NTG. There was a mean follow-up period of 12.3 years, and over this time GBE significantly slowed the progression of visual defects.[25] It must be noted however that not all studies have replicated these results. Guo et al[26] also completed a prospective randomised, placebo-controlled crossover study of Chinese patients with NTG. A similar method was used to the study carried out by Quaranta et al but this trial gave conflicting results, with GBE showing no effect on defect or contrast sensitivity. Patel et al[27] later performed a systematic review and meta-analysis of the effect of flavonoids in patients with glaucoma and ocular hypertension and concluded that there is a significant benefit on visual fields. However this study did not show a significant effect on IOP.

4) Conclusions

The benefits of GBE in practice for treatment of glaucoma are still uncertain with conflicting results being found. Despite the lack of definitive evidence of the benefit of GBE, many ophthalmologists now use GBE in patients with glaucoma,[28] especially those with normal tension glaucoma, or those who continue to deteriorate despite normalization of IOP with conventional therapies.[28] The positive effects of GBE seen in experimental models and the theoretical impact on the underlying mechanisms make it a good candidate for an alternative glaucoma treatment.

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DATE OF ORIGINAL RELEASE

Date of original release: October 2016. Approved for a period of 12 months.

This issue is accredited for Continuing Medical Education (CME) by the Physicians' Chamber of Baden-Württemberg, Germany (Local Medical Responsible: Andreas Buchholz, MD, PhD, ROph).

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