

The Glaucoma Guidelines of the Swedish Ophthalmological Society

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Preface

In 1995, the Swedish Glaucoma Society proposed *Guidelines for the Management of Open-Angle Glaucoma and Ocular Hypertension*, which were subsequently accepted and recommended by the Swedish Ophthalmological Society. In 1997, the Swedish National Board of Health and Welfare published a state-of-the-art report entitled *Open-Angle Glaucoma*.

Requests to update these documents were long expressed, and it seemed rather reasonable that that should be performed considering the important advances that have been made in the field of glaucoma over the past decade, for example, in large randomized studies of this disease. Nonetheless, it was necessary to put such improvement on hold pending the outcome of several years' work on an extensive systematic evaluation of treatment and diagnostics of glaucoma. The results of that assessment were published by SBU in October 2008 in the report *Diagnostics, follow-up, and treatment in open-angle glaucoma: a systematic review of the literature*.

After the SBU report appeared, it was logical that the next step would be to develop new guidelines. Work on that task was commissioned by the Swedish Ophthalmological Society and was performed by the members of the SBU Expert Panel (Albert Alm, Boel Bengtsson, Berit Calissendorff, Christina Lindén and myself) and two experts from the Board of the Swedish Glaucoma Society (Anders Bergström and Bertil Lindblom). On assignment from the Swedish Ophthalmological Society, the guidelines that were created were reviewed by Björn Friström and Enping Chen and subsequently revised.

It is the ambition of the Swedish Ophthalmological Society that these new guidelines be put to widespread use in glaucoma care in Sweden.

The authors also hope that these Guidelines will be of interest to an international readership, when they have now been translated into English for publication in *Acta Ophthalmologica*.

Anders Heijl
on behalf of the Expert Panel
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Conflicts of Interest

Anders Heijl is a paid consultant to Carl Zeiss Meditec, Allergan and Alcon. Boel Bengtsson is a paid consultant to Carl Zeiss Meditec. Anders Bergström briefly served as a paid consultant to Alcon. Christina Lindén is a member of the Allergan Nordic Advisory Board. Bertil Lindblom, Berit Calissendorff and Albert Alm have no potential conflicts to declare.

List of Contents

1 DEFINITION OF GLAUCOMA, VISUAL DISABILITY, AND QUALITY OF LIFE	6		
DEFINITION OF GLAUCOMA	6		
RISK OF VISUAL DISABILITY AND BLINDNESS	6		
QUALITY OF LIFE	6		
Assessment of QoL	6		
QoL in glaucoma patients	7		
2 EPIDEMIOLOGY AND RISK FACTORS	7		
EPIDEMIOLOGY	7		
RISK FACTORS FOR OPEN-ANGLE GLAUCOMA AND GLAUCOMA PROGRESSION	8		
Risk factors—individuals	8		
Age	8		
Ethnicity/Race	8		
Heredity	8		
Risk factors—eyes	8		
Increased IOP	8		
Fluctuations in IOP	8		
Perfusion pressure	8–9		
Exfoliation syndrome	9		
Myopia	9		
Central corneal thickness (CCT)	9		
Signs of glaucoma	9		
Risk factors—general diseases	9		
Blood pressure	9		
Cardiovascular disease	9		
Diabetes mellitus	9		
Migraine and Raynaud's syndrome	9		
Sleep apnoea	9–10		
Medications	10		
Lifestyle factors	10		
3 CLINICAL FINDINGS AND DIAGNOSTICS	10		
THE OPTIC DISC AND RETINAL NERVE FIBER LAYER	10		
The optic disc	10		
The retinal nerve fiber layer	11		
Examination techniques	11		
Ophthalmoscopy	11		
Direct ophthalmoscopy	11		
Indirect ophthalmoscopy	11		
Biomicroscopy	11		
Optic disc photography	11		
Analogue (film) photography	11		
Digital photography	11		
Methods for analyzing the optic disc and nerve fiber layer	11		
Scanning laser tomography	11		
GDx VCC and GDx ECC	11–12		
Optical coherence tomography (OCT)	12		
PERIMETRY	12		
Examination techniques	12		
Screening and threshold programs	13		
Interpretation of visual field test results: diagnosis	14		
Follow-up: Interpretation of visual field tests and progression	14–15		
Event analysis	15		
Trend analysis	15		
High-pass resolution (ring) perimetry	17		
IOP AND TONOMETRY	17		
Normal IOP	17		
Variation in IOP	17		
Factors that influence IOP	17–18		
Methods	18		
The Goldmann applanation tonometer	18		
Perkins tonometer	19		
“Air-puff” or non-contact tonometry (NCT)	19		
Ocular response analyzer (ORA)	19		
Tonopen®	19		
Dynamic contour tonometry (DCT)/Pascal®	19		
Rebound tonometry/Icare®	19		
CORNEAL THICKNESS AND PACHYMETRY	19		
Methods	19		
Ultrasound pachymetry	19		
Orbscan®—slit-scan pachymetry	20		
Future aspects	20		
GONIOSCOPY	20		
Methods	20		
Static gonioscopy	20		
Dynamic gonioscopy	20		
Assessment of anterior chamber depth by van Herick's method	20		
4 PRINCIPLES FOR MANAGEMENT OF GLAUCOMA	21		
MAKING A DIAGNOSIS	21		
Optic nerve damage with a normal visual field	21		
Visual field damage with a normal optic nerve	21–22		
Instrumental examination of optic disc topography and thickness of the retinal nerve fiber layer	22		
Radiological investigations	22		
GENERAL TREATMENT PRINCIPLES	22		
Goal of treatment	22		
Treatment methods and effects	22–23		
Risk analysis and target IOP	23		
Rate of progression	23		
Individualized glaucoma management	24		
Overall assessment	24		
5 TREATMENT METHODS	25		
PHARMACOLOGICAL TREATMENT OF GLAUCOMA	25		
Beta-receptor-blocking drugs	25		
Prostaglandin analogues	25		
Sympathomimetics	25–26		
Parasympathomimetics	26		
Carbonic anhydrase inhibitors	26–27		
Combination preparations	27		
Use in children and during pregnancy and lactation	27		
Treatment stages and strategies	27		
Switch or add	27		
Combination treatments	27–28		
MEDICAL TREATMENTS OTHER THAN PRESSURE REDUCTION	28		
WHEN ARE EYE DROPS INSUFFICIENT?	28		
LASER TREATMENT	28		
LTP/ALT	28		
SLT	28–29		
Primary laser treatment	29		
Diode laser cyclophotocoagulation	29		
SURGERY	29		
Surgical methods	29		
Trabeculectomy	29–30		
NPT techniques (deep sclerectomy, viscocanalostomy)	30		
Shunts	30		
Cyclodestructive procedures	30		
Cyclocryotherapy	30		
Diode laser cyclophotocoagulation	30		
Intraoperative antimetabolites	30		
Radiation	30		
Postoperative management	30–31		
Massage	31		
Suture removal	31		
Parameters for laser suture lysis	31		
Releasable and adjustable sutures	31		
Needling	31		
YAG laser goniotomy	31		
Postoperative 5-FU	31		
6 MANAGEMENT OF SUSPECTED GLAUCOMA AND OCULAR HYPERTENSION	31		
OCULAR HYPERTENSION	31–32		
SUSPICIOUS OPTIC DISCS	32		

OPTIC DISC HAEMORRHAGE	32
EXFOLIATION SYNDROME	32
GLAUCOMA AND POSITIVE FAMILY HISTORY	32
7 POPULATION SCREENING AND CASE FINDING	32–33
REFERENCES	33–38

1 Definition of Glaucoma, Visual Disability, and Quality of Life

Definition of glaucoma

Glaucoma is defined as a progressive disease that causes characteristic degenerative changes in the optic disc, the retinal nerve fibre layer and the visual field. Increased intraocular pressure (IOP) was initially considered to be a prerequisite for a diagnosis of open-angle glaucoma, whereas such a rise in pressure is no longer included in the definition of this disease. Patients with normal IOP were previously classified as having low-tension glaucoma. However, today a diagnosis of primary open-angle glaucoma is given to patients who have elevated IOP as well as those who have normal pressure, and the disease in the latter group is preferably called normal-tension rather than low-tension glaucoma. In primary open-angle glaucoma, the anterior chamber angle is open and there are no identifiable causes of the disease.

Exfoliation glaucoma is regarded as a secondary form of glaucoma in most parts of the world, although not always in the Nordic countries. Exfoliation glaucoma is a synonym for the terms pseudoexfoliation glaucoma and capsular glaucoma, which were used more often in the past.

Risk of visual disability and blindness

In the Western world, open-angle glaucoma is the second most common cause of blindness after macular degeneration (Resnikoff et al. 2004). About 3–5% of patients with glaucoma are blind (Quigley & Broman 2006), but glaucoma is a progressive disease and thus that proportion increases with advancing age. Consequently, a larger number of people with glaucoma go blind during their lifetimes, with figures in the range 6–15% at the last examination before death (Hattenhauer et al. 1998; Forsman et al. 2007). It is more common to be blind in one eye only.

Intraocular pressure is no longer included in the definition of glaucoma
A large minority of all glaucoma patients become blind in both eyes during their lifetimes, and blindness in one eye is common

The main risk factor for blindness is having extensive visual impairment at diagnosis (Chen 2004), although younger age at diagnosis obviously increases the risk as well. The average age at diagnosis is approximately 70 years, and hence a 60-year old who is diagnosed with manifest glaucoma must be regarded as a relatively young patient (Rudnicka et al. 2006).

The proportion of blind individuals varies with the definition of blindness. The WHO definition (sidebar) is used in Sweden. The United States has introduced disability benefits for glaucoma patients with severe visual impairment defined as a mean deviation (MD) value worse than –22 dB on Humphrey threshold perimetry in the best eye (section 2.03 at <http://ssa.gov/disability/professionals/bluebook/2.00-SpecialSensesandSpeech-Adult.htm>)

The WHO defines blindness as visual acuity < 3/60 or a remaining visual field with a diameter < 10°

Quality of life

Research and interest in quality of life (QoL) have increased steadily in recent years. The influence of QoL is highly important from the perspective of the patient. Information about QoL helps to create a more balanced picture of the consequences of the disease than would be possible if only functional impairments caused by the disease were to be included in the description.

There is no scientific basis for overall assessment of quality of life

Assessment of quality of life

The concept of QoL is multidimensional and complex in that it includes physical and psychological functions, and also mental and general health, as well as social and economic aspects. The way a patient experiences QoL depends on the person's state of mind and possible presence of comorbidities. In addition, many survey instruments are designed to address an issue more from the perspective of the researcher (i.e. considering the expected outcome of the disease) than from the standpoint of the individual patient.

Awareness of the significance of the survey tools has led to development and validation of an increasing number of instruments over the last decade. Depending on the topic of interest, various validated instruments are available:

- (1) *General/Global instruments* measure general dimensions of QoL and are used to compare different groups of disorders.
- (2) *Vision-specific instruments* assess visual function in relation to QoL.
- (3) *Utility* estimates patients' own evaluations of their state of health.

Some general or global QoL instruments have been validated for comparing groups or for conducting intraindividual assessment over time. The SF-36 Health Survey questionnaire is used most widely and has been translated into several different languages. EuroQoL (EQ-5D), which is based on British material, is frequently used in Europe, and it is also the instrument employed most often in both clinical and population studies in Sweden. Inasmuch as the type of disease *per se* affects QoL, in recent years specific strategies have been developed for investigating various disorders. An example of this is the Visual Activities Questionnaire (VAQ), which has been modified to assess certain eye diseases. The vision-related instrument VFQ-25 has also been translated into Swedish and validated. A review article published by Severn et al. (2008) illustrates the difficulties associated with designing instruments that can adequately evaluate QoL in patients with glaucoma.

To achieve a better basis for allocation of resources, an instrument that assesses patient 'benefit' (utility) has also been developed to allow patients' own experiences of their diseases to be correlated with cost efficiency. This tool measures how a patient evaluates a given state of health on a scale ranging from perfect health (score 1) to death (score 0).

Quality of life is so complex and multidimensional in nature that there are no instruments for comprehensive assessment of this concept. Furthermore, validity problems and the lack of a 'gold standard' make it difficult to interpret and compare findings. Indeed, even internationally approved and validated questionnaires can

provide disparate results when analyzing the same patient material.

Quality of life in patients with glaucoma

Most studies of QoL in glaucoma have concerned visual function and have shown that marked loss of vision leads to lower QoL (Gutierrez et al. 1997; Sherwood et al. 1998; Janz et al. 2001; Hyman et al. 2005; Varma et al. 2006). However, there is no consensus regarding what degree and type of impairments reduce QoL. Many eye-specific assessment instruments focus on visual acuity, and few concern any particular visual field defects, which makes it difficult to compare results. Conclusions are also contradictory with respect to whether QoL is affected by the treatment provided or by economic factors. On the other hand, there is agreement that being informed of the diagnosis has a negative impact on the patient. Nonetheless, the initial anxiety decreases over time, as shown in some longitudinal studies (Janz et al. 2007).

Receiving a diagnosis of glaucoma has a temporary negative impact on quality of life
Strongly impaired vision reduces quality of life

Two large treatment studies called the Early Manifest Glaucoma Trial (EMGT; Hyman et al. 2005) and the Collaborative Initial Glaucoma Treatment Study (CIGTS; Janz et al. 2001) have compared the effects of different therapeutic strategies on QoL during long-term follow-up. After 5 years in the CIGTS, local eye problems were found to be somewhat more common in the surgically treated patients than in those given only medications, although the two patient groups were essentially comparable in other aspects and showed relatively good QoL. In the EMGT, no difference in QoL was observed between treated and untreated patients at 6-year follow-up.

One of the difficulties in assessing QoL in patients with glaucoma, compared to individuals who do not have this disease, is the above-mentioned choice of survey instrument. Other problems are related to finding age-matched controls. Control patients are often younger. Also, some investigators have found no definite difference in

QoL between patients with glaucoma and controls (Gutierrez et al. 1997; Parrish et al. 1997; Wandell et al. 1997), whereas others have noted lower QoL in patients with glaucoma (Sherwood et al. 1998; Wilson et al. 1998). In Sweden, Wandell et al. (1997) compared patients with glaucoma with an age-matched group of nonglaucomatous subjects by using the Swedish version of the general Health-Related Quality of Life (HRQoL) questionnaire. These authors found no difference in QoL between the two groups, nor did it appear that QoL was affected by treatment with beta-blockers.

Quality of life is not necessarily lower in patients with glaucoma as a group than in corresponding age-matched control subjects

2 Epidemiology and Risk Factors

Epidemiology

Glaucoma is the most widespread age-related eye disease after cataract (Ryskulova et al. 2008), and it is the second most common cause of blindness in the world (Resnikoff et al. 2004; Quigley & Broman 2006). It has been estimated that about 60 million people over the age of 40 would be affected in 2010, and that one-fourth of those would have angle-closure glaucoma and the rest open-angle glaucoma. Calculations have indicated that the prevalence of open-angle glaucoma (i.e. the proportion of the population suffering from the disease) is approximately 2% in populations over the age of 40 (Quigley & Broman 2006), although the rate varies depending on the age group and the population under consideration.

In the European population, the prevalence of glaucoma has been found to be 2% in people over the age of 40 (Quigley & Broman 2006) or 6% in people over the age of 70 (Rudnicka et al. 2006). Similar results were obtained in the large Swedish screening study entitled the Malmö Eye Survey, which showed a prevalence of more than 5% in 75-year-olds (SBU, 2008) and more than 2% in the age group 57–79 years. Other investigations in Sweden have indicated both lower

(Bengtsson 1981) and higher (Ekström 1996; Åström et al. 2007) prevalences. Some of these discrepancies might be explained by the occurrence of exfoliation syndrome.

Exfoliation syndrome is common in Sweden, predominantly in women (Ekström 1996; Åström & Lindén 2007), and prevalence increases substantially with greater age (Åström et al. 2007). In the north of Sweden, Åström and colleagues (2007) detected exfoliations in 23% of all 66-year-olds, and, after 21 years of follow-up (subjects aged 87), 61% of the cohort had developed exfoliations in one or both eyes.

Ocular hypertension (elevated IOP without signs of glaucoma damage) is another risk factor that increases with age. A number of studies have found prevalence of 5–9% for this condition, which is several times higher than the level noted for open-angle glaucoma. In the Malmö Eye Survey, ocular hypertension was found to be twice as common as glaucoma (SBU, 2008).

Glaucoma is the second most common age-related eye disease
In Sweden, ocular hypertension is twice as common as glaucoma

Since there is no difference in life expectancy between people with and without glaucoma (Grødum et al. 2004), age-specific prevalence data can be used to estimate the incidence of this disease (i.e. the proportion who recently developed glaucoma; Podgor et al. 1983). Since the prevalence increases exponentially with advancing age, most markedly in the white population, it can be concluded that the incidence also rises with age (Rudnicka et al. 2006). Accordingly, older age is associated with a greater risk of developing glaucoma. Only a few studies in the literature have addressed the incidence of glaucoma, and several of them were conducted in Sweden. The incidence found in those investigations varies from 0.24% among 65- to 80-year-olds in Dalby (Bengtsson 1989) to 0.64% in the corresponding age group in Tierp (Ekström 2008) and 0.9% in 66- to 87-year-olds in Skellefteå (Åström et al. 2007). Such high incidence numbers have otherwise only been reported in a black population (Leske et al. 2007b).

It has been shown that half (Ekström 1996; Quigley 1996) or more

than half (Quigley & Broman 2006) of all cases of glaucoma revealed by population surveys are undiagnosed. It is not known exactly how many people in Sweden have been identified as having glaucoma. Nonetheless, the number has been estimated to be approximately 100 000, although that value is highly uncertain. Considering that 4.6 million people in Sweden are over the age of 40 (SCB. Statistiska Centralbyrån 2008), 100 000 known cases of glaucoma would imply the following:

- (1) most of the people with glaucoma in this country are identified, which is contradicted by prevalence studies performed thus far;
- (2) or glaucoma prevalence is higher than 2%, an assumption for which there is some support;
- (3) or the estimate is incorrect and also includes, for example, patients with ocular hypertension.

In a fairly recent meta-analysis that comprised 25 studies including more than 60 000 subjects, 1355 of them with glaucoma, Rudnicka et al. (2006) noted that glaucoma prevalence was more than about 1.4 times greater in men than in women. However, other analyses have provided conflicting results.

At least half of all glaucomas are undiagnosed

In Sweden, the number of people with a glaucoma diagnosis is uncertain but has been estimated to be 100 000

Patients with glaucoma identified in clinical practice differ from those detected by screening

The prevalence of open-angle glaucoma in the adult population is approximately 2% in Europe and the rest of the world, and at least 2% in Sweden

It is not clear whether there are gender-related differences

Patients with glaucoma detected by population screening differ in many ways from patients who are diagnosed at an eye department. Individuals in the latter group are much more likely to exhibit higher IOP, more extensive visual field damage and bilateral disease (Grødum et al. 2002a), as well as exfoliation syndrome. In Malmö and Tierp, exfoliation glaucoma constituted 44% and 60% of clinically diag-

nosed patients with glaucoma, respectively, but only 16% of the cases detected at screening, in both cities. On the other hand, normal-tension glaucoma was detected more often by screening. In Malmö, half of the cases identified by screening had low-tension glaucoma, one-third in Tierp. Clinically diagnosed patients were considerably fewer, 14% and 0% in Malmö and Tierp, respectively (Ekström 1996; Grødum et al. 2002a). These observations suggest that normal-tension glaucoma is frequently overlooked in clinical examinations.

Exfoliation syndrome is common in Sweden and occurrence increases with age

Risk factors for open-angle glaucoma and glaucoma progression

A risk factor is an event, a condition, a behaviour or some other aspect that can have an impact on development of a disease. There is both a causal and a statistical relationship between a risk factor and the illness in question. A simple statistical relationship between the risk and the disease can suffice as a marker or an indicator of risk. In many cases, we do not distinguish between these two concepts and instead, somewhat imprecisely, refer to them as risk factors, which also applies in these guidelines. Many risk factors are confirmed in cross-sectional epidemiological studies, and hence it is important to have a uniform definition of the disease when studying risk factors. Vision 2020 is a global initiative that was established jointly by the WHO and other organizations with the intention of eliminating all avoidable blindness. Vision 2020 defines glaucoma as both structural and functional damages.

In some cases, for instance, optic disc changes or abnormal values in a visual field index are interpreted as risk factors for glaucoma. These are signs of disease and thus cannot actually be regarded as risk factors for developing glaucoma. A number of other factors have been reported to increase the risk of both occurrence and progression of glaucoma. However, although these factors are often the same, it seems that they may differ

regarding their impact on development and progression of the disease.

Risk factors—individuals

Age

Older age is strongly related to glaucoma. Both incidence and prevalence increase with age (Gordon et al. 2002; de Voogd et al. 2005; Miglior et al. 2007b; Leske et al. 2008), and older age is also a risk factor for glaucoma progression (Lichter et al. 2001; The advanced glaucoma intervention study (AGIS) 2002; Leske et al. 2007a,b; Chauhan et al. 2008b).

Ethnicity/race

Prevalence of glaucoma is higher in people of African descent than in those of European ancestry (Leske et al. 1994). In one study (Tielsch et al. 1991), prevalence in the comparatively young age range of 51–60 years was found to be four times higher in black Americans than in white Americans.

Heredity

Glaucoma in first- or second-degree family members is a risk factor, regardless of IOP (Hulsman et al. 2002; Leske et al. 2008). The risk may be greater if a sibling has glaucoma than if a parent has the disease (Wolfs et al. 1998). Recommendations concerning medical checkups are given in the section headed Glaucoma and positive family history (p. 32).

Risk factors – eyes

Increased intraocular pressure

Elevated IOP is the most important risk factor for both development (Kass et al. 2002) and progression (Heijl et al. 2002) of glaucoma. In addition, raised eye pressure is the only treatable risk factor.

Fluctuations in intraocular pressure

There is no evidence that fluctuation in IOP is an independent risk factor for development or progression of glaucoma. Several studies have provided contradictory results (Singh & Shrivastava 2009).

Perfusion pressure

Several investigations have demonstrated a relationship between low ocular perfusion pressure and both development and progression of glaucoma (Leske 2009). The clinical significance of these observations is not clear.

Elevated IOP is the most important and the only treatable risk factor for both development and progression of glaucoma

Perfusion pressure is related to how blood pressure can affect circulation in the eye, but this concept is much too imprecise to be used in the management of individual patients. In 'Terminology and Guidelines for Glaucoma' published by the European Glaucoma Society (2008, p. 89), ocular perfusion pressure is defined as the difference between arterial blood pressure and IOP. However, perfusion pressure is a concept based on general physiological principles, and it does not take into account the decrease in pressure between the eye and the heart, which is also determined by the position of the body or by the drop in pressure in the small vessels leading to the eye. Measuring blood pressure and IOP in a single patient cannot give a definite picture of the perfusion pressure in the eye that is examined in that particular person.

Exfoliation syndrome

The risk of glaucoma is markedly increased in the presence of exfoliation syndrome accompanied by elevated IOP, although it seems that exfoliation syndrome alone does not raise the risk of glaucoma (Grødum et al. 2005; Ekström & Alm 2008). Exfoliation syndrome is also a strong risk factor for glaucoma progression, and there is evidence that this is independent of IOP (Leske et al. 2003). Exfoliation syndrome is common in the Nordic countries. For more information, see the section of this chapter entitled Epidemiology (p. 7). For recommendations regarding management of patients with exfoliation syndrome, see page 32 in the chapter entitled 'Management of suspected glaucoma and ocular hypertension'.

Myopia

Myopia is a risk factor for glaucoma in people with normal IOP (Grødum et al. 2001; Oku et al. 2009). It is more difficult to detect glaucoma damage in eyes with small optic discs (Heijl & Mölder 1993). Accordingly, larger discs in myopic eyes might explain the association between myopia and glaucoma, although the results of studies of optic disc size and refraction are contradictory (Miglior et al. 1994; Varma et al.

1994). Myopia is probably not a risk factor for progression (Leske et al. 2007a,b).

Increased IOP in connection with exfoliation is a very strong risk factor for developing glaucoma

Exfoliation syndrome is a strong and likely independent risk factor for glaucoma progression

Central corneal thickness

The Goldmann applanation tonometer gives erroneously low measurements in eyes with a thin cornea and inaccurately high values in those with a thick cornea. Therefore, a thin cornea is a risk factor for developing glaucoma (Kass et al. 2002) but represents a nonimportant risk for progression (Leske et al. 2007a,b).

Signs of glaucoma

Structural and functional changes included in the definition of glaucoma cannot be regarded as risk factors for developing this disease. Consequently, the impact or the size of such changes can only be evaluated in relation to progression of glaucoma. The disease progresses at a faster rate in eyes that have more visual field loss than in those with less loss (Leske et al. 2007a,b). Optic disc haemorrhages increase the risk of progression (Siegener & Netland 1996; Leske et al. 2007a,b; Bengtsson et al. 2009a).

Risk factors – general diseases

Blood pressure

There is a positive correlation between blood pressure and IOP, whereas no association exists between blood pressure and development or progression of glaucoma (Tielsch et al. 1995b). An explanation for this might be that high blood pressure improves ocular perfusion pressure and thereby reduces the risk caused by elevated IOP.

Cardiovascular disease

Reports in the literature on this subject are not unequivocal. Some recently published epidemiological studies found an association between cardiovascular disease and glaucoma (Lee et al. 2006; Wu et al. 2008), which other earlier investigations had not been able to demonstrate (Klein et al. 1995; Borger et al. 2003). In the Early Manifest Glaucoma Trial conducted in Sweden, cardiovascular dis-

ease was not a significant risk factor for progression of glaucoma after 6 years of follow-up, whereas it was such a factor after 8 years (Leske et al. 2007a,b). In a longitudinal study performed in Canada (Chauhan et al. 2008b), an association was observed after 5 years of follow-up.

Diabetes mellitus

Diabetes has long been considered a risk factor for glaucoma, which may be explained by bias: patients with diabetes undergo regular eye examinations, which other groups do not, and hence there is a greater probability of detecting glaucoma in diabetics. Notwithstanding, the Blue Mountains Eye Study did find a relationship between diabetes and glaucoma (Mitchell et al. 1997), whereas several other contemporary studies obtained no indication that diabetes was a risk factor for glaucoma in the subjects that were examined, even though IOP was higher in those with diabetes (Tielsch et al. 1995a; de Voogd 2006). Also, in the Ocular Hypertension Treatment Study (Gordon et al. 2002), diabetes was observed to protect against glaucoma. Thus, it seems that there is no evidence that diabetes is a risk factor for glaucoma.

Migraine and Raynaud's syndrome

It has been suggested that vasospasm, which occurs in both migraine and Raynaud's syndrome, entails a risk for normal-tension glaucoma (Gasser et al. 1990). However, it is not clear whether these two conditions are related to existence or progression of glaucoma. Both the Blue Mountains Eye Study (Wang et al. 1997) and the Beaver Dam Eye Study (Klein et al. 1993) found migraine to be a risk factor for glaucoma, but the definition of migraine differed in those two investigations and has been disputed. The Swedish Early Manifest Glaucoma Trial found neither migraine nor Raynaud's syndrome to be risk factors for progression of glaucoma (Leske et al. 2003).

Sleep apnoea

It is uncertain whether sleep apnoea is associated with glaucoma. Two clinical studies (Mojon et al. 2000; Girkin et al. 2006) have suggested that such a relationship does exist, whereas other investigations (Geyer et al. 2003;

Bendel et al. 2008; Roberts TV et al. 2009b) have not found any connection.

Medications

It has long been known that use of eye drops containing cortisone increases IOP. Moreover, oral corticosteroid therapy has been shown to raise the risk of ocular hypertension and glaucoma (Garbe et al. 1997). The results of a subsequent study (Mitchell et al. 1999) suggest that nasal sprays and inhalants containing corticosteroids increase the risk of ocular hypertension and glaucoma, particularly in people with a family history of glaucoma. The patients in the cited investigations had both ocular hypertension and glaucoma, and apparently no studies have focused solely on patients with glaucoma. Therefore, it seems reasonable to assume that the risk of glaucoma posed by corticosteroids is mediated indirectly through ocular hypertension.

Lifestyle factors

No associations have been found between glaucoma and physical activity (Passo et al. 1991), smoking, body mass index (BMI), alcohol or coffee consumption, or diet.

There is no association between lifestyle factors and glaucoma

3 Clinical Findings and Diagnostics

The optic disc and retinal nerve fibre layer

The optic disc

The basis for the glaucoma diagnosis is optic nerve damage. Such damage is almost always associated with visual field loss. However, damage to the optic disc can occur either with or without accompanying visual field damage (the latter is called preperimetric glaucoma). Also, visual field defects without any identifiable optic disc damage are seen in rare cases involving an unusually small disc. It can be difficult to detect the glaucomatous damage in such a disc, particularly if the disease is bilateral and

thus there is no healthy disc for comparison.

Therefore, it is of fundamental importance to assess the size of the optic disc during an examination. Exact measurement is difficult to achieve and is seldom of clinical interest. To estimate disc size, the height of the split beam can be adjusted to coincide with the vertical (or horizontal) disc diameter, and the readings are converted according to the auxiliary lens that is used (Lim et al. 1996). Another simple method is to compare optic disc diameter (DD) with disc-to-fovea distance (DM) measured from the centre of the disc to the fovea. The mean of the ratio of DM to DD is 2.5 (Mok & Lee 2002). With increasing experience, it is often possible to estimate the size of the optic disc without relying on measured values. In this context, it can suffice to roughly divide discs into these five classes: very large, large, medium sized, small and very small. A large optic disc will usually have a large physiologic cup (excavation) that can easily be mistaken for glaucomatous damage (Heijl & Mölder 1993). The cup in a small optic disc will normally be very small or lacking, and thus it will be difficult to detect early glaucomatous changes. Therefore, when analysing the appearance of the optic disc, it is important not to concentrate on the size of the cup, but instead to focus on assessing the appearance of the neuroretinal rim and, if possible, also the thickness of the retinal nerve fibre layer (Fig. 1).

Assessment of optic disc size is essential in diagnosis of glaucoma

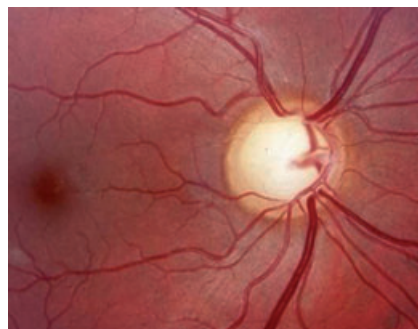


Fig. 1. A large normal optic disc with a large physiologic cup (excavation). The neuroretinal rim is intact and even in width.



Fig. 2. Glaucomatous optic disc showing notching of the neuroretinal rim (arrow).

In glaucoma, a definite sign of optic disc damage is a focal thinning of the neuroretinal rim, which is called a notch (Fig. 2). Such a disc change is associated with localized thinning of the retinal nerve fibre layer in the same area.

Another less reliable sign of optic disc damage in glaucoma is a general thinning of the neuroretinal rim (an enlarged cup). The size of the optic disc is of vital importance in this context. A measurement such as the cup-to-disc (C/D) ratio is of very little value, unless it is considered in relation to disc size. Moreover, this ratio offers low sensitivity as a measure in longitudinal follow-up, and thus it can be questioned whether C/D should be used at all.

Nonetheless, the thickness of the neuroretinal rim can facilitate the analysis. According to the ISNT rule, in a normal rim the inferior (I) area is thickest, followed by the superior (S), nasal (N) and temporal (T) areas (Jonas et al. 1988a). Deviation from this rule should raise suspicion of glaucomatous damage, although it is neither a sensitive nor a specific sign of glaucoma (Sihota et al. 2008).

It is important to notice any difference in size between the cups in the two eyes, but it is first necessary to verify that there is no corresponding size divergence between the optic discs.

A common finding in glaucoma is a small haemorrhage on either the edge or the surface of the optic disc (Drance 1989). Such haemorrhages are more common in normal-tension glaucoma than in high-pressure glau-

coma (Kitazawa et al. 1986), and they are often of short duration. The cause of these haemorrhages is unclear, although it is known that they occur more frequently in persons who have diabetes or use medications containing salicylic acid (Grødum et al. 2002b; Soares et al. 2004). Even though disc haemorrhages are seen in individuals who do not have glaucoma (Healey et al. 1998), they should arouse suspicion of this disease, especially if other risk factors are also present (Diehl et al. 1990).

Optic disc haemorrhage is a common finding in open-angle glaucoma

When assessing optic discs, a potential source of error is that it can be difficult to delineate the margin of discs exhibiting peripapillary atrophy. If the atrophy is mistakenly included in the disc area, the degree of cupping will be underestimated (Fig. 3). Peripapillary atrophy is common in glaucoma, but this finding is not specific and often occurs in older people who do not have glaucoma (Curcio et al. 2000) and in individuals with eye conditions other than glaucoma, such as severe myopia (Jonas et al. 1988b)

The retinal nerve fibre layer

Thinning of the retinal nerve fibre layer is often seen at an early stage of glaucoma. Among the factors that can facilitate evaluation are clear media, dense pigmentation and young age of the subject. It is usually difficult to assess a general decrease in the thickness of the nerve fibre layer. Localized defects are easier to detect, either by direct ophthalmoscopy (red-free light facilitates examination) or by fundus photography (Airaksinen & Nieminen 1985).

Examination techniques

Ophthalmoscopy

Several new techniques have been developed for analysis of the optic disc and retinal nerve fibre layer topography, but ophthalmoscopy and disc photography still represent important examinations for diagnosis of glaucoma. The methods used to evaluate the fundus differ.

Direct ophthalmoscopy

Advantages. Provides an image with high magnification.

By far the best method for inspecting the retinal nerve fibre layer, particularly when using red-free light.

Disadvantages. Monocular viewing.

Indirect ophthalmoscopy

Advantages. Easier viewing through a small pupil.

Disadvantages. Low magnification. Monocular viewing.

Biomicroscopy

Advantages. High magnification, particularly with the 60D lens.

Binocular viewing (may require pupil dilation).

Disadvantages. Requires a slit-lamp microscope.

Optic disc photography

Photography of the optic disc is the most important method of permanent documentation. Modern techniques for topographical analysis of the optic disc or the retinal nerve fibre layer are under rapid development, but there is no guarantee that the equipment used in the future will be compatible with the instruments that are available today. Therefore, regardless of the equipment used, it is essential to obtain photographic records of the appearance of the optic disc, at least during diagnosis. An exception to this might be cases involving very advanced disc damage; it can be impossible to detect disease progression in a totally cupped optic disc.

Analogue (film) photography

Advantages. Excellent image quality.

Disadvantages. Time-consuming. Difficult to assess the results.

If possible, the optic disc should be photographed at the time glaucoma or ocular hypertension is diagnosed

Digital photography

Advantages. Fast.

Results can be assessed immediately. Easy to process images.

Disadvantages. Image quality can be suboptimal, particularly with older equipment.

Opinions differ regarding the importance of stereoscopic imaging. Obviously, use of three-dimensional imaging can facilitate evaluation of optic disc cupping. On the other hand, stereophotography is seldom done with a fixed stereo base, which may



Fig. 3. Glaucomatous optic disc with peripapillary atrophy. The arrow indicates the neuroretinal rim.

represent a source of error in the assessment.

Methods for analysing the optic disc and nerve fibre layer

Scanning laser tomography

This is a confocal technique that uses laser light to acquire multiple images at different levels in the fundus. The images are subsequently integrated to form a three-dimensional picture. The instrument in most widespread use is the Heidelberg Retina Tomograph (HRT; Heidelberg Engineering, Heidelberg, Germany). A third version of this instrument (HRT III) is now available, which is compatible with the earlier versions. In the HRT III system, the optic disc is classified by both Moorfields regression analysis and the Glaucoma Probability Score (Fig. 4). Because an HRT instrument analyses the appearance of the optic disc cup, it includes a source of error that is the same as that associated with ophthalmoscopic disc analysis: there is a risk of over-diagnosis of glaucoma damage in large optic discs, whereas the opposite is true for smaller discs.

GDx VCC and GDx ECC

The GDxVCC (Carl Zeiss Meditec Inc, Dublin, CA, USA) uses laser light to analyse the retinal nerve fibre layer (RNFL). The light is polarized as it passes through the RNFL, and measurements of the changes in the polarization state (birefringence) are used to calculate the RNFL thickness. Polarization can also occur in other

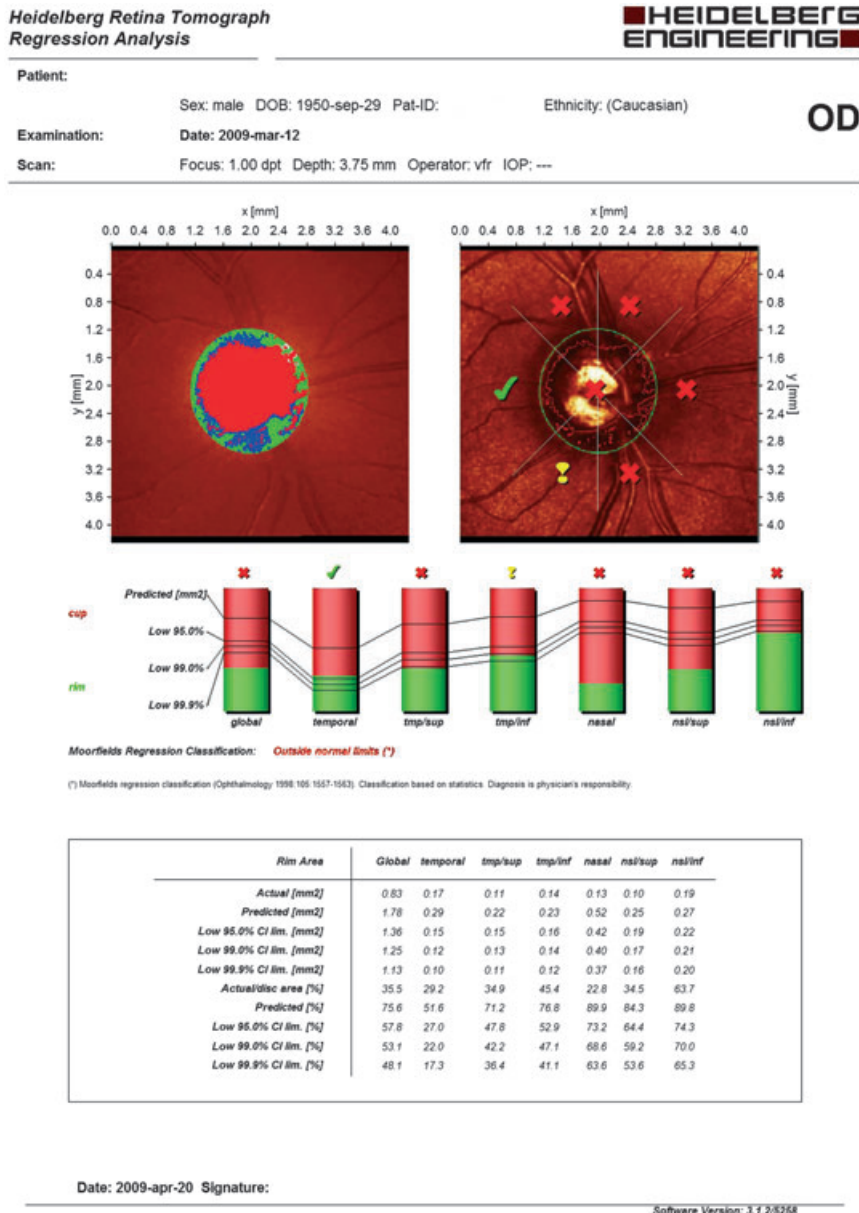


Fig. 4. Printout of Heidelberg Retina Tomograph Moorfields regression analysis.

structures in the eye, and later versions of this instrument compensate for such sources of birefringence, primarily the cornea. The abbreviations VCC and ECC stand for variable corneal compensation and enhanced corneal compensation, respectively.

Optical coherence tomography

The Stratus Optical coherence tomography (OCT) (Carl Zeiss Meditec Inc.) is the most widely employed instrument of this type. Most eye departments in Sweden have a Stratus OCT, because it is used to diagnose retinal diseases. There are several newer instruments on the market, but as of yet there is limited experience in using

them to diagnose glaucoma. OCT is based on interferometric analysis of light that is reflected back from the retina, and thus it can illustrate the various layers of the retina. For diagnosis of glaucoma, it is primarily the retinal nerve fibre layer that is of interest. However, this layer is thin in comparison with the resolution of the OCT instruments currently in use, although systems offering higher resolution are being developed.

Perimetry

Glaucomatous changes in the optic disc and the retinal nerve fibre layer cause damage in the visual field. At

an early stage, the impairment usually appears in the central 20–30° of the field in the form of reduced sensitivity in a certain area, for example, in the superior or inferior nasal quadrants or as arcuate scotomas in the superior or inferior paracentral area. The most central part of the visual field is often intact until very late stages of the disease. Reproducible, albeit somewhat varying, defects arising within the same area of the visual field are a reliable sign of glaucoma, above all if they coincide with damage to either the optic disc or the retinal nerve fibre layer. Early glaucomatous damage to the visual field is almost always localized to a specific area (Fig. 5A), whereas diffuse loss occurring as a general reduction in addition to the localized defects usually appears at a later stage. Diffuse loss that is not accompanied by any other forms of impairment is nearly always caused by cataract or some other media opacity (Fig. 5B). As the disease advances, damage to the visual field also progresses, and thus in many cases only a small area of central vision remains during late stages – the patient has tunnel vision. In some cases, only a temporal island of vision remains, but testing of the visual field is seldom carried out at that stage, because fixation is no longer possible.

Examination techniques

Standard automated perimetry (SAP) is based on the principles of the Goldmann perimeter using white stimuli on a white background. The Goldmann instrument is used mainly for kinetic perimetry, in which the stimulus is moved manually from the periphery towards the point of fixation. Static perimetry shows stimuli at predetermined test locations, and it can detect glaucomatous visual field damage at an earlier stage than is possible with kinetic perimetry (Aulhorn 1967; Heijl 1976; Johnson et al. 1979). Standard automated perimetry uses static stimuli. The Octopus perimeter (Haag-Streit, Bern, Switzerland) and the Humphrey Field Analyzer (Carl Zeiss Meditec, Dublin, California) are by far the most extensively used instruments for SAP.

Kinetic perimetry is not sensitive enough to detect early to moderately glaucomatous field loss with any certainty, and thus this method should

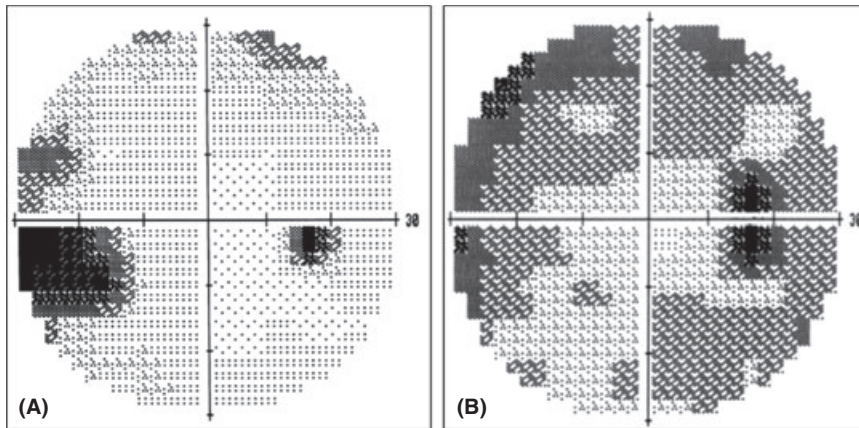


Fig. 5. (A) Visual field showing localized loss in the inferior nasal area caused by glaucoma. (B) Visual field with generally reduced sensitivity caused by cataract.

not be used to diagnose glaucoma. By comparison, computerized static perimetry is much more sensitive for identifying such defects.

Other techniques referred to as selective perimetry have also been developed. These were supposed to allow detection of glaucomatous defects at an earlier stage than is possible by SAP, although there is no evidence that this objective has been achieved (SBU, 2008; van der Schoot et al. 2010). A selective method called high-pass resolution perimetry, or ring perimetry, is a Swedish innovation that is relatively common in certain parts of this country and is therefore discussed further in a separate section at the end of this chapter (see p. 17). Otherwise, the rest of this chapter primarily concerns tests and interpretation programmes that are available in Octopus and Humphrey perimeters for detection and follow-up of patients with glaucoma.

Screening and threshold programmes

Screening programmes can be used to test patients with low suspicion of glaucoma, for example, individuals with a family history of the disease. These algorithms are intended to allow rapid and highly specific testing to determine whether a visual field is normal. The intensity of the stimulus in the screening test should be supraliminal, that is, the light should be brighter than the threshold value for normal eyes, and thus it can be expected that the stimuli will be visible to all individuals with normal visual fields. A screening test should

include relatively few test points that are concentrated within the central 20–30°. In glaucoma, essentially no isolated visual field defects occur beyond 30°. It should be pointed out that the screening programme of a selective method called frequency doubling perimetry (Carl Zeiss Meditec) has been shown to offer high specificity (81–99%) and satisfactory sensitivity (49–96%) at a test time of 30–60 seconds per eye (SBU, 2008). There is no need for corrective lenses or patching. Even if this method is most suitable for visual field examinations outside the eye clinic (e.g. in population screening), it can also be used in the clinical setting, for instance, to test people with a family history of glaucoma.

Threshold programmes are used to quantify the visual field, which means that early (shallow) defects can be detected. Hence, it is suitable to employ these tests to assess patients with strong suspicion of glaucoma or a high-risk profile, or to monitor progression in glaucoma follow-up. Threshold measurement entails determining the boundary between visible and invisible stimuli. This method is obviously more time-consuming than a screening test, but it provides more sensitive detection of defects.

A rapid screening test with good specificity is suitable, if there is low or moderate suspicion of glaucoma (e.g. because of family history of the disease)
A threshold test is more sensitive and should always be used for accurate diagnosis and follow-up

On the Humphrey perimeter, the newer and faster threshold algorithms SITA Standard and SITA Fast are at least as sensitive and specific as the more time-consuming Full Threshold and Fastpac. The threshold value is determined more accurately in SITA Standard (Bengtsson et al. 1997; Bengtsson & Heijl 1998) than in SITA Fast. SITA Fast is somewhat more difficult to manage for patients with no experience of threshold-measuring perimetry. The two tests offer fairly similar diagnostic accuracy, as indicated by studies showing sensitivity and specificity of over 90% (Budenz et al. 2002; Pierre-Filho Pde et al. 2006). Compared to SITA Standard, SITA Fast shows somewhat greater test-retest variability (Artes et al. 2002), which indicates that it is somewhat less sensitive in detecting early progression. Both of the SITA programmes work well in routine clinical practice, but it is advisable to choose one or the other to avoid programme variability that can render assessment of progression more difficult.

Considering the Octopus perimeter, the new and faster threshold programme Dynamic Range offers sensitivity that is equivalent to that of the older, more time-consuming Normal Strategy. The Octopus instrument also has an extremely fast test strategy called tendency-oriented perimetry (TOP). Tendency-oriented perimetry is not actually a threshold test, since the measured “threshold sensitivity” can never be better than the age-matched normal reference value.

Threshold perimetry can be performed with different test point patterns within the central 30° of the visual field. The 24-2 pattern is used most often on the Humphrey perimeter, and this involves testing in the central 24°. Compared to the 30-2 pattern, 24-2 is a bit faster and has slightly higher specificity, but it also has somewhat lower sensitivity (Heijl et al. 2008).

Appropriate test point patterns are 30-2 or 24-2 on a Humphrey perimeter and G1/G2 or 32 on an Octopus perimeter; these programmes test within the central 30° of the visual field (or the central 24° for Humphrey 24-2)

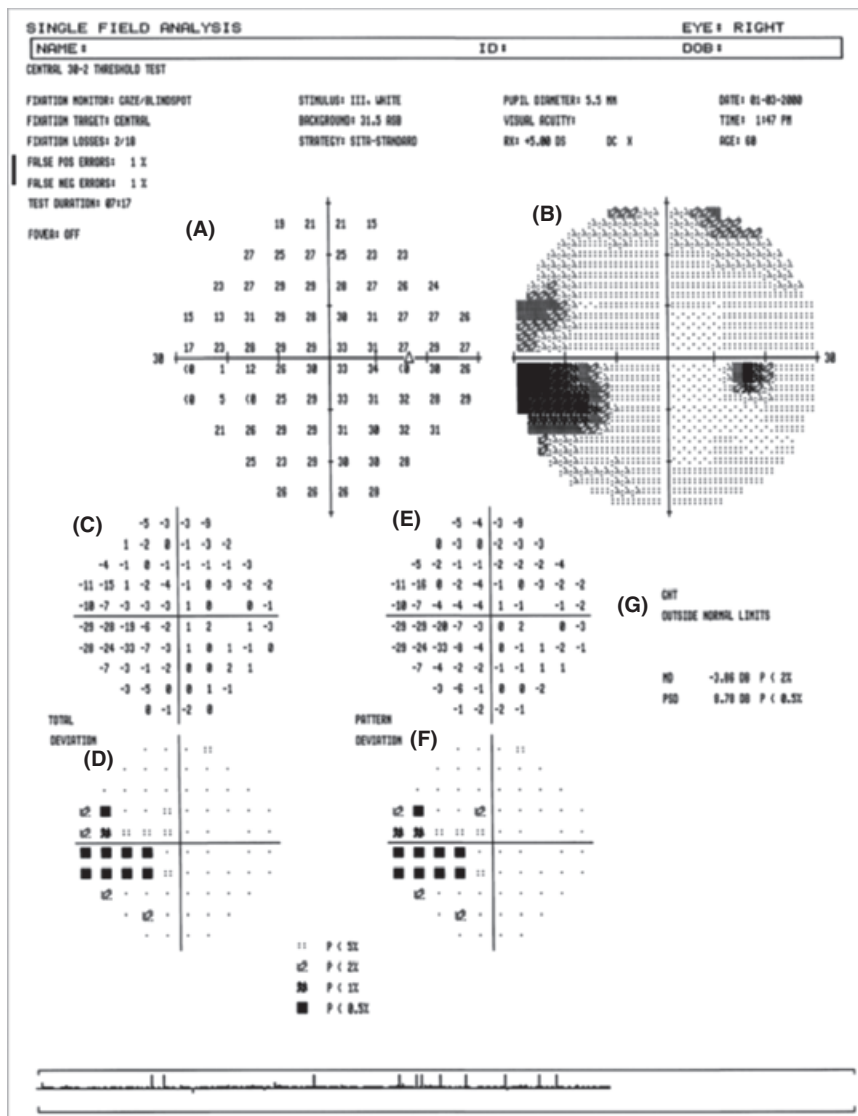


Fig. 6-1. Single Field Analysis of a visual field test on a Humphrey Perimeter. A) Numerical threshold values. B) Grey scale map of measured threshold values. C and E) Deviation from normal age-adjusted threshold values. D and F) Probability maps that highlight test points showing a significant loss compared to the normal age-related level after adjustment for general lowering of the threshold sensitivities. G) Glaucoma Hemifield Test. I) Reliability index, that is, false-positive and false-negative responses and fixation losses.

Interpretation of visual field test results: diagnosis

A printout of a visual field test contains several maps and indices (Fig 6-1 and 6-2).

As a rule, glaucomatous visual defects can be seen in probability maps (Fig. 6D,F) before they can be clearly discerned in numerical maps (Fig. 6C,E) or the grey or colour scale of the measured threshold values (Fig. 6B). The best aid in interpreting results is provided by a probability map that has been adjusted for both age-related and general loss (Fig. 6F);

such a map can reveal the location and extent of glaucomatous defects without being disturbed by media opacities such as cataract. The Humphrey Glaucoma Hemifield Test (Fig. 6G) and the Octopus cumulative defect curve (Fig. 6H) are two other indices that can facilitate detection of early glaucomatous visual field damage. Global visual field indices like mean deviation (MD), pattern standard deviation (PSD) and the visual field index (VFI) on the Humphrey perimeter, mean defect (MD) and loss variance (LV) on the Octopus prime-

ter are not suitable for making a diagnosis.

The reliability parameters false-positive (FP) responses, false-negative (FN) responses and fixation losses (FL) (Fig. 6I) are meant to show how reliably a patient performs during a test. FP responses indicate that the person being tested pressed the button too often, that is, that he or she responded even if no stimulus was shown. Today, the upper limit of reliability is set at 15%, and that level is based on data representing a large normal population ($n \approx 330$) (Bengtsson & Heijl 2000a). Visual fields with more than 15% FP responses cannot be evaluated, and a patient with such results should be given new and probably different instructions on how to perform the test. A test with a large proportion of FN responses suggests that the patient did not react to visible stimuli. However, the method used to measure FN responses cannot be applied to individuals who have visual field defects (Katz & Sommer 1988; Bengtsson & Heijl 2000b), and thus a high rate of such responses by patients with glaucoma should be disregarded. On the other hand, the rate of FN responses should be low for people who have healthy eyes with a normal visual field.

Probability maps, particularly those that are adjusted for both age and general loss (often caused by cataract), provide valuable information about the extent and location of visual field defects, and these are called either pattern deviation probability maps (Humphrey) or corrected probability maps (Octopus).

Follow-up: interpretation of visual field tests and progression

In most cases, several visual field tests are needed to correctly estimate the rate of visual field progression or to ascertain whether progression has occurred. Test-retest variability is greater in a glaucomatous visual field than in a healthy one (i.e. reproducibility is poorer in glaucoma), which explains why a number of examinations must be performed to achieve satisfactory precision regarding progression. Sudden large changes are rare in glaucoma, but it can appear that such events have occurred if visual field testing is not performed often enough.

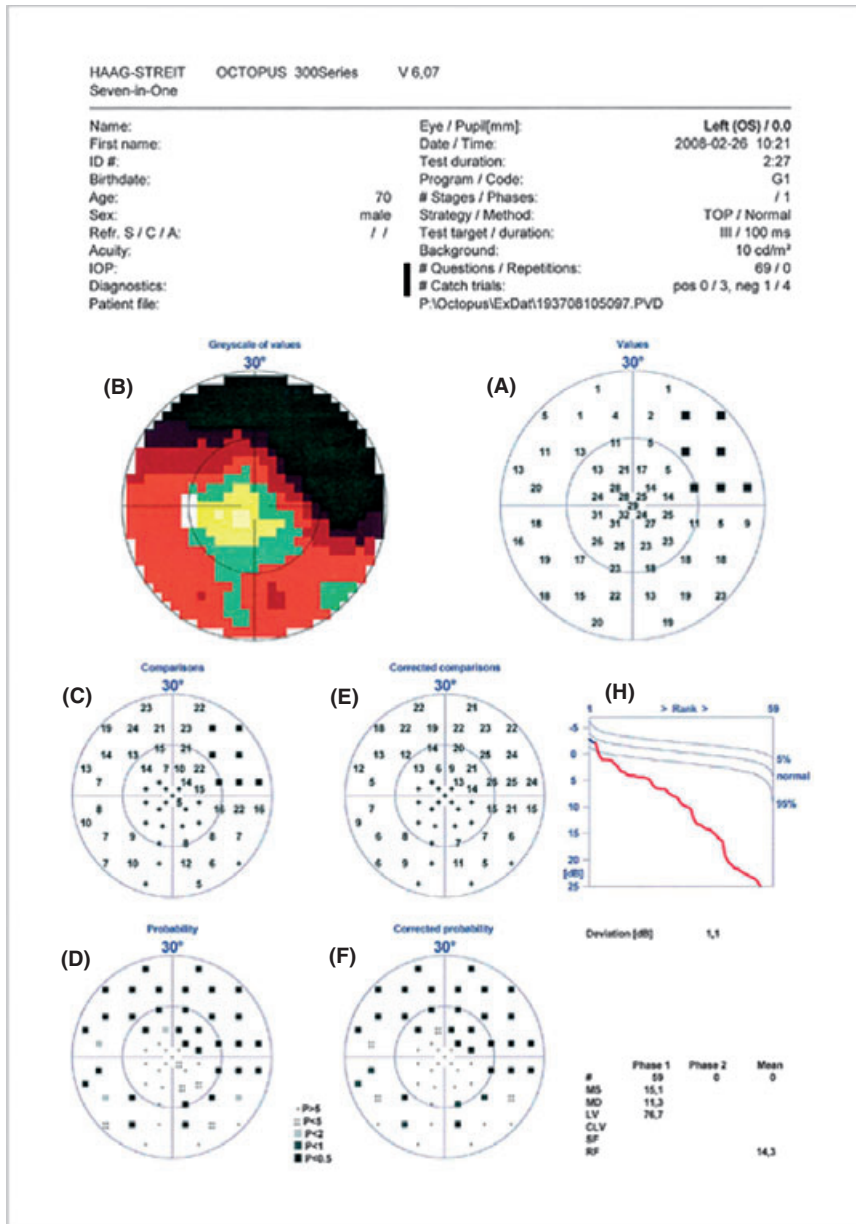


Fig. 6-2. Seven-in-One printout from an Octopus perimeter. A) Numerical threshold values. B) Colour scale map of measured threshold values. C and E) Deviation from normal age-adjusted threshold values. D and F) Probability maps that highlight test points showing a significant loss compared to the normal age-related level after adjustment for general lowering of the threshold sensitivities. H) Octopus cumulative defect curve. I) Reliability index, that is, false-positive and false negative responses and fixation losses.

Of course, visual field progression can be subjectively estimated simply by skimming through a pile of papers or scrolling on a computer screen. Unfortunately, such a method is insensitive, and there is also substantial variation between the people who use it (Viswanathan et al. 2003). Both Humphrey and Octopus perimeters have built-in software to facilitate interpretation of visual field series, and these programmes cover chiefly two methods of evaluating progres-

sion: event analysis, which reveals whether progression has occurred; trend analysis, which quantifies and illustrates the rate of progression.

Use of the Humphrey Glaucoma Hemifield Test or the Octopus cumulative defect curve facilitates diagnosis of glaucoma

Glaucomatous visual fields with a high proportion of FN responses should not be discarded, whereas fields with more than 15% FP responses are unreliable

Event analysis

The glaucoma change probability maps of the Humphrey perimeter (Fig. 7) flag test points (triangles) if they show significant deterioration ($p < 5\%$), that is, if they indicate more deterioration than expected based on the random test-retest variability. Since the visual field test includes a relatively large number of test points, and each test point is at 5% risk of being falsely flagged, it is possible that the analysis will flag progression at a few test points by chance only. If, however, the same triangles appear in two consecutive visual fields, it is more likely that progression has actually occurred, and the certainty is even greater if they appear in three or more consecutive tests. Therefore, the triangles recorded on different occasions are illustrated in different ways: in white at the first event, in black/-white (bisected) if apparent worsening as compared to baseline is present in two consecutive tests, and in black on the third and subsequent tests. In addition, progression is defined as stipulated in the Early Manifest Glaucoma Trial (Leske et al. 1999): a text message indicating possible progression is displayed when there are three or more black/white triangles, and a message indicating likely progression is displayed when there are three or more black triangles.

Event analyses are used to detect visual field progression and significant deterioration at test points (Humphrey perimeter)

Trend analysis

A global index that summarizes and plots the results of visual field tests over time can illustrate the trend in field progression. The Humphrey perimeter has an index called mean deviation (MD), which gives a value that represents the mean deviation from the normal age-adjusted sensitivity at all test points. The corresponding index on the Octopus perimeter is called mean defect (also designated MD), which describes the difference between the mean sensitivity and the normal age-adjusted visual field. Under the assumption that progression is linear, a coefficient is calculated that shows the extent of the annual deterioration in MD of the visual field. This coefficient is a measure of the rate of

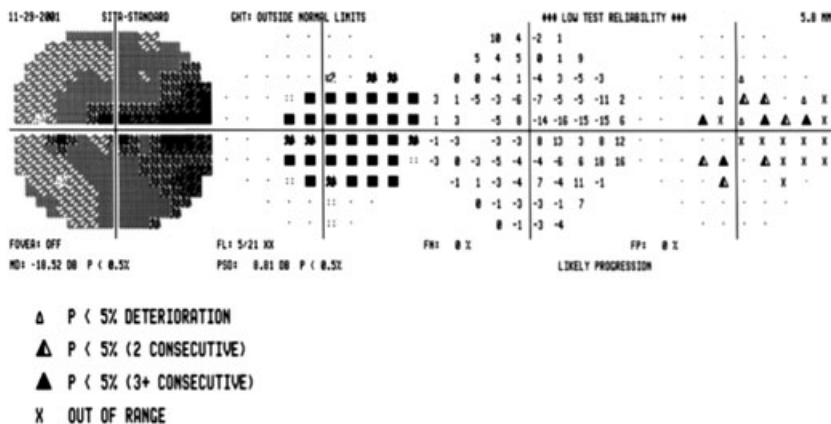


Fig. 7. The event analysis of the Humphrey perimeter. To the right is a glaucoma change probability map with triangles at points showing significant deterioration. The triangles vary in appearance, and those in black indicate that significant progression was flagged on three consecutive tests.

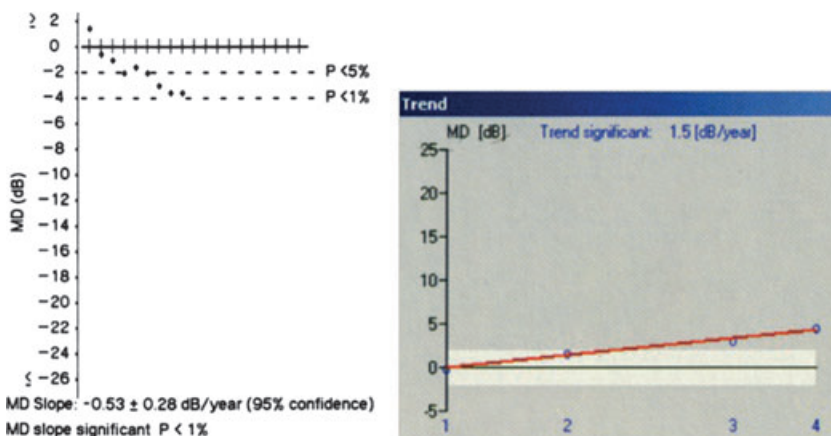


Fig. 8. The rate of progression according to the global MD index over time in Humphrey (left) and Octopus (right) perimetry. The eye tested on the Humphrey instrument showed a total loss of 0.5 dB/year in age-adjusted mean sensitivity, whereas the mean defect in the eye tested on the Octopus perimeter increased by 1.5 dB/year (i.e. progressed three times faster).

progression (Fig. 8), which varies substantially between patients with glaucoma. Knowledge of the rate of progression helps us determine whether there is a risk that a person with glaucoma will develop visual disability during his/her lifetime. The rate of progression is an important factor in management of patients with glaucoma (see the section headed *Rate of progression* p. 23).

There are also other global indices based on measures of variability, such as standard deviation and variance (Pattern Standard Deviation in Humphrey perimetry and Loss Variance in Octopus perimetry). Both Octopus and Humphrey perimeters provide graphs of these indices that are similar to the graphs of MD, but they do not indicate the rate of progression. They

show the course of intratest variability of measured threshold sensitivities, which is not linear. Standard deviation/variance is small for both a normal visual field and one approaching blindness. Trend analysis of these indices, therefore, cannot contribute to the assessment of progression rate.

The Humphrey perimeter includes the new global Visual Field Index (VFI) (Fig. 9), which, compared to MD, has the advantage of being much less sensitive to the effects of increasing cataract severity. The Octopus perimeter has two new indices called diffuse defect (DD) and abnormal response area (ARA), also designated local defect), both of which are used to describe trends. DD illustrates development of the diffuse visual field loss over time and is sensitive to cataract. ARA reveals development of local defects over time, and it is no longer applicable when local defects occupy more than 50% of the total visual field. ARA correlates well with LV and is also nonlinear over time.

In some ways, trend analysis is more important than event analysis. By definition, glaucoma is a progressive disease, which means that deterioration can be expected in most patients with

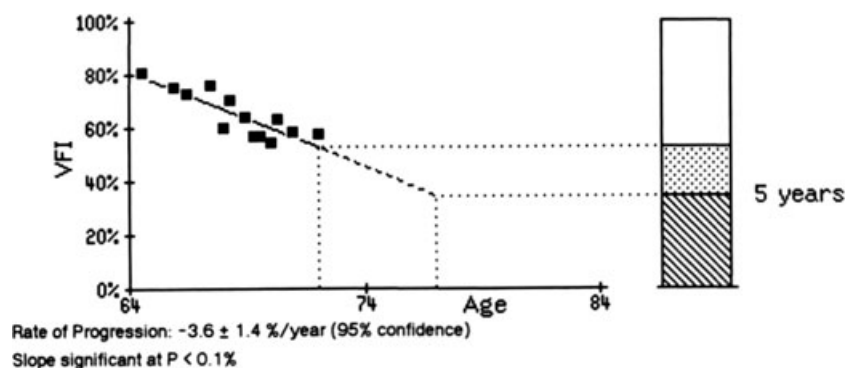


Fig. 9. Rate of progression with the new VFI in the Humphrey perimeter. The VFI is expressed as per cent of a normal age-adjusted visual field: 100% is a normal field and 0% a perimetrically blind field. This example shows that 80% of a full field remains and that the patient was 64 years old at the time for diagnosis, and is now 71. With the treatment regimen prescribed, this patient has lost 3.6% of visual function each year. Today, the patient is 72 years old and approximately 60% of the visual field remains. If this trend continues, only about 40% will remain by the time the patient reaches the age of 77.

glaucoma, if they are followed for a sufficiently long period and are tested using methods that allow reasonably sensitive measurement of progression. Trend analysis can identify patients who exhibit rapid progression and require special attention and intensified treatment. It can also reveal patients who can be examined less frequently, because their disease is advancing slowly and it appears that the efficacy of the treatment they are receiving is satisfactory. Nevertheless, compared to trend analysis, event analysis can detect progression earlier, and thus it is valuable in management of newly diagnosed patients with glaucoma. Severe and acute changes are very rare in glaucoma and usually depend on some other factor, such as stroke or retinal vessel occlusion. Obviously, both event and trend analysis are affected by such visual field damage and cannot distinguish it from glaucoma. Accordingly, in cases involving substantial acute changes, the examiner should suspect some other disease and, depending on the patient's condition, create a new visual field baseline to allow continued monitoring of glaucoma progression. Event and trend analysis complement each other: both use the same visual field tests, and both analyses are available in the perimeters.

High-pass resolution (ring) perimetry

High-pass resolution perimetry (HRP) was introduced in 1987 (Frisén 1987) as a test method that would be better correlated with the density of retinal ganglion cells compared to conventional perimetry. This test also had the benefit of being fast and patient friendly, although the time advantage compared to traditional perimetry was later reduced by the development of SAP.

The method is called high-pass resolution or ring perimetry, because it uses low-contrast, high-spatial-frequency-filtered, ring-shaped test targets. The targets vary in size during the examination. The results are presented in a straightforward manner: the smaller the rings, the better the visual function. In a normal visual field, the rings are small in the central test locations and are successively larger towards the periphery. Deviation from the expected progression is con-

sidered abnormal. Testing is facilitated by various indices in the same way as in SAP. High-pass resolution perimetry global deviation is a measure of the total age-related deviation, which corresponds to the Humphrey MD. In the same way, local deviation corresponds to Humphrey PSD and Octopus LV. High-pass resolution perimetry has no equivalent to the Humphrey Glaucoma Hemifield Test. However, an older version of ring perimetry includes an instrumental assessment to determine whether a visual field is normal, whereas such a tool is not included in the Windows-based HRP. Longitudinal follow-up can be achieved as in SAP by printing a series of visual fields and obtaining a plot of the global deviation against time. Notwithstanding, the ring perimeter lacks the newer, more detailed methods for evaluating glaucoma progression, which are available primarily in the Humphrey perimeter.

A number of studies have indicated that HRP is comparable to SAP with regard to the capacity to detect early glaucomatous damage and progression of glaucoma (Martinez et al. 1995; Chauhan et al. 1999; Sample et al. 2006). No larger investigations have been performed on this topic.

Intraocular pressure and tonometry

It is now accepted that IOP affects the development (Kass et al. 2002) and the progression (Collaborative Normal-Tension Glaucoma Study Group, 1998a,b; Heijl et al. 2002) of glaucoma: the higher the pressure, the greater the risk of both occurrence and progression of the disease. All available treatments are intended to lower IOP, and therefore measurement of IOP is always included in the diagnostic and follow-up examinations of patients with suspected or confirmed glaucoma.

Normal intraocular pressure

From a functional perspective, all levels of IOP that are not deleterious for the eye are 'normal'. However, the level that is harmful varies between individuals, and thus it is often impossible to unambiguously determine whether IOP can be considered normal after only a few measurement occasions. The clinically less relevant cut-off value of 21 mmHg emanated

from numerous population studies in which the mean pressure was found to be approximately 16 mmHg in adults, with a standard deviation of 2.5 mmHg (Schiose 1990). However, among people over the age of 40, IOP is not normally distributed, but there is a skewness towards higher values. Since glaucoma can develop at all IOP levels, measurement of IOP alone cannot suffice in glaucoma screening, although more attention should be given to patients with high pressure.

Intraocular pressure is lower in children than in adults. The pressure is 6–8 mmHg at birth and increases by approximately 1 mmHg every other year until the age of about 12 years (European Glaucoma Society 2008, p. 61). In healthy individuals, the IOP is fairly stable or rises somewhat with increasing age (Gabelt & Kaufman 2005), perhaps a millimetre each decade after the age of 40 (Martin 1992).

Variation in intraocular pressure

Measurement of IOP provides a snapshot of the level at the time of examination, but the pressure actually varies with time. Diurnal fluctuations are proportional to the level of IOP (Bengtsson & Heijl 2005b). In most studies, such fluctuations are in the range ≤ 6 mm in normal individuals (Shield 2005), whereas the average distribution is broader in patients with elevated IOP. Knowledge of variation in IOP levels is of uncertain value.

To gain an understanding of the untreated IOP, repeated measurements can be performed before initiating therapy. This is usually possible in patients with chronic open-angle glaucoma, because the course of the disease is slow in most cases. Owing to the diurnal variation in pressure, it can be beneficial to make several measurements at different time-points. It is recommended that the time at which each measurement is performed be recorded, in particular to enable comparison of the results with those obtained in subsequent examinations.

Factors that influence intraocular pressure

Many different factors affect IOP.

- (1) External pressure on the eye: for example, caused by eyelid position, squinting, or vigorous crying in babies.

- (2) Episcleral venous pressure: can be raised by actions such as the Valsalva manoeuvre or wearing of a tight collar or necktie, which increases IOP.
- (3) Eye or head position: IOP is often slightly elevated during up-gaze or downgaze, and it is higher when leaning backwards than when sitting (Anderson & Grant 1973; Jain & Marmion 1976; Krieglstein et al. 1976), and even higher when doing a headstand (Weinreb et al. 1984).
- (4) Repeated IOP measurements: will lower IOP if performed over a short period of time.
- (5) Certain drugs: IOP is raised by LSD but lowered by alcohol and cannabinoids.
- (6) The cardiac cycle: causes changes known as ocular pulse amplitude (OPA); these are usually in the range 1–2 mmHg, although there can be larger differences between diastole and systole.
- (7) General anaesthesia: in children, it is common to use fluorinated hydrocarbons such as sevoflurane and halothane (inhalation anaesthetics), which lower IOP, or ketamine (e.g. intramuscular administration), which increases IOP. After procedures in which intravitreal gases, for example, SF₆ or perfluorocarbon, are used, nitrous oxide should not be administered because it can diffuse into closed spaces, expand and interact with the intravitreal gas to markedly increase IOP (Yang et al. 2002; Åström et al. 2003).

Methods

Measurement of IOP (tonometry) for clinical purposes is always taken from outside the eye, and thus the results obtained represent an estimation of the actual pressure inside the eye. Four fundamentally different measurement methods are in use today. Traditionally, we differ between *indentation* tonometry and *applanation* tonometry, which deform the cornea through controlled force achieved by either indentation (depression) or applanation (flattening), respectively. Many tonometers combine both these principles. Moreover, in recent years,

other techniques have been introduced that are based on two additional concepts called *contour-matching* and *rebound* tonometry. An overview of the methods used to measure IOP was published in the journal *Survey of Ophthalmology* in 2008 (Kniestedt et al. 2008).

The Goldmann applanation tonometer

Goldmann applanation tonometry using a slit-lamp microscope is still the gold standard for measuring IOP, and thus all new instruments developed for this purpose are compared with the Goldmann tonometer (ISO 1997, 2009). The Goldmann instrument is based on the Imbert-Fick law: $P = F/A$ (P , pressure; F , force; A , area). The measuring prism has an applanating area with a diameter of 3.06 mm. The built-in duplication system of the prism divides the fluorescein-stained tear film into two semicircles. Magnification in the microscope and the vernier reading of the inner margins of the semicircles contribute to the precision of the Goldmann method.

Procedure for measuring IOP with a Goldmann applanation tonometer

- (1) The examination is performed with the patient seated at the slit-lamp microscope.
- (2) If there is not a high degree of corneal astigmatism, place the measuring prism in its holder so that the white line is aligned with the '0' or the 180° marking.
- (3) Use 10× magnification, blue light and a wide slit and angle the beam from the side to achieve maximum illumination of the measuring prism.
- (4) To anaesthetize the surface of the eye and dye the tear film, either administer one drop of combined anaesthetic-fluorescein

or give the anaesthetic and dye separately.

- (5) Set the force knob to 10 mmHg.
- (6) Move the tonometer towards the eye so that the measuring prism comes in contact with the centre of the cornea.
- (7) Adjust the microscope vertically and horizontally until the two semicircles appear to be equal in size when looking through the oculars. Adjust the force knob so that the inner edges of the two semicircles are just touching (Fig. 10).
- (8) Read the value on the force knob and multiply it by 10 to obtain the IOP in mmHg.

Sources of error

Amount of fluorescein

Instilling an excessive amount of fluorescein in the eye results in thick semicircles and a falsely high-pressure measurement. Conversely, an insufficient amount of fluorescein gives thin semicircles and a falsely low IOP reading.

Semicircles not the same size

If vertical or horizontal adjustment is incorrect (i.e. the tonometer cone is not centred), the semicircles will not be equal in size, which will increase volume displacement and give a falsely high IOP measurement.

Central corneal thickness

A thick cornea renders a falsely high IOP value, and a thin cornea gives a falsely low measurement.

Corneal oedema

Corneal oedema does make the cornea thicker but also changes its texture, making it 'spongier'. The latter effect has a substantial impact on IOP measurement, yielding falsely low values (Whitacre & Stein 1993).



Fig. 10. The semicircles in Goldmann tonometry.

Corneal curvature

Increased refractive power leads to falsely high IOP measurements and reduced refractive power results in falsely low values. A rule of thumb is that a shift in refractive power of 3 dioptres leads to a change in IOP of approximately 1 mmHg.

Astigmatism

If there is pronounced corneal astigmatism ($>3D$), it is recommended that the measuring prism be rotated so that the negative cylinder axis is aligned with the red marking on the holder (i.e. 43°). A simpler approach is to take two pressure readings, one horizontal and one vertical, and then calculate the mean value.

Refractive surgery

Methods involving modification of the cornea to correct myopia (e.g. PRK, LASIK and LASEK) lead to underestimation of IOP (Rosa et al. 1998; Jóhannesson et al. 2012).

Reproducibility

Measurement results for an individual eye vary between repeated examinations. If the same examiner measures twice on a particular eye, the results will differ by 2 mmHg or more in 8% of the cases. The corresponding proportion will be 40% if two different examiners conduct the measurements (Thorburn 1978).

Perkins[®] tonometer

The Perkins tonometer is a hand-held, portable version of the Goldmann instrument that can be used with the patient in a sitting or supine position.

'Air-puff' or noncontact tonometry

This method uses an air jet of increasing intensity to flatten the cornea. It is performed without anaesthesia. The measurements are of such short duration that the ocular pulse exerts a significant effect. One of the drawbacks of noncontact tonometry (NCT) is that the results are more variable.

Ocular response analyser[®]

The Ocular response analyzer (ORA) is a further development of air-puff tonometry. It also measures corneal hysteresis, which in this context describes the viscoelastic properties of the cornea.

Tonopen[®]

The Tonopen is a hand-held portable device. It is brought in contact with the cornea, which is simultaneously applanated by the central plunger. The force required to keep the plunger at the same level as the foot plate is related to the IOP. Each measurement requires several applanations, and topical anaesthesia is necessary.

Dynamic contour tonometry/ Pascal[®]

The Dynamic contour tonometry (DCT) instrument has a design similar to that of the Goldmann tonometer and is mounted on a biomicroscope. It has been claimed that this method is less influenced by corneal properties. The tonometer cone matches the contour of the cornea, and the central piezoresistive pressure sensor, measuring the IOP, is thereby less influenced by extraneous forces. Even though it is the diastolic IOP that is measured, there is a tendency for assessments to give higher values than those obtained by Goldmann tonometry. Furthermore, differences are greater at lower pressures (Schneider & Grehn 2006; Jóhannesson et al. 2008). Pressure is recorded continuously, and hence it is possible to monitor OPA. Some examiners find this technique more difficult to use compared with other methods of measuring IOP (Chihara 2008; Jóhannesson et al. 2008).

Rebound tonometry/Icare[®]

Icare is a hand-held portable tonometer that measures IOP by rapidly propelling a very thin metal probe out of a magnetic field and bouncing it on the cornea. The change in the speed of the probe as it bounces back is related to the IOP. On average, this method gives higher IOP values compared to Goldmann tonometry (ElMallah & Asrani 2008; Jóhannesson et al. 2008). It can be performed without anaesthesia, and that feature, together with the relative simplicity of the technique, has made rebound tonometry a popular choice in paediatric care.

Corneal thickness and pachymetry

Corneal thickness is known to affect the results of IOP measurement (Goldmann 1959; Doughty & Zaman 2000). A thin cornea gives a falsely low value and is also considered to increase the

risk of developing glaucoma (Gordon et al. 2002). A meta-analysis has shown that a deviation of 10% from the mean corneal thickness of $544 \mu\text{m}$ (measured by ultrasound pachymetry) represents a pressure difference of 3.4 mmHg in healthy individuals (Doughty & Zaman 2000). According to another model called the Dresdner correction table (Kohlhaas et al. 2006), which is based on 125 cannulated eyes, the applanation IOP value that is obtained should be adjusted by approximately 1 mmHg for every $25 \mu\text{m}$ of deviation from $550 \mu\text{m}$. However, the results of different studies vary substantially, and hence considerable caution should be observed when using any of the numerous formulas that exist for adjusting IOP in relation to corneal thickness.

There are many methods for measuring corneal thickness, although ultrasound pachymetry is the most widely applied technique when there is suspicion of glaucoma. It is also possible to employ new instruments such as Orbscan[®] or a Scheimpflug camera, which not only measure corneal thickness, but also reveal the appearance of the cornea by use of topographic and tomographic imaging. However, the results of different measurement methods are not completely comparable.

Goldmann applanation tonometry is still the gold standard for measuring intraocular pressure
Avoid frequent switching between methods
Measurement of corneal thickness is a simple procedure that can be performed with high precision

The cornea is thinnest at its centre and thicker in the periphery. If not otherwise stated, information given usually concerns central corneal thickness (CCT). It has been found that corneal thickness is fairly stable throughout life in white adults (Doughty & Zaman 2000). Thus, it seems that a single measurement should suffice when considering glaucoma, as long as there is no reason to suspect corneal oedema.

Methods

Ultrasound pachymetry

Many different instruments are available to conduct ultrasound pachyme-

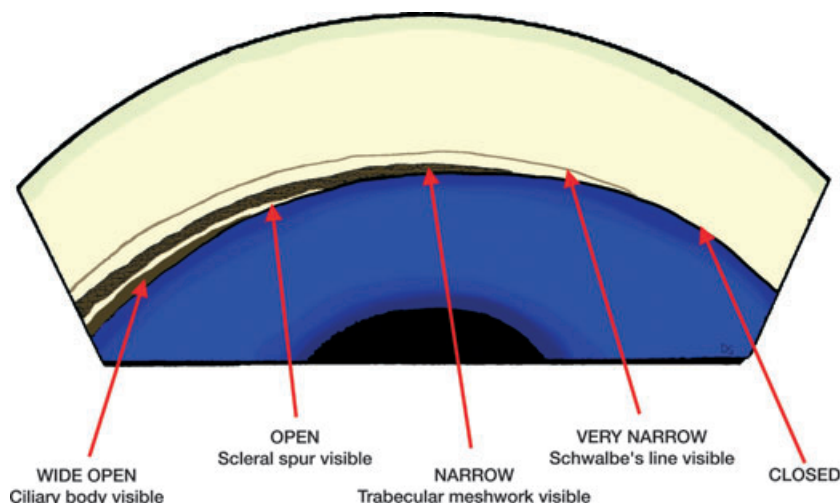


Fig. 11. Angle width in gonioscopy.

try. The probe is placed on the cornea, and the time difference between the echoes from the anterior and posterior corneal surfaces is determined. This difference is directly related to the thickness of the cornea.

Advantages

Easy to use.
Most instruments are portable.

Disadvantages

Requires topical anaesthesia.
The probe must be cleaned and sterilized between patients.

Orbscan®—slit-scan pachymetry

Orbscan slit-scan pachymetry is an imaging method. Measurement is achieved by use of a computer-based platform that controls a projection (slit-scan) and reflection (placido) system. This system provides images of the anterior as well as the posterior portion of the cornea, and thus it illustrates both the corneal curvature and the corneal thickness.

Advantages

No anaesthesia required.
No probe to clean and sterilize.

Disadvantages

Patient fixation necessary.
Instruments not portable and more expensive.

Corneal thickness is more important in ocular hypertension than in manifest glaucoma

In some cases it can be of value to roughly classify the cornea as thin, normal or thick, particularly in patients with ocular hypertension. It is probably more important to treat eyes with ocular hypertension if the cornea is thin than if it is thick. However, measurement of corneal thickness is of uncertain value in eyes with manifest glaucoma, because development of the disease *per se* will already have indicated a pressure that must be lowered. A simple rule of thumb is that a thin cornea measures $< 500 \mu\text{m}$ and a thick cornea $> 600 \mu\text{m}$.

Future aspects

The current widespread interest in research on the biomechanical properties of the eye has emerged from the results of the Ocular Hypertension Treatment Study (Kass et al. 2002) and the expansion of refractive surgery. In addition to corneal thickness, several other factors affect measurement of IOP. Instruments that can measure OPA and viscoelastic properties of the cornea are already on the market, although their clinical usefulness is not yet clear.

Gonioscopy

Methods

Indirect gonioscopy is conducted in a slit-lamp microscope to examine the anterior chamber angle. There are two main methods called static gonioscopy and dynamic (indentation) gonioscopy (Fig. 11). Examination of the chamber angle should always be performed in a dark room using an illumination beam that is as narrow as possible.

Static gonioscopy

Static gonioscopy is the most widely used examination method. It is performed using a Goldmann gonioscopy lens or some other lens of that type. The gonioscopy lens has a large contact area.

Advantages

Excellent image quality.
Easy to learn the technique.

Disadvantages

Contact fluid must be used.
Indentation not possible.

Dynamic gonioscopy

This method is most suitable in routine practice, but it is difficult to master. A four-mirror lens is used, which has a small corneal contact area.

Advantages

Contact fluid not required.
Indentation can be done.

Disadvantages

Too much pressure can be applied unintentionally, which can reduce image quality and cause inadvertent opening of a closed chamber angle.

Both methods work well in most cases, although indentation gonioscopy is essentially a prerequisite for correct diagnosis of some conditions, particularly plateau iris syndrome.

All patients with ocular hypertension or suspected or manifest glaucoma should be examined using van Herick's test to assess anterior chamber depth

Gonioscopy should be performed if the depth of the peripheral anterior chamber is less than half the thickness of the cornea or if there are other reasons to suspect angle-closure glaucoma

Assessment of anterior chamber depth by van Herick's method

The test developed by van Herick et al. (1969) allows fast and easy evaluation of the depth of the anterior chamber (Fig. 12, Table 1). When performed correctly (i.e. in a dark room with the narrowest possible slit beam and no light through the pupil), this is an excellent technique that can be used instead of gonioscopy in eyes with normal anterior chamber depth and no suspicion of angle-closure

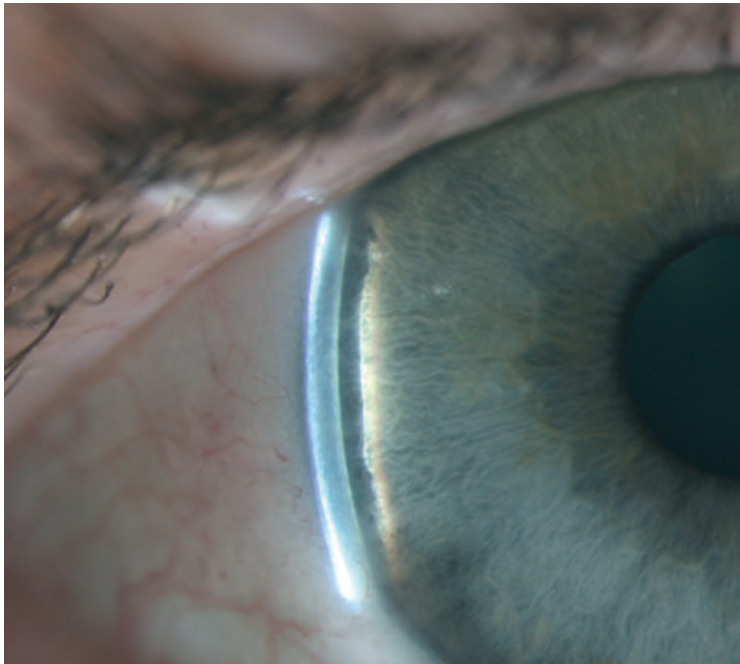


Fig. 12. Assessment of the peripheral anterior chamber depth using van Herick's test. In this case, the peripheral chamber depth is greater than half the thickness of the cornea.

Table 1. Estimation of the depth of the anterior chamber according to van Herick.

Peripheral anterior chamber depth compared with corneal thickness	Degree (Shaffer)
$\geq 1/2$	4
$1/4-1/2$	3
$1/4$	2
$< 1/4$	1
0	0

glaucoma (e.g. no pressure peaks or pain). Gonioscopy is recommended if the peripheral chamber depth is less than half the thickness of the cornea. If the depth is less than one-fourth of the corneal thickness, gonioscopy must be done on at least one occasion during the course of the investigation.

The website <http://www.gonioscopy.org> provides all pertinent information about gonioscopy and is highly recommended.

4 Principles for Management of Glaucoma

Making a diagnosis

In many cases, confirming a diagnosis of glaucoma is a straightforward process based on typical changes in both the optic disc and the visual field. However, it can be difficult or nearly impossible to reach a diagnosis in some

patients, and factors that can hamper this work include the following:

- (1) Abnormal appearance of the optic disc (often very small or very large)
- (2) Optic disc anomalies (e.g. hypoplasia, myopia or optic disc drusen)
- (3) Media opacities
- (4) Visual field measurement impossible (in children, people with dementia or the very elderly)
- (5) Previous eye diseases (e.g. retinal vessel occlusions)

Notwithstanding, a diagnosis is usually confirmed by observation of combined damage to the optic nerve and visual field, in many cases supported by elevated IOP. To achieve a definite diagnosis, it can be stipulated that the damage must be progressive. However, this principle cannot be applied in clinical practice, because it would take too long to confirm progression.

Optic nerve damage with a normal visual field

If it is found that the optic disc shows glaucomatous damage despite normal results of a visual field examination, the following should be considered:

- (1) Is the optic disc (and its cup) unusually large? Such discs represent a common explanation for

over-diagnosis of glaucoma (Heijl & Mölder 1993). Are there convincing localized optic disc findings, such as notching or rim loss?

- (2) Is the visual field examination reliable? (This issue is discussed in Chapter 3.) A large proportion of false-positive (FP) responses give unreliable visual field results, although a high rate of false-negative (FN) responses does not indicate an unreliable visual field in glaucomatous eyes.

Glaucoma can be present even if the results of visual field testing are normal. Confirmation of such 'preperimetric' glaucoma can be difficult and is based entirely on evaluation of the appearance of the optic disc and/or the retinal nerve fibre layer. Obviously, IOP plays an important role in this context: elevated pressure increases the likelihood of glaucoma.

In general, a large optic disc will have a large physiologic cup, and a small optic disc will have a small physiologic cup. Therefore, assessment of disc size is fundamental in glaucoma diagnostics.

If there is doubt regarding the presence of glaucoma, it is acceptable to wait and follow development in most patients, possibly with the exception of young people or those who have markedly elevated IOP. Indeed, if the IOP is normal or only slightly increased, there is good reason to defer treatment.

In almost all cases, a diagnosis of glaucoma is based on both optic disc and visual field damage

Visual field damage with a normal optic nerve

When evaluating the results of a visual field test, it is important to bear in mind that appearance of the visual field is never completely pathognomonic of glaucoma. Arcuate nasal defects that respect the nasal horizontal meridian are nearly always caused by glaucoma, especially if they are found in both the superior and the inferior half of the field. Nonetheless, even such visual fields cannot with absolute certainty be correlated with glaucoma disease.

If the visual field exhibits changes that concur with glaucoma-induced

damage but the optic nerve appears normal, the following should be taken into consideration:

- (1) Is the optic disc unusually small? If so, is the cup disproportionately large in relation to the diameter of the optic disc? A small disc generally has a small physiologic cup or no cup at all, and even a small cup can be associated with glaucomatous damage.
- (2) Are there signs of optic disc drusen or other disc anomalies?
- (3) Are there signs of present or past retinal disease?
- (4) Is the eye severely myopic? White atrophic retinal areas in such eyes correspond with definite visual field defects.
- (5) Is it possible to assess the retinal nerve fibre layer? Under favourable conditions, damage to the nerve fibre layer can be detected even if the optic disc appears normal.
- (6) Was the patient co-operative during visual field testing? (See above and Chapter 3.)
- (7) Was the examination performed using very inaccurate correction (e.g. +3 instead of -3)? Such an error will result in a general decrease in sensitivity.
- (8) Are there pronounced changes in the ocular media (e.g. cataract)? Cataract does not give rise to local visual field defects (Hayashi et al. 2001) but does cause a general reduction in sensitivity.
- (9) A relative afferent pupil defect demonstrated by a swinging flashlight test indicates neuronal injury. If there is asymmetric optic nerve damage, there is often a relative afferent pupil defect in the damaged or most damaged eye. Inasmuch as glaucoma is seldom strictly symmetrical, this also applies to bilateral disease (Kala-boukhova et al. 2007).

Instrumental examination of optic disc topography and thickness of the retinal nerve fibre layer

As mentioned in the previous chapter (see p. 11), investigation of structural changes in the appearance of the optic disc or the retinal nerve fibre layer is of considerable value in diagnosis and/or monitoring of glaucoma. However,

computer-based examination of the disc and the nerve fibre layer (e.g. using HRT, GDx, or OCT) offers only moderate diagnostic accuracy (SBU, 2008), which is nonetheless comparable to that achieved by glaucoma experts. Reliable long-term follow-up data are lacking with regard to the capacity of available instruments to detect progression of glaucoma.

Radiological investigations

Today, a large number of CT and MRI examinations are performed on patients with suspected glaucoma, particularly if they have normal IOP. Those investigations nearly always prove to be unnecessary, and they are also experienced as unpleasant by the patients and entail considerable cost to the health care system. On the other hand, it is not unusual that conditions involving compression of the optic nerve or chiasm are erroneously diagnosed as glaucoma, which in some cases results in visual impairment that might have been prevented by correct diagnosis and treatment. Presence of optic disc changes that are typical of glaucoma should be a prerequisite for confirming a diagnosis of normal-tension glaucoma (see p. 10). Ordinarily, in the presence of such optic disc changes, a radiographic investigation is *not* indicated (Greenfield 1999); normal-tension glaucoma is not a diagnosis of exclusion. Visual field defects in the absence of such optic nerve damage should lead to further investigation, which can, among other things, include radiographic examination. As already mentioned, in cases involving suspected optic nerve damage, it is important to determine whether a relative afferent pupil defect is present. If there is uncertainty regarding occurrence of glaucomatous optic nerve damage, before deciding whether a radiological examination is necessary, it is advisable to perform optic disc photography, preferably including the opinions of one or more additional examiners.

A diagnosis of low or normal-tension glaucoma is not a diagnosis of exclusion, that is, it can be made without more extensive investigation in patients with visual field defects and a glaucomatous optic disc

General treatment principles

Goal of treatment

The goal of glaucoma treatment is to preserve the patient's visual function and quality of life (QoL), not to maintain IOP below a certain level. Studies of QoL in glaucoma have often shown that definite, measurable effects on QoL are relatively small and do not occur until there are already extensive visual field defects in the best eye (Wändell et al. 1997; Hyman et al. 2005). However, other investigators (Varma et al. 2006) have suggested that even minor field defects have some impact on QoL, and increased risk of slip-and-fall and traffic accidents has been observed in people with minor to moderate loss of visual function (McGwin et al. 2005; Coleman et al. 2007; Freeman et al. 2007; Haymes et al. 2007, 2008). Also, the right to drive a motor vehicle can be affected by even relatively minor visual field damage, if both eyes show field defects.

If the aim of treatment is to maintain QoL, it is obvious that efforts should be made to ensure that patients do not lose 50% or more of the field of vision in the best eye during their lifetime. It is likely that this goal is not sufficiently stringent because of the above-mentioned factors. Moreover, the instruments for measuring QoL that are available today may be far too insensitive.

Treatment methods and effects

It is now well established that lowering IOP reduces the risk of visual field loss and decreases the rate of disease progression (Collaborative Normal-Tension Glaucoma Study Group, 1998b; Heijl et al. 2002). No such effects have been found for other therapeutic approaches, such as neuroprotection or the use of saline or nifedipine to raise blood pressure in patients with low-tension glaucoma.

Lowering IOP is effective in treating glaucoma, both in patients whose untreated pressure is higher than the statistically normal range and in cases of normal-tension glaucoma (Collaborative Normal-Tension Glaucoma Study Group, 1998b; Heijl et al. 2002). Reducing IOP also lessens the risk of developing glaucoma in patients with ocular hypertension (Kass et al. 2002).

The effect of reducing IOP is greater than previously assumed. In the Early Manifest Glaucoma Trial (Leske et al. 2003), it was found that every 1-mmHg decrease in pressure lowered the risk of progression by 10–14%. Other studies have obtained similar reduction in risk per mmHg of pressure reduction (Chauhan et al. 2008b) and also in ocular hypertension (Gordon et al. 2002; Miglior et al. 2007a,b). Obviously, this does not imply that it is always best to try to lower IOP as much as possible. However, studies in the literature suggest that if the IOP reduction achieved is not adequate (e.g. because progression is too rapid at that IOP level), even reducing the pressure a few mmHg extra may be clearly beneficial.

The goal of treatment in glaucoma is to preserve the patient's visual function and quality of life

Reduction of intraocular pressure, even below statistically normal levels, can retard progression of glaucoma

It seems that every 1-mmHg decrease in pressure can have an impact

Risk analysis and target intraocular pressure

The risk of blindness, disability, or reduced QoL is greatest in patients who already have extensive visual field damage in both eyes at the time of diagnosis. Conversely, the risk is low in older patients who have limited or unilateral visual impairment. Clearly, age plays an important role, and thus younger patients with visual field defects should always be regarded as being at risk of serious visual impairment during their lifetime. The rate of progression in the individual patient will not be measurable until several years have passed, but can then be used to calculate the risk of future visual incapacity.

Increased intraocular pressure is another important factor. Patients with higher IOP are at increased risk of progression compared to patients with lower IOP. It is also known that the natural history of progression of open-angle glaucoma is much more favourable in normal-tension glaucoma than for primary open-angle glaucoma with elevated IOP (Heijl et al., 2009). Additional independent

risk factors include exfoliation syndrome and optic disc haemorrhages (cf. pp. 21, 27, and 86).

The target pressure depends on all of the mentioned factors. Concurrently, a proportional decrease in IOP from the untreated level is almost invariably part of the definition of target pressure, often in combination with a numerically designated highest acceptable IOP. This means that it should be possible to accept somewhat higher tension in patients who have a higher IOP at the time of a glaucoma diagnosis, and, conversely, that lower target IOP levels should be required in those who have had lower pressures during development of the disease.

Thus, all of the following factors point towards a lower target IOP (and the opposite conditions suggest a somewhat higher target pressure):

- (1) Younger age
- (2) Larger visual field defects
- (3) Lower untreated IOP
- (4) Exfoliation syndrome
- (5) Optic disc haemorrhages.

It is not possible to stipulate a numerical limit that can apply to all patients with glaucoma. It was long assumed that 'normalization' of IOP (to <21 mmHg) was equivalent to good pressure control. However, even if there is now scientific evidence that a more ambitious approach should be used, it is probably best not to decide on any specific numerical recommendation that is intended to apply in all cases.

When diagnosing glaucoma, several untreated IOP measurements should be made to better assess the effectiveness of the implemented therapy.

It is important to understand that the target pressure is dynamic. The various formulae that are used to define target IOP, which often take the untreated pressure into account, are of greatest interest when the patient has just received a diagnosis of glaucoma. After the patient has been under observation for a few years, and the rate of progression can be estimated, it is much easier to determine whether the target pressure that was originally specified can be regarded as correct. In short, the amount of visual field damage, the progression rate and the life expectancy should be taken into consideration to help establish whether the

reduction in IOP has been sufficient or if a new target pressure must be stipulated at a level lower than the IOP measurements recorded during the treatment period.

At diagnosis, lower target pressure is indicated by the following factors: younger age, larger visual field defects, lower untreated pressure, exfoliation and optic disc haemorrhages

Rate of progression

Glaucoma is a progressive disease, and most patients show progression even if they receive treatment and IOP remains within the statistically normal range. It is no longer particularly realistic to assume that all deterioration can be prevented. However, it is also known that the rate of progression varies markedly among patients, even in those with the same IOP level, age and other risk factors. A sizeable minority of treated patients with glaucoma exhibit rapid disease progression, despite treatment and moderate IOP levels. Important goals of modern glaucoma care should be to identify these patients in time to allow intensification of treatment and also to estimate the rate of progression in all patients. The European Glaucoma Society (2008, p. 87) supports the recommendation of performing three visual field tests annually during the first two years after diagnosis (Chauhan et al. 2008a), although measurements made every six months over the first three years can also provide a good estimation of the progression rate.

The rate of progression varies substantially between patients

Frequent visual field testing during the first few years after diagnosis (e.g. six fields during the first two to three years) can help identify harmful progression before damage has become too extensive

Considering that the goal of glaucoma treatment is related to visual function, the rate of progression of visual impairment is of primary interest. Loss of vision is measured by repeated visual field examinations, and thus it should be possible to estimate the progression rate after a few years of follow-up.

Visual function affects QoL, and thus it seems logical to initially follow the patient by visual field testing. Documentation of the optic disc and retinal nerve fibre layer do not provide the same possibility of assessing visual disability, which is why these methods are usually not an alternative to visual field measurements. The primary reason for electing to document the optic disc and/or retinal nerve fibre layer is that such an approach can provide an early warning of any changes that occur during the course of the disease. There is less need for a series of examinations if optic disc photography is performed than if visual fields are used.

Once it is determined that a patient's disease is progressing at a dangerously rapid rate, and measures have been taken to lower IOP more to halt further deterioration, it is very important, if possible, to re-examine the patient at relatively short intervals (visual field testing two or three times a year). That is the only way to ascertain whether the rate of progression has been reduced, or if the target pressure should be even lower. However, if the pressure is already at a level that is considered to be so low that it probably cannot be reduced any further, it is obviously of little value to monitor glaucoma damage by performing visual field tests or measuring the optic disc or retinal nerve fibre layer.

After a few years of follow-up, the rate of progression should be available based on repeated visual field tests

Individualized glaucoma management

Management of patients with glaucoma should always be individualized, and this applies to the choice of examination techniques, as well as the follow-up interval and the treatment prescribed. The objective is to prevent visual disability and an accompanying decrease in QoL, and hence the risk of visual impairment should be the primary factor guiding the selection of treatment and the frequency of monitoring.

Groups of patients that are at only limited risk of serious disease can be

identified immediately, and these include patients with unilateral disease or very old persons who have only small visual field defects despite the presence of bilateral disease. Individuals with ocular hypertension, at least if they are 70 years of age or older, constitute another group with only very little risk of reduced QoL. At the other end of the spectrum are patients at substantial risk of visual impairment, and these include individuals diagnosed with significant bilateral visual field defects or younger people with field defects. A 60-year-old patient with bilateral field defects must be regarded as being at high risk of visual disability during his/her lifetime, even if the defects are initially relatively small.

If measurement of the rate of disease progression is reasonably accurate, it is possible to extrapolate visual field development for the number of years the patient is expected to live. Of course this estimation will be uncertain, although a linear extrapolation can be regarded as the best prediction of the subsequent course of the disease if treatment remains unchanged (Bengtsson et al. 2009a). If such extrapolation indicates that the patient is at risk of losing at least half of the visual field in both eyes during his/her lifetime, it can be concluded that there is a very high risk of reduced QoL and/or visual disability. It is essential that the fairly large number of patients who fit this description be identified sufficiently early, and that treatment and follow-up be performed at shorter intervals in these cases.

Glaucoma management should be individualized so that patients at higher risk of serious impairment will be treated and monitored more extensively than those at lower risk

On the other hand, it is often warranted to lengthen the follow-up interval in patients who have been under prolonged observation and have a measured rate of progression that is presumed to entail a low risk of visual disability, even in a lifelong perspective. According to this line of thinking, it is quickly apparent that longer follow-up intervals (e.g. every other year) can be used in elderly patients with ocular hypertension.

Overall assessment

In management of patients with glaucoma, it is essential to perform an overall assessment of the development of the disease at intervals of a few years. This should include judging whether the rate of progression can cause concern about QoL (see the section above headed *Rate of progression*). If the progression rate is high and clearly suggests future visual disability, the IOP levels that were recorded during the follow-up period should be considered, a *substantially* lower target pressure should be chosen. Attempts should then be made to reach the designated level, even if that can require expanding treatment in a way that might be problematic for the patient, for example, by necessitating usage of several bottles with eye drops or exposure to the risks of surgery. If the rate of progression is possibly unsafe, treatment should be intensified, as long as such an approach does not involve any obvious disadvantages.

If the data are still inadequate to allow assessment of the rate of progression, but the IOP seems unnecessarily high and the patient is on monotherapy, it can be necessary to increase treatment. This strategy can also be contemplated in a patient who is stable or shows only very slow progression, if the IOP starts to increase compared to earlier levels at which development of the disease was regarded as tolerable. Conversely, in an elderly patient who has been under observation for a long period of time and exhibits little damage or progression, treatment can be reduced, if the patient finds it difficult to manage taking eye drops or to tolerate harmless and minor side-effects of the glaucoma treatment.

Such overall assessments can be much faster and easier, if they are performed by ophthalmologists or ophthalmic nurses with extensive experience in this context. Also, it will definitely be beneficial if as many patients with glaucoma as possible can be treated by professionals who have special expertise and interest in glaucoma care. This is at least as important as the aspect of continuity, which is another important factor affecting the quality of care.

Overall assessment of the patient is important

Physicians as well as ophthalmic nurses play an important role in glaucoma care
Special interest and continuity of care are positive factors

5 Treatment Methods

Pharmacological treatment of glaucoma

The main objective of pharmacological treatment of glaucoma is to lower IOP. That goal is achieved either by reducing the production of aqueous humour or by increasing the outflow through the trabecular meshwork or the uveoscleral pathway.

When selecting a therapeutic regimen, several other factors besides a pressure-reducing effect must be taken into consideration, including possible adverse effects, cost, QoL and the likelihood of good compliance. In many cases, a preservative can cause local reactions, and, if that occurs, it is preferable to prescribe unit-dose vials without preservatives. It has also been assumed that a simpler dosage schedule, including fewer drop bottles and instillations, can improve compliance, although the literature offers little support for that assumption (Gray et al. 2009).

Only approximately 20% of the content of an eye drop is absorbed by the eye (Mishima 1981; Korte et al. 2002). The amount that is absorbed by the nasopharyngeal mucosa has no effect on the eye but can give rise to general side-effects. Using a silicone plug to occlude the lacrimal duct reduces the overall uptake (Salminen 1990) and markedly increases absorption in the eye (Lindén & Alm 1990). However, there is no evidence that the amount of drug that is actually absorbed by the eye can be significantly increased by either closing the eye or applying pressure on the lacrimal duct for one minute after administering a drop of medication (Lindén & Alm 1990).

The pharmaceutical preparations that were available in Sweden in autumn 2010 are described below (see also Table 2). The values given represent the maximum pressure-reducing effect (the peak level) given as a per cent of the untreated IOP and the

lowest pressure-reducing effect (the trough level) measured soon before time for the next dose. These values were obtained from van der Valk et al. (2005) in a meta-analysis of 27 randomized studies of patients treated for at least 1 month with the drugs in question. For more detailed information about the individual medications investigated, see the *Swedish Pharmacopeia* (FASS). The classes of drugs that are of interest here are discussed in the following sections.

Beta-receptor-blocking drugs

The ciliary body epithelium contains adrenergic beta receptors, chiefly beta-2 receptors, and stimulation increases the production of aqueous humour. Timolol is a nonselective beta adrenergic receptor blocker that can lower the production of aqueous humour by 30–40% during daytime (Brubaker 1991). The relatively selective beta-1 receptor antagonist betaxolol presumably exerts its effect by blocking beta-2 receptors, but it is not as efficacious as timolol (Gaul et al. 1989), which is also reflected by its effect on IOP. At night, the activity of the adrenergic beta receptors is so low that a blocking agent has no substantial impact on the basal rate of aqueous humour production during that time (Topper & Brubaker 1985; Brubaker 1991).

For timolol and betaxolol, the recommended dose is once a day for depot formulations and once or twice a day for solutions. Timolol at a concentration of 0.008% (0.08 mg/ml) has a measurable effect on IOP (Mottow-Lippa et al. 1990), and the effect of a daily dose on IOP is the same regardless of whether given in the morning or at night (Letchinger et al. 1993). This suggests that instillation of the lower dose once daily can suffice for most eyes.

The systemic effect of topical beta-blockers is not negligible (Korte et al. 2002), and timolol is contraindicated in patients with asthma, serious lung disease, uncompensated cardiac insufficiencies, or grade II or III AV block. Betaxolol has the same cardiac contraindications, and a certain degree of caution should be observed in patients with asthma, even if the risk of clinically significant blockade of beta-2 receptors in the lungs is small.

Prostaglandin analogues

Compared to the parent compound prostaglandin F₂ alpha (PGF_{2α}), the analogues latanoprost, travoprost, bimatoprost and tafloprost are more selective for FP receptors (Stjernschantz 2001) and consequently have less effect on blood vessels and cause less irritation (Stjernschantz et al. 2000). Prostaglandins lower IOP by increasing the uveoscleral outflow (Stjernschantz 2001). This is brought about through a reduction in the collagen content of the ciliary muscle, which in turn affects hydraulic resistance in the uveoscleral outflow pathway (Sagara et al. 1999). This action is long-lasting, and the drug should be given only once daily; in fact, more frequent administration reduces the effect (Alm et al. 1995).

Prostaglandins are not believed to cause systemic side-effects. The adverse reaction that has received most attention is a colour change of the iris, which occurs in about one-third of eyes treated with latanoprost (Alm et al. 2004) but is considered to be solely of cosmetic concern (Albert et al. 2008). The change in colour is attributed to an effect on melanin production, which can also lead to darker and longer eyelashes and/or increased pigmentation of the skin of the eyelids. In contrast to the altered colour of the iris, the effects on the eyelids are reversible and disappear within a few months after withdrawal of the drug. Conjunctival hyperaemia is seen in connection with all prostaglandin analogues. Caution should also be observed in eyes at increased risk of intraocular inflammation, including cystoid macular oedema.

Sympathomimetics

The adrenergic alpha-2 agonists apraclonidine and brimonidine activate a receptor in the ciliary body epithelium, which reduces the production of aqueous humour. Apraclonidine should only be used temporarily to prevent a rise in IOP in patients who have undergone argon laser trabecular surgery or are scheduled for filtering surgery. Brimonidine is a much more selective adrenergic alpha-2 receptor agonist (Burke & Schwartz 1996), and it is also rather fat soluble and can pass through the blood-brain barrier.

The recommended dose of brimonidine is one eye drop twice daily, and the maximum effect on IOP is equivalent to that achieved using timolol but declines more before it is time for the next dose (Table 1; van der Valk et al. 2005).

Common local side-effects are dryness of mouth, eye allergy and follicular conjunctivitis. Systemic reactions are related to the central nervous system (CNS) and include fatigue and/or drowsiness. Brimonidine should not be given together with monoamine oxidase (MAO) inhibitors or drugs that can affect noradrenergic transmission, such as tri- or tetracyclic antidepressants. Because of its effects on the CNS (somnolence and apnoea), brimonidine is also contraindicated in children less than 2 years of age and should be used with extreme caution

in children aged two to 7 years (body weight < 20 kg).

Parasympathomimetics

Cholinergic agonists increase the outflow of aqueous humour through the trabecular meshwork by causing the ciliary muscle to contract and pull the scleral spur, an action that separates the lamellae of the meshwork and lowers outflow resistance (Kaufman & Barany 1976). At present, these are the only drugs that can influence the outflow facility, which is the component of aqueous humour dynamics that is believed to be affected by the course of glaucoma and to induce the increase in IOP that is associated with this disease. These agents have a relatively short time of action and must be administered three times daily to achieve

good effect over 24 hr, and hence they are used less often today.

An initial headache is not unusual. Other side-effects include a strong impact on muscles of the iris and ciliary body, including marked miosis and also varying degrees of myopia in younger patients.

Carbonic anhydrase inhibitors

During formation of aqueous humour, the enzyme carbonic anhydrase catalyses production of HCO_3^- from OH^- and CO_2 . There are at least 12 isoforms of carbonic anhydrase, and two of them in the eye (in the ciliary process) designated CA II and CA IV. A full dose of the peroral carbonic anhydrase inhibitor acetazolamide can suppress the flow of aqueous humour by 30–40% (Brubaker 1991). The topical carbonic anhydrase inhibitors dor-

Table 2. Ocular hypotensive drugs available in Sweden in 2010. Peak and trough effects from van der Valk et al. (2005)

Group	Active ingredient	Drug name	Strength	Dosage	Peak	Trough
Parasympatho-mimetics	Pilocarpine	Isopto-Pilocarpin Pilokarpin	20 and 40 mg/ml	1*2–3		
	Carbacholine	Isopto- Karbakolin Karbakolin-klorid	30 mg/ml	1*1–3		
Sympato-mimetics	Pilocarpine- Physostigmine	Pilokarpin-Fysostigmin	40 and 2 or 4 mg/ml			
	Aprachlonidine	Iopidin	5 and 10 mg/ml			
	Brimonidine	Alphagan Brimoratio Glaudin	2 mg/ml	1*2	25	18
		Diamox tablets For i.v. injection	125 and 250 mg 500 mg			
Carbonic anhydrase inhibitors	Acetazolamide	Trusopt	20 mg/ml	1*3	22	17
	Dorzolamide	Azopt	10 mg/ml	1*2–3	17	17
Adrenergic betareceptor blockers	Timolol	Blocadren Optimol Timolol	2.5 and 5 mg/ml	1*1–2	27	26
		Blocadren Depot	5 mg/ml	1*1		
	Betaxolol	Betoptic Betoptic S	5 mg/ml 2.5 mg/ml	1*2	23	20
Prostaglandin analogues	Latanoprost	Xalatan	50 µg/ml	1*1	31	28
	Bimatoprost	Lumigan	0.3 mg/ml	1*1	33	28
	Travoprost	Travatan	40 µg/ml	1*1	31	29
	Tafluprost	Taflotan	15 µg/ml	1*1		
Combinations	Pilocarpine + Timolol	Fotil and Fotil Forte	20 and 5 mg/ml 40 and 5 mg/ml	1*2		
	Dorzolamide + Timolol	Cosopt	20 mg/ml 5 mg/ml	1*2		
	Brinzolamide + Timolol	Azarga	10 mg/ml 5 mg/ml	1*2		
	Brimonidine + Timolol	Combigan	2 mg/ml 5 mg/ml	1*2		
	Latanoprost + Timolol	Xalcom	50 µg/ml 5 mg/ml	1*1		
	Travoprost + Timolol	Duotrav	40 µg/ml 5 mg/ml	1*1		
	Bimatoprost + Timolol	Ganfort	0.3 mg/ml 5 mg/ml	1*1		

zolamide and brinzolamide are not as efficacious as acetazolamide (Maus et al., 1997), possibly by not completely blocking both CA II and the membrane-bound CA IV (Larsson & Alm 1998).

Acetazolamide is given in the form of tablets at a dose of 0.5–1 g/day. For dorzolamide and brinzolamide, the recommended dose is one drop two to three times a day; the lower dosage is sufficient if used in combination with timolol, because timolol reduces the flow of aqueous humour and thereby decreases the rate at which other drugs are removed from the eye.

Since carbonic anhydrase is present in most tissues of the body, and acetazolamide is known to effectively inhibit most isoforms of this enzyme, peroral treatment with this drug causes distressing adverse effects such as fatigue, paraesthesia, loss of appetite, nausea and other gastrointestinal disturbances. Carbonic anhydrase inhibitors also increase the risk of kidney stones, because they decrease urinary excretion of citrate, which in turn leads to higher risk of calcium deposits in the urinary tract. These drugs are chemically similar to sulphonamides and can result in agranulocytosis, thrombocytopenia and aplastic anaemia. Furthermore, many patients discontinue treatment (Lichter et al. 1978), and therefore peroral therapy is rarely prescribed today.

Dorzolamide and brinzolamide are given as eye drops, and, as expected, they are associated with a much lower risk of systemic side events. Patients with serious kidney or liver damage should not be treated with these drugs. Common adverse effects include headache, a bitter taste in the mouth and local irritation including allergic reactions.

Combination preparations

All combination eye drops include the beta-blocker timolol together with some other drug. Contraindications and adverse effects depend on the components in the formulation.

Use in children and during pregnancy and lactation

When IOP-lowering treatment is deemed necessary in a child or a pregnant or nursing woman, there is little data available on which to base a reli-

able assessment of the risks of foetal damage or negative effects on the child.

In most cases, treatment with eye drops is considered to be associated with a low risk of foetal injury, particularly with the drugs pilocarpine and timolol, which have long been in use. Use of timolol eye drops during pregnancy does not affect birth weight (Ho et al. 2009), and there is no evidence that the concentration of timolol present in breast milk involves any risk for a healthy infant (Madadi et al. 2008). Accordingly, it is reasonable to regard timolol as the drug of choice in pregnant women who have elevated IOP and are considered to need pressure-lowering therapy where laser treatment is not an option.

Topical beta-blockers at low concentrations, topical carbonic anhydrase inhibitors and latanoprost are well tolerated by young children (Ott et al. 2005; Coppens et al. 2009). Beta-blockers should obviously not be used if there are contraindications to these drugs. Miotics are of little interest because of the effect they have on the lens. Also, adrenergic alpha-2 agonists should not be given to children aged 2 years or younger, and they should be used with caution in children who are 2–7 years old or weigh less than 20 kg because of possible adverse effects on the CNS (Al-Shahwan et al. 2005).

Treatment stages and strategies

Initially, only one drug is used. The IOP-lowering effects and side-effect profiles of the various medications suggest that timolol or a prostaglandin analogue should be the first choice for treatment, if there are no contraindications. The maximum pressure-reducing effect is usually reached within one to two hours with most of the available drugs, except the prostaglandin analogues, which show peak effect after 6–8 hr (Alm & Villumsen 1991). The effect of beta-blockers and prostaglandin analogues can persist for several weeks after discontinuation (Schlecht & Brubaker 1988; Lindén et al. 1997).

Beta-blockers or prostaglandin analogues are first choice alternatives if there are no contraindications

Switch or add

If monotherapy does not achieve the target IOP, it is necessary to alter treatment either by testing a different drug or by adding another pressure-reducing agent. If monotherapy was recently initiated and has had good effect on IOP but has not succeeded in reaching the target pressure, it is reasonable to add another drug. Alternatively, if the effect of the original therapy has been limited, the first step should be to test some other drug. In both those cases, laser treatment can also be a suitable option. In some patients, the IOP can rise after prolonged successful treatment with a particular drug, and it can be impossible to ascertain whether this change is attributable to diminishing effect of the agent used or to increased resistance in the aqueous outflow pathway. Under such circumstances, it can be appropriate to add some other medication, and later to try to withdraw the drug that is currently in use, or to immediately switch to another drug.

Combination treatments

In many cases, more than one drug is needed to achieve a designated target IOP, and various combinations of products have been shown to provide the desired pressure reduction. Notwithstanding, the use of prostaglandin analogues combined with cholinergic agonists such as pilocarpine has been questioned because contraction of the ciliary body might prevent a prostaglandin analogue from reaching its target – the ciliary muscle. However, the intense contraction of the ciliary muscle is of short duration, and the pressure-lowering effect has been found to be additive (Friström & Nilsson 1993; Lindén & Alm 1997).

When combining two drugs to lower IOP, it is often recommended that agents with different modes of action be used, for example, one that affects outflow and another that influences production of aqueous humour. As of yet, no studies have been conducted to determine differences between various drug combinations with regard to their impact on progression rate.

Prescriptions should as a rule not include more than two bottles of IOP-lowering eye drops for simultaneous

use, because that can be difficult for patients to manage and can lead to noncompliance. However, many combination drops containing two different active ingredients in the same bottle are currently available, and these can make it fairly easy for patients to handle three active medications at the same time. It can be assumed that adding a fourth agent will not provide any appreciable enhancement of the pressure-reducing effect.

A dosage schedule should be simple to facilitate compliance

For eye drops, more than two applications a day and use of more than two bottles on each dosing occasion should be avoided if possible

Medical treatments other than pressure reduction

In glaucoma treatment, considerable discussion has focused on possible positive effects of two types of drugs that do not influence IOP, namely, agents that increase blood flow and those that have a potentially neuroprotective effect (i.e. prevent cell death in nervous tissue). However, thus far, no studies have convincingly demonstrated that a drug that does not reduce IOP can have any impact on the course of disease. Moreover, there are no conclusive data showing that the glaucoma drugs that are presently in use have any effect on blood flow in the optic nerve or the retina (Costa et al. 2003).

The NMDA glutamate receptor agonist memantine is the only neuroprotective agent that has been tested in a randomized, blinded study on patients with glaucoma. It is a registered product (Ebixa®) for treatment of mild Alzheimer's disease. However, research has not shown any effect of memantine on the progression of glaucoma (Osborne 2009).

There is no evidence that treatment other than intraocular pressure-lowering can affect the course of glaucoma

When are eye drops insufficient?

In patients whose disease progresses at a rate that can result in visual

impairment despite maximum treatment, or in those who have difficulty following prescribed therapy, surgery or laser treatment should be considered if not already implemented. These alternatives should also be considered if eye drops cannot achieve sufficient pressure reduction without causing considerable side-effects.

In the short term, it is obvious that treatment of glaucoma cannot be guided solely by visual field progression, which is why the concept of target IOP is used (see *Risk analysis and target IOP* in Chapter 4). Isolated pressure measurements that are above the target level do not necessarily call for adjustment of the therapeutic regimen. However, if high pressures are recorded on several occasions even though the patient is receiving what is judged to be maximum treatment, there is reason to suspect inadequate efficacy or poor compliance. In that situation, laser treatment or surgery should be considered.

Laser treatment

LTP/ALT

Here, the terms argon laser trabeculoplasty (ALT) and laser trabeculoplasty (LTP) are used synonymously (Wise & Witter 1979).

Good knowledge of the anatomy of the anterior chamber angle is important in laser treatment (see the section headed *Gonioscopy* on pages 20–21). When LTP was introduced, treatment was carried out on 360° of the anterior chamber angle. However, an effect can be achieved by treating only 180°, and thus it is suitable to start with half the angle and wait with the other half (Fig. 13). The laser beam is applied to the pigmented (anterior) portion of the trabecular meshwork. The power setting should cause only limited formation of gas bubbles and no visible whitening; if the mentioned effects are more pronounced, the power level is probably too high, which will increase the risk of peripheral anterior synechiae (Rolim de Moura et al. 2007). The parameters and time-point of the treatment should be noted in the patient's records to aid any subsequent supplementary treatment.

LTP parameters

Spot size: 50 µm

Duration: 0.1 seconds

Power setting: varies depending on the equipment used, usually 400–1000 mW
50 nonoverlapping laser pulses applied over 180°

Laser trabeculoplasty can give rise to what is usually only minor irritation of the iris, which can be handled by short-term treatment with a topical steroid if necessary. At least initially, the IOP-reducing therapy that the patient is already receiving can remain unchanged, because it often takes from a few weeks up to a month or more for the effect of LTP to become apparent. It is generally recommended that LTP should not be repeated at the same location, because it is assumed that such an approach can lead to more extensive inflammation and a greater risk of increased IOP. As of yet, there are no conclusive research results to support that suggestion.

Randomized controlled studies have shown that LTP has a better IOP-reducing effect than can be achieved by the older classes of eye drops. However, investigations are needed to compare LTP with newer drugs such as prostaglandin analogues, brimonidine and topical carbonic anhydrase inhibitors (Rolim de Moura et al. 2007).

SLT

Selective laser trabeculoplasty (SLT) is a newer type of LTP (Realini 2008) that requires the use of a Q-switched, frequency-doubled YAG laser. One hundred laser spots are applied over 360° of the trabecular meshwork, although, as in LTP, it is possible to begin by treating only a smaller portion of the circumference (Chen et al. 2004).

SLT parameters

Spot size: 400 µm

Pulse duration: 3 ns

Power setting: start at 0.8 mJ and then adjust to the highest level at which no gas bubbles are formed

Selective laser trabeculoplasty has proven to have an IOP-lowering effect equivalent to that of LTP (Damji et al. 2006; Realini 2008) and even that of latanoprost (Nagar et al. 2005). Selective laser trabeculoplasty

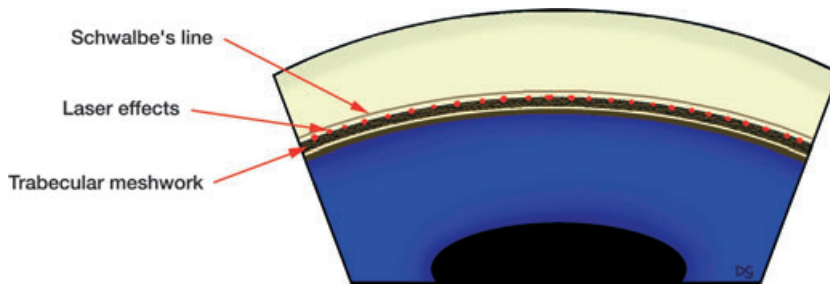


Fig. 13. Placement of the laser beam in argon laser trabeculoplasty.

delivers less energy to the trabecular meshwork, and the theoretical advantage of this method is that it allows repeated treatment of the same area in the meshwork. However, no controlled studies have yet been performed that can confirm that assumption, even though SLT has been available for many years.

Primary laser treatment

Primary LTP has long been discussed (The glaucoma laser trial (GLT) 1990; Bergeå et al. 1994), and it is definitely an alternative, particularly if there is reason to avoid eye drops, such as in elderly patients who have difficulties applying that type of medication.

Diode laser cyclophotocoagulation

Trans-scleral treatment of the ciliary body using diode laser cyclophotocoagulation is an alternative for treating patients with advanced glaucoma (Bloom et al. 1997; Walland 1998; Fankhauser et al. 2004). This method is based on the same principle as cyclocryotherapy (see p. 30), and it is used mainly on blind eyes and requires adequate anaesthesia (e.g. retrobulbar block or subtenon anaesthesia).

Parameters for cyclophotocoagulation performed using an 810-nm IRIS diode laser, blind eye

Duration: 2000 ms

Power setting: 1500–2000 mW

Approximately 20 pulses applied over 360°; the G probe is placed on the border of the limbus and is moved half the width of the probe between each pulse

If a decision is made to use this method to treat an eye that still has vision, greater caution should be observed because of the risk of phthisis. Inflammation is one of the com-

mon complications of this laser approach, which is why topical steroids should be used after the treatment. Less common complications include hypotonia and phthisis, and there have also been reports of scleral perforation (Amariotakis et al. 2007), staphyloma (Prata et al. 2008), suprachoroidal haemorrhage (Tay et al. 2006) and sympathetic ophthalmia (Roberts et al. 2009a).

Depending on local practice, many institutions now use this method as an alternative to shunts (Yildirim et al. 2009). The advantage of a diode laser is that it entails a smaller and faster intervention. The drawbacks are that it is difficult to regulate, and several treatments are often required, which can lengthen the time needed for the series of treatments.

Surgery

The main indication for filtering surgery is progression of glaucoma in which medical or laser treatment cannot provide adequate reduction in IOP. Accordingly, this procedure is not the first choice for treatment of glaucoma, primarily because of the low, but real, risks of serious and vision-threatening complications that are associated with surgery. On the other hand, it is clear that surgery is more effective than both drug and laser therapy in reducing IOP (Migdal et al. 1994; Lichter et al. 2001). Similar to laser treatment, filtering surgery does not require patient compliance. The impact of compliance on drug treatment of glaucoma is often a topic of discussion, although conclusive data are lacking with regard to the effect of poor compliance. Missing a few doses is probably of little consequence, because most of the drugs that are used today have a residual

effect that is still apparent long after administration of the latest dose.

The risks associated with surgery often constitute the reason for postponing a surgical procedure, which is regarded as a last resort. Two studies (Migdal et al. 1994; Lichter et al. 2001) have compared filtering surgery and drug therapy with respect to post-operative risks and effects on the course of disease. In both those investigations, it was clearly demonstrated that filtering surgery provided better IOP reduction, and that the risks associated with surgery were at an acceptable level. Nonetheless, overall assessment of the results of those studies has not yet been able to show that filtering surgery is more beneficial than treatment with medicines. The Advanced Glaucoma Intervention Study (The advanced glaucoma intervention study (AGIS) 2000) conducted a *post hoc* analysis and found that visual fields were stable over a prolonged period in most eyes that had persistently low IOP levels after surgery (i.e. pressure < 18 mmHg at all follow-up visits). Also, the EMGT and other prospective studies (Heijl et al. 2002; Chauhan et al. 2008a,b) have shown that the risk of glaucomatous progression in treated eyes decreases with each 1-mmHg reduction in IOP. Together, these observations indicate that it should presently be assumed that filtering surgery offers benefits that clearly justify the risks. This procedure should be considered at an early stage in cases involving either initially very high IOP or progression occurring early in the course of the disease.

Surgical methods

Randomized controlled studies of glaucoma surgery are often lacking, and thus the scientific knowledge base in this area is inadequate.

Trabeculectomy

Trabeculectomy is the gold standard in glaucoma surgery (Sugar 1961; Cairns 1968; Linnér 1970). The underlying principle is to construct a new pathway for aqueous humour outflow. In short, an opening is created in the trabecular meshwork or peripheral cornea under a scleral flap, and the fluid is drained through the opening and then flows to the sub-

conjunctival space (Fig. 14). This procedure is still widely used.

Trabeculectomy has several drawbacks:

- (1) The procedure is associated with complications. Of greatest concern is the risk of endophthalmitis that can occur during either the acute phase or later after surgery. Early postoperative hypotony is also a potentially serious complication, which, if prolonged, can cause visual impairment, choroidal detachment and macular oedema.
- (2) Even if the operation is initially successful and provides good IOP reduction, there is a tendency for the pressure to return to an unacceptably high level over time. One of the main reasons for this is that the opening that is created can heal and close even long after the surgery.

NPT techniques (deep sclerectomy, viscocanalostomy)

Nonpenetrating trabeculectomy (NPT) was developed to circumvent the often troublesome early complications involving hypotonia. There are several different NPT techniques that do or do not include filtration to the subconjunctival space. In contrast to traditional trabeculectomy, NPT leaves a thin membrane instead of creating an actual opening into the anterior chamber, and thus the remaining barrier to outflow is somewhat larger with this approach (Fig. 15). Compared to penetrating trabeculectomy, the NPT techniques

offer the advantages of being associated with less frequent postoperative hypotonia and a lower risk of endophthalmitis, because there is no intraocular surgery. Among the disadvantages are that the operation is more difficult to perform and has a lower IOP-reducing effect (Mendrinós et al. 2008), although the results of deep sclerectomy can be improved by subsequent YAG laser goniopuncture (see below) (Mendrinós et al. 2008).

Glaucoma surgery *per se* is a fairly simple task for an experienced ophthalmic surgeon – the difficulty is deciding which patients should undergo the procedure

Shunts

Several different types of shunts or implants have been described. Molteno and Baerveldt shunts allow flow in both directions, whereas Ahmed and Krupin shunts have a valve that prevents or restricts backflow, and thus the latter two devices are even called valves. In a recent randomized multicentre study of 212 eyes, shunts were found to be superior to trabeculectomy after 3 years of follow-up (Gedde et al. 2009). Some investigators have shown that the surface area of the plate is of consequence being proportional to the IOP-reducing effect (Minckler et al. 2006). However, research findings are not conclusive, and it is also more difficult to insert a larger plate. There are risks and problems connected with all aqueous shunts.

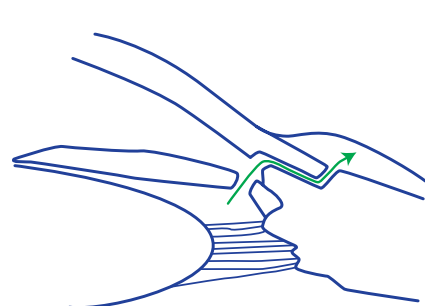


Fig. 14. Trabeculectomy. Aqueous humour is drained from the anterior chamber through a hole in the trabecular meshwork/cornea under a scleral flap and is then diverted into the subconjunctival space, where it is reabsorbed by the conjunctival blood vessels. A peripheral iridectomy is performed to ensure that the iris is not pulled towards the area of the trabeculectomy.

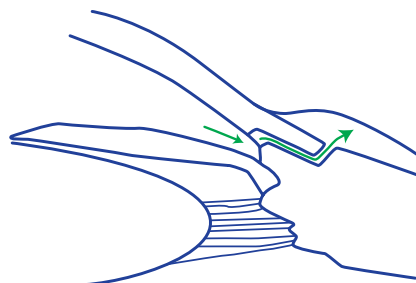


Fig. 15. In contrast to trabeculectomy, NPT does not require cutting all the way into the anterior chamber. Instead, the thin innermost trabeculocorneal layer is left intact. This thin membrane can prevent pronounced hypotonia but still allow gradual drainage of aqueous humour by percolation. Inasmuch as there is no opening into the anterior chamber, there is no need for a peripheral iridectomy.

Cyclodestructive procedures

The method involving destruction of the ciliary body has been employed for quite some time and is still used in treatment of glaucoma (Fankhauser et al. 2004).

Cyclocryotherapy

Cyclocryotherapy is an older cyclodestructive procedure that requires only adequate anaesthesia and a cryoprobe. This technique has not been standardized, and the results obtained vary considerably. A drawback of this method is that it causes relatively severe postoperative pain, inflammation and swelling.

Diode laser cyclophotocoagulation

See the section headed *Laser treatment* on page 28.

Intraoperative antimetabolites

A rapid and aggressive healing response in both the conjunctiva and sclera is a general problem in all types of surgery aimed at lowering IOP. To avoid this problem, techniques have been developed that use chemotherapeutic agents such as 5-fluorouracil (5-FU) and mitomycin C (MMC) as intraoperative adjuvants. The antimetabolite is applied locally to the target area, and the dose and duration used vary. Antimetabolites augment reduction in IOP, but they also cause adverse effects in the form of postoperative hypotonia, wound leakage, endophthalmitis, and late scleral and conjunctival thinning, which are limiting factors. There is some evidence that the risk of cataract is also increased (Wilkins et al. 2005).

Radiation

Intraoperative radiation therapy, usually using strontium-90, has been shown to enhance the reduction in IOP. Cataract is the main adverse effect (Kirwan et al. 2009).

Postoperative management

Postoperative follow-up is an extremely important and resource-consuming process. The patient should be seen the day after surgery and thereafter every or every other week for a period of 6–8 weeks. It is standard practice to treat with local steroids; the doses and duration vary, but treatment should be continued until the filtering bleb is pale. Cycloplegics

and topical NSAIDs are also prescribed in some cases. If there is a tendency towards aggressive healing with an accompanying rise in IOP, the following measures can be considered: massage, suture removal, needling, goniotomy and 5-FU injections. Use of any of those methods will require more frequent follow-up.

Massage

Early occlusion of the surgically created drainage opening can occur because of formation of a clot or a fibrous plug, and can be removed by massaging the eye with the patient seated at a slit lamp. The eyelid is kept closed, and a clean finger or a cotton-tipped applicator is used to massage the globe on and around the scleral flap. Alternatively, a sterile glass rod can be applied directly on the globe.

Suture removal

The commonly used scleral sutures (e.g. 10-0 nylon) are dark in colour and thus can easily be removed using a laser, if the surgical area is not hidden by blood or an oedematous conjunctiva. A burning laser (e.g. an argon laser) is used to melt and thereby cut sutures. The procedure can be facilitated using a tool such as the tip of a glass rod or a specially designed Hoskins lens to push surrounding tissue out of the way.

Parameters for laser suture lysis.

Spot size: 50–100 μm
Duration: 0.1–0.2 seconds
Power: moderate (200–400 mW)

Releasable and adjustable sutures

If releasable or adjustable sutures are used during surgery, it will later be easy to remove or adjust them by use of a forceps and a slit lamp. A large number of different suture knots have been described (de Barros et al. 2008).

Needling

To open up an encapsulated filtering bleb, the patient should be seated at a slit lamp (or lying on an operating table) and given topical anaesthesia (drops). A very fine hypodermic needle is inserted in the conjunctiva to reach the filtering bleb, where it is used to puncture or cut open either

the conjunctiva or the sclera (under the scleral flap). This is performed to improve drainage from the trabeculotomy or other routes. The alternative method of using IOP-reducing eye drops to treat eyes with an encapsulated bleb can provide equally satisfactory results. Notably, according to the Cochrane Collaboration, only one randomized study has been performed in this area thus far (Feyi-Waboso & Ejere 2004), and it actually showed that a better outcome was achieved with eye drops than by needling.

YAG laser goniotomy

YAG laser goniotomy can only be performed after NPT, because NPT leaves a thin membrane consisting of the innermost trabeculocorneal layer. With the aid of the gonioscopy lens, the laser is used to create a hole in the membrane and thereby improve filtration. In some cases, the effect that is achieved can continue long (up to years) after surgery. It is often necessary to use a surprisingly high energy level with this technique.

Postoperative 5-FU

The methods described above can be combined with repeated postoperative injections of 5-FU, which are given under the conjunctiva after anaesthetic eye drops, with the patient seated at a slit lamp. Corneal erosions are the most common adverse effect, and thus it is necessary to examine for such erosions before each injection. If erosions do occur, the injections must be discontinued. A study has shown that 5-FU can improve IOP reduction, if it is administered as five 5-mg injections, but not if it is given at a lower dosage or in fewer injections (Wormald et al. 2001).

Postoperative follow-up is particularly important and requires relatively extensive resources, because both glaucoma surgery and the postoperative course vary markedly, thus necessitating more frequent monitoring and readiness to implement postoperative measures

Unfortunately, few randomized controlled studies have been performed, and thus much still depends on the experience and routine of the surgeon

The Moorfields Safe Surgery System website is very helpful: <http://www.ucl.ac.uk/iao/research/khawlibrary.htm>

6 Management of Suspected Glaucoma and Ocular Hypertension

Many patients with suspected glaucoma are monitored at eye care centres. Ocular hypertension is the most common cause, but suspect glaucoma can occur also without an elevated IOP. Such cases of suspect glaucoma usually involve eyes with large physiologic cups, suspected notching or defects in the retinal nerve fibre layer. As a rule, patients who fit this description should not be treated unless, of course, they have manifest glaucoma with visual field loss.

Ocular hypertension

Ocular hypertension is defined as elevated IOP (>21 mmHg) that is not accompanied by damage to the visual field, the optic disc or the retinal nerve fibre layer. Ocular hypertension is more common than manifest glaucoma, and the risk of developing glaucoma is five times greater in patients with ocular hypertension than in those with normal IOP (Ekström 1993). The Ocular Hypertension Treatment Study (OHTS) included eyes with IOP levels of 24–32 mmHg, and damage was found in 9.5% of the untreated eyes after a mean follow-up time of 6 years, although more than half of those eyes still had normal visual fields (Kass et al. 2002). The risk of glaucoma is greater at higher IOP and/or if the central corneal thickness is low (Gordon et al. 2002).

Patients whose IOP levels frequently exceed 25 mmHg should be offered annual or biennial follow-up as long as the elevated pressure persists. Treatment should be considered if the IOP is above 28–30 mmHg or exfoliation is present (see below). Age should also be taken into consideration: there is more reason to treat younger patients. Follow-up examinations should be done at intervals of one to two years and should aim to identify possible glaucomatous damage by including repeated visual field testing or imaging of the optic disc.

Eyes with IOP levels above 35 mmHg have not been included in the studies mentioned above. Such eyes require more frequent monitoring (initially every three months) or

treatment. Patients who have both ocular hypertension and exfoliation syndrome represent a special risk group. Compared to eyes that have neither exfoliation syndrome nor ocular hypertension, eyes that have only exfoliation syndrome are at 5–10 times greater risk of developing glaucoma, and those with both ocular hypertension and exfoliation are at 50 times greater risk of glaucoma (Ekström 1993) and in many cases also show glaucomatous damage after 10 years (Grødum et al. 2005). Exfoliation syndrome with normal IOP occurs in a very large proportion of the elderly population (Åström et al., 2007), and thus it is not realistic to offer this group regular eye examinations.

Suspicious optic discs

The size of the optic disc should be determined if an eye is found to have a large physiologic cup, because measurements of these two structures are strongly correlated in normal eyes (Bengtsson 1976). Normal optic discs that are large are often mistakenly classified as glaucomatous (Heijl & Mölder 1993), and hence the term preperimetric glaucoma should be used with particular caution if the IOP is normal. In many people, asymmetric cups are the result of different sized optic discs (Bengtsson 1980). Accordingly, if glaucoma is suspected on the basis of cup asymmetry, the patient's optic disc sizes should be measured. If disc diameters differ between eyes, it is highly likely that the person does not have glaucoma.

Optic disc haemorrhage

Optic disc haemorrhages are probably more significant than a slightly elevated IOP as a risk factor for glaucomatous damage. Eyes with such haemorrhages but no visual field defects should be examined at intervals of several years.

Exfoliation syndrome

In Sweden, exfoliation syndrome is common in older people and is highly prevalent among the elderly (Åström & Lindén 2007). Therefore, a patient with exfoliation but normal IOP does

not need to undergo regular examinations, whereas the situation is completely different if the IOP is elevated (Grødum et al. 2005), as discussed above.

Glaucoma and positive family history

Knowledge concerning inheritance of glaucoma is increasing rapidly, but as of yet that information is of little value in routine clinical practice. Many patients with glaucoma are elderly and do not know or cannot remember whether any of their relatives had the disease. Furthermore, glaucoma is still frequently confused with cataract. Indeed, there is seldom convincing data to support the advice given and examinations performed. For clinical use, it can be appropriate to limit the definition of a family history of glaucoma to having at least one first-degree relative (parent, sibling or child) who has (or has had) some form of the disease as an adult. If resources are available, people who are over 50 years of age and have a family history of glaucoma should be offered an ophthalmic investigation. Increased intraocular pressure measurement alone is not sufficient; it is also necessary to conduct one or more tests that can detect glaucomatous damage, such as visual field analysis or evaluation of the optic disc and retinal nerve fibre layer. If the results of all tests are normal, the person in question can be offered further examination every 5 years. Examinations should be done more often in families that have several members with glaucoma, especially if the disease appeared at a younger age. When examining people who have a history of glaucoma (most of whom are healthy), it is important to perform tests that provide high specificity and instead accept lower sensitivity. A visual field screening technique is suitable for this purpose (see p. 13).

If patients with a family history of glaucoma are to be referred to an optometrist or optician for examinations, this professional should be able not only to measure IOP, but also to perform visual field testing and/or optic disc photography. Development of such co-operation agreements must

be guided by local availability of resources and circumstances.

The examination protocol should be planned locally with regard to content and the person or persons in charge, and also with the understanding that it must be designed to identify glaucomatous damage and thus cannot include only tonometry.

Encourage patients with glaucoma to urge their siblings and children to have regular examinations for glaucoma after the age of 50.

Recommend that an examination be done every 5 years.

7 Population Screening and Case Finding

Many patients with glaucoma already have serious visual impairment at the time they are diagnosed with the disease, which is a major problem, particularly because the risk of permanent visual disability is greatest when diagnosis is made at a late stage (Chen 2004). In a study conducted in Malmö (Grødum et al. 2004), it was found that patients with glaucomatous damage in both eyes at the time of clinical diagnosis had, on average, lost more than half of the visual field in the worst eye. By comparison, visual impairment was much less extensive in patients identified by screening. Indeed, a fairly significant number of patients with normal-tension glaucoma revealed by screening had been missed in previous clinical examinations performed because of a positive family history of glaucoma. It is well known that at least 50% of people with glaucoma remain undiagnosed in developed countries.

It is essential that glaucoma is diagnosed at earlier stages than today, and there is certainly more to gain here, than by trying to achieve earlier diagnosis in patients who are already under observation because of suspected glaucoma (e.g. because they have ocular hypertension). Today, suspicion of this disease is usually based on tonometry results (Quigley & Jampel 2003), but this is not sufficient.

Tonometry performed by an optometrist or optician can identify some patients, but that is not a complete solution to the problem, because the majority of people with undetected

glaucoma have normal or only slightly elevated IOP values. To be able to identify the unidentified cases, we cannot recommend that a low limit for IOP be used as a prerequisite for referral to an ophthalmologist. Such an approach would result in a large number of 'false alarms', which in turn would reduce the amount of resources available for patients who actually have glaucoma.

The following can be recommended to enable earlier diagnosis of glaucoma:

- (1) Consistently encourage patients with glaucoma to urge their children and siblings to have regular examinations for glaucoma after they reach the age of 50.
- (2) Examine the optic disc considering the possibility of glaucoma in all who are over the age of 60, who are undergoing an ophthalmic examination.
- (3) Population screening should be investigated but cannot be recommended at present (Wilson et al. 2006).

Ad (1) This examination should not consist solely of tonometry.

Ad (2) For example, all cataract patients.

Ad (3) It is important that all population screening for glaucoma be limited to certain risk groups. For example, the prevalence of undetected glaucoma at younger ages is so low that screening people under the age of 60 years can hardly be justified. The incidence of glaucoma is also low, and thus frequent screening examinations are unnecessary (Stoutenbeek et al. 2008). Furthermore, it is essential to use highly specific methods to strongly limit the number of false-positive cases. Since very high specificity cannot be combined with high sensitivity, it must be accepted that screening will not detect all cases of very early or early glaucoma. On the other hand, it is hardly acceptable to use screening methods that can fail to detect more advanced glaucomatous damage. Before population screening can be recommended, it must be eval-

uated in large-scale studies conducted in the same setting as where it will be undertaken in the future, such as at optometry services.

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Keyword index

- acetazolamide, 27
- adjustable sutures, 31
- age, 8, 23, 31
- air-puff or noncontact tonometry, 19
- alcohol, 10, 18
- antimetabolites, 30
- applanation tonometry, 18
- apraclonidine, 25
- ALT, 28
- ARA, 16
- argon laser trabeculoplasty, 28

- benefit, 6
- beta-receptor-blocking drugs, 25
- betaxolol, 25
- bimatoprost, 25
- biomicroscopy, 11
- blindness, 6
- blood flow, 28
- blood pressure, 9
- BMI, 10
- body mass index, 10
- brimonidine, 26
- brinzolamide, 26

- cannabinoids, 18
- carbachol, 25
- carbonic anhydrase inhibitors, 26, 27
- cardiovascular disease, 9
- case finding, 32
- cataract, 12, 22
- CCT, 9, 18
- C/D ratio, 10
- central corneal thickness, 9, 18
- chamber depth, 21
- children, 26
- coffee consumption, 10
- combination preparations, 27
- combination treatments, 27
- compliance, 29
- continuity, 24
- corneal thickness, 19
- corticosteroids, 10
- cortisone, 10
- CT examination, 22
- cumulative defect curve, 14
- cup, 10
- cyclodestructive procedures, 30
- cyclocryotherapy, 30

- DCT, 19
- deep sclerectomy, 30
- definition of glaucoma, 6

- diabetes, 9
- diagnosis, 21
- diffuse defect (DD), 16
- diode laser cyclophotocoagulation, 29
- disc diameter, 10
- disc haemorrhages, 11
- diet, 10
- documentation of the optic disc, 24
- dorzolamide, 27
- dynamic contour tonometry, 19
- dynamic gonioscopy, 21
- dynamic range, 13

- effect of reducing IOP, 23
- endophthalmitis, 30
- epidemiology, 7
- ethnicity/race, 8
- event analysis, 15
- excavation, 10
- exfoliations, 7, 32
- exfoliation syndrome, 8, 32
- extrapolation, 24
- EuroQoL, 6

- factors that influence intraocular pressure, 17
- false-negative responses (FN), 14
- false-positive responses (FP), 14
- family history, 8, 13, 32
- Fastpac, 13
- fetal damage, 27
- fetal injury, 27
- filtering surgery, 29
- fluctuations in IOP, 8
- 5-fluorouracil, 30
- FN responses, 14
- follow-up, 24
- FP responses, 14
- frequency doubling perimetry, 13
- 5-FU, 31
- Full Threshold, 13

- GDx, 11, 22
- GDx ECC, 11
- GDx VCC, 11
- general anaesthesia, 18
- glaucoma, 6
- glaucoma and positive family history, 8, 13, 32
- glaucoma change probability maps, 15
- Glaucoma Hemifield Test, 14
- Glaucoma Probability Score, 11
- global deviation, 17

- goal of treatment, 22
- Goldmann applanation tonometer, 18
- gonioscopy, 20
- gray scale, 14

- Heidelberg Retina Tomograph (HRT), 11
- heredity, 8, 13, 32
- high blood pressure, 9
- high-pass resolution perimetry, 13, 17
- HRQoL, 7
- HRT, 22
- Humphrey Field Analyzer, 12
- hypotonia, 30

- i-care tonometer, 19
- incidence, 7
- individualized glaucoma management, 24
- interpretation of visual field tests, 15
- intervals, 24
- intraocular pressure, 8, 17
- IOP, 8, 17
- ISNT rule, 10

- kinetic perimetry, 12

- laser trabeculoplasty, 28
- laser treatment, 28
- latanoprost, 25
- life expectancy, 7
- lifestyle factors, 10
- likely progression, 15
- loss variance (LV), 14
- lowering IOP, 22
- low-tension glaucoma, 6
- LSD, 18
- LTP, 28

- management of glaucoma, 21
- management of ocular hypertension, 31
- management of suspected glaucoma, 31
- massage, 31
- measurement of IOP, 17
- mean defect (MD), 14
- mean deviation (MD), 14
- media opacity, 12
- memantine, 28
- migraine, 9
- mitomycin C, 30
- MMC, 30

- Moorfields regression analysis, 11
MRI examination, 22
myopia, 9
- natural history, 23
needling, 31
neuroprotection, 22
neuroprotective, 28
neuroretinal rim, 10
nifedipine, 22
non-penetrating trabeculectomy, 30
normal intraocular pressure, 6
normal-tension, 6
NPT, 30
NPT techniques, 30
numerical maps, 14, 15
numerical threshold values, 14
nursing, 27
- occlude the lacrimal duct, 25
OCT, 22
Octopus perimeter, 12
ocular hypertension, 7
ocular response analyser (ORA), 19
open-angle glaucoma, 6
ophthalmoscopy, 11
optic disc, 10
optic disc haemorrhage, 32
optic disc photography, 11
optical coherence tomography, 12
ORA, 19
orbscan, 20
overall assessment, 24
- pachymetry, 20
parameters for cyclophotocoagulation, 29
parameters for laser suture lysis, 31
parasympathomimetics, 26
Pascal, 19
pattern deviation probability maps, 15
pattern standard deviation, 14
peak level, 25
perfusion pressure, 8
perimetric glaucoma, 10
perimetry, 12
peripapillary atrophy, 11
- Perkins tonometer, 19
pharmacological treatment, 25
physical activity, 10
pilocarpine, 26
population screening, 32
possible progression, 15
postoperative 5-FU, 31
postoperative management, 30
pregnancy, 27
pregnant woman, 27
preperimetric glaucoma, 21
preservative, 25
prevalence, 7
primary laser treatment, 29
probability maps, 14, 15
progression, 27
prostaglandin analogues, 25
PSD, 14
- QoL, 6, 22
quality of life, 6, 22
- radiation, 30
radiological investigations, 22
rate of progression, 14, 16, 23
rate of visual field progression, 14, 16, 23
Raynaud's syndrome, 9
rebound tonometry, 19
reliability parameters, 14
retinal nerve fibre layer, 10
ring perimetry, 13
risk analysis, 23
risk factors, 8
- salicylic acid, 11
SAP, 12
scanning laser tomography, 11
screening and threshold programmes, 13
selective laser trabeculoplasty, 28
selective perimetry, 13
seven-in-one, 14
severely myopic, 22
SF-36, 6
shunts, 30
single-field analysis, 14
- SITA Fast, 13
SITA Standard, 13
size of the optic disc, 10, 32
sleep apnea, 9
slit-scan pachymetry, 20
SLT, 28
SLT parameters, 28
smoking, 10
standard automated perimetry (SAP), 12
static gonioscopy, 20
static perimetry, 13
supraliminal, 13
surgery, 28, 29
suspicious optic discs, 32
suture removal, 31
switch, 27
sympathomimetics, 25
- tafloprost, 25
target intraocular pressure, 23, 28
tendency-oriented perimetry, 13
timolol, 25
tonometry, 17
tonopen, 19
TOP, 13
trabeculectomy, 29
traffic accidents, 22
travoprost, 25
treatment methods, 25
treatment methods and effect, 22
treatment stages, 27
trough level, 25
- ultrasound pachymetry, 20
utility, 6
- van Herick's method, 20
VFI, 16
VFQ-25, 6
viscocanalostomy, 30
visual disability, 6, 24
visual field index (VFI), 14
- YAG laser goniotomy, 31