RISK FACTORS FOR PRIMARY OPEN ANGLE GLAUCOMA AND ANGLE CLOSURE GLAUCOMA

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CHAPTER CONTENTS

INTRODUCTION 1
RISK FACTORS IDENTIFIED FROM PATIENT HISTORY 1
RISK FACTORS DETERMINED BY OCULAR EXAMINATION 2
SUMMARY OF RISK FACTORS 7
OCULAR RISK FACTORS FOR ANGLE CLOSURE GLAUCOMA 8

INTRODUCTION

Numerous risk factors for primary open angle glaucoma (POAG) exist and can be divided into those identified from the patient history and those identified from ocular examination.
POAG and angle closure glaucoma (ACG) have some common and some separate risk factors.

RISK FACTORS IDENTIFIED FROM PATIENT HISTORY

Demographic risk factors for POAG include age, race and family history of glaucoma.

AGE

The risk of POAG increases significantly with increasing age. There is a 3.5x higher prevalence in individuals over 70 (Baltimore Eye Study). This is particularly true of Hispanics, who have a very high prevalence of glaucoma in people over the age of 80.

The risk of ACG also increases with age, particularly for Chinese individuals.

ETHNIC ORIGIN

POAG: Black Africans and persons in the United States and the Caribbean with African heritage, have a significantly higher risk (3-4x) of POAG compared to white or European-derived populations. Hispanics also have a significantly higher risk of POAG compared to white populations, especially in people older than 60 years of age.
ACG: Eskimo populations have the highest risk of ACG. East Asian and Indian populations also have a high prevalence of ACG.

FAMILY HISTORY

While the genetics of POAG are largely unknown, numerous studies indicate that family history of POAG is a significant risk factor. A history of a sibling with POAG carries the highest risk - as much as 4-9x the risk according to some studies. The genetics of ACG are not well understood, but a family history of ACG is also a significant risk factor for the disease.

GENDER

There is no clear indication that POAG is more commonly found in women or men.
However, females are more likely to develop both acute angle closure (AAC) and ACG than males.

SYSTEMIC RISK FACTORS

Systemic risk factors for POAG are not as well-defined as other risk factors. However, there is some support for the following as potential risk factors:

- Diabetes mellitus (increased risk if uncontrolled)
- Long-standing systemic hypertension
- Smoking
- Thyroid disease
- Sleep apnea
- Steroid use (oral and nasal)
- Increased episcleral venous pressure e.g. tight neckties, headstands in yoga, playing wind instruments
- Blood loss
- Cardiovascular disease

No systemic risk factors have been identified for the development of ACG.

RISK FACTORS DETERMINED BY OCULAR EXAMINATION

Ocular risk factors for POAG include elevated intraocular pressure and myopia.

ELEVATED IOP

While elevated IOP is no longer included in the definition of POAG, it remains one of the strongest risk factors for its development. The higher the IOP, the stronger is the risk of glaucoma. However, glaucoma can occur at any IOP level, so IOP is not a good screening tool for the disease. IOP should be considered as a continuum of risk rather than as specific thresholds for concern. IOP remains one of the only ***modifiable*** risk factors for glaucoma.

- The level of IOP regarded as the threshold for defining increased IOP varies in the published literature. That 95% of the normal population has an IOP between 10 and 21 mm Hg is the explanation for the traditional use of 21 mm Hg as being the upper limit of ‘normal’ for IOP findings (Hatt, Wormald, Burr et al., 2006).

- For individuals with IOP from 20 to 23 mm Hg, the risk of developing glaucoma is reported as four times greater than for individuals with IOP below 16 mm Hg. This risk increases exponentially to 10 times when the IOP is ≥24 mm Hg, and to more than 40 times the risk, when IOP is >30 mm Hg (Sommer, Katz, Quigley et al., 1991).
- Different individuals vary in the degree of susceptibility of their optic nerves to damage at a particular IOP. This susceptibility depends in part upon the individual nerve constitution, systemic factors such as blood pressure and the presence and severity of disease.
- Individuals with glaucoma who have IOP in the 'normal' range are labelled as having normal tension glaucoma (NTG).
- High or fluctuating IOP remains a risk factor for all types and all stages of glaucoma. There is strong evidence that every 1 mm Hg increase in mean IOP level is associated with a 10% increased risk of progression from ocular hypertension (OHTN) to glaucoma, and in progressive glaucomatous damage.

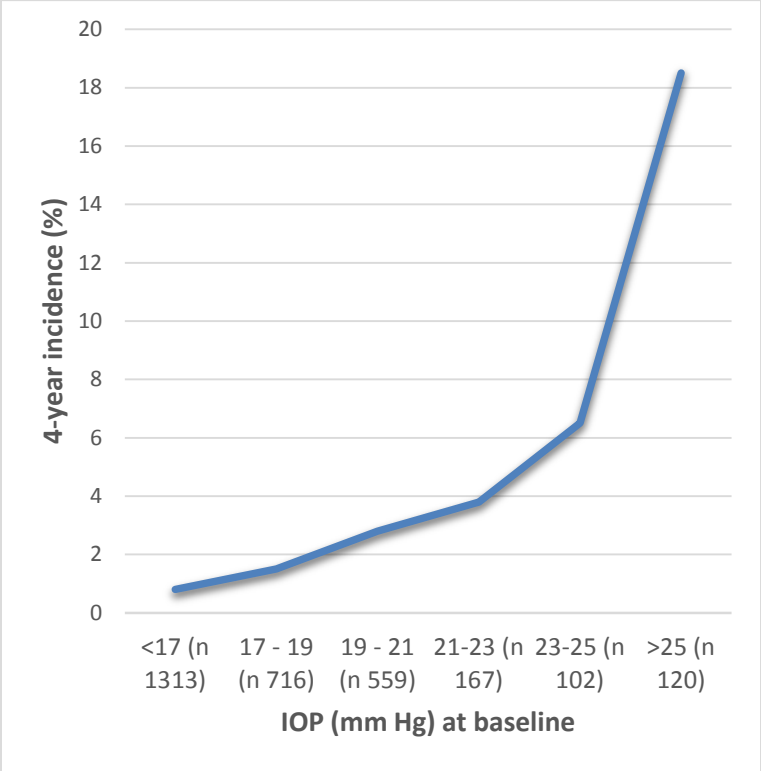

Figure 10.1: *Relationship between IOP and POAG (Baltimore Eye Study)*

Intraocular Pressure (mm Hg)	Incidence with optic nerve damage (%)
20-24	3
25-29	7
30-34	14
35-39	52
40-44	61
45-49	75
50-54	83
55-59	83
<60	70

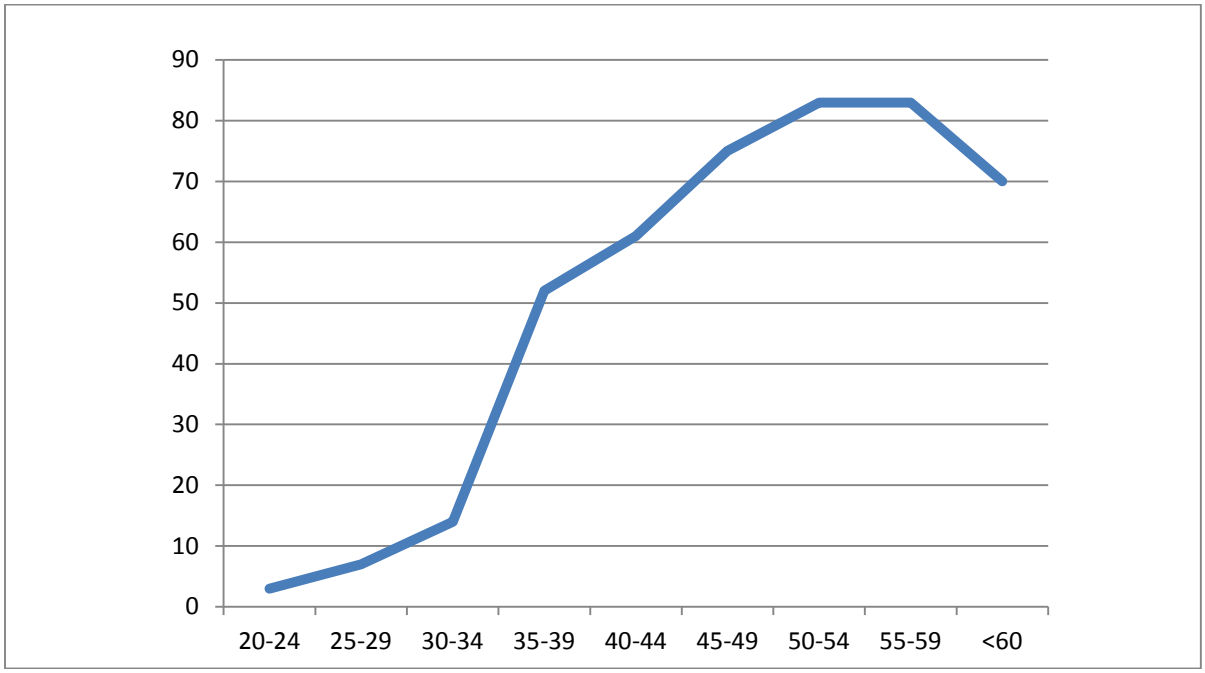

Table 10.1 and Figure 10.2: *Incidence (%) of optic nerve damage related to IOP (mm Hg)*

HA Quigley, S.Vitale. Models of open-angle glaucoma prevalence and incidence in the United States. Invest Opthalmol Vis Sci 1997;38(1):83-91

MYOPIA

Several studies indicate that myopia, particularly a high degree of myopia, is a risk factor for POAG. This is considered to be from a weakening of the sclera which occurs with longer axial lengths seen in higher degrees of myopia.

CENTRAL CORNEAL THICKNESS

Thinner corneal thickness is associated with increased risk of developing glaucoma (Ocular Hypertension Study) and is an independent risk factor for the development of glaucoma.

Central corneal thickness (CCT) data from the Ocular Hypertension Treatment Study (Budenz et al 2006) suggest that individuals with thinner corneas are at increased risk of developing glaucoma. This study showed that regardless of the IOP, progression to glaucoma was more likely in individuals with thinner central corneas. For instance, in the OHTS study, it was found that an individual with an IOP of less than 23 mmHg and a CCT of less than 555 µm had a 17% risk of developing glaucoma in 5 years, while an individual with an IOP greater than 26 mmHg and a CCT of greater than 588 µm had a 5 year risk of glaucoma of 6%. Similarly, another individual who also had an IOP greater than 26mmHg and a CCT of less than 555µm had a risk of progression of 26%.

Corneal thickness is also known to affect the calibration of applanation tonometry, commonly used to measure IOP. Goldmann applanation tonometry measurements are based on the assumption that a normal corneal thickness is 520 µm; therefore any CCT higher or lower than this will give slightly inaccurate measurements. People with thin corneas will yield an IOP measurement that is lower than the actual measurement. Thus, whilst the role of CCT as a risk determinant of glaucoma still requires clarification, assessment of CCT is considered to be a useful component of an overall assessment.

INCREASED CUP/DISC RATIO

A high vertical cup/disc ratio, vertical cup/disc ratio asymmetry and pattern standard deviation on visual field analysis are good predictors of the onset of POAG, as reported in the European Glaucoma Prevention Study (European Guidelines Society [EGS] 2003) and the Ocular Hypertension Study (OHTS).

Other guidelines (Royal College of Ophthalmologists, 2004) state the risk factors for conversion to POAG as follows:

- increased cup/disc ratio
- cup/disc ratio asymmetry > 0.2
- previous history of disc haemorrhage
- reduced CCT
- retinal nerve fiber defects even in the absence of optic head pathological changes

The cup/disc ratio is a value obtained by dividing the cup diameter by the disc diameter. The closer this value is to 1, the greater the level of tissue loss and therefore damage to the disc.

OPTIC DISC HAEMORRHAGE

Optic disc rim haemorrhages are significant risk factors for the development of glaucoma, as indicated in the Blue Mountains Eye Study (Mitchell et al 1996).

The Ocular Hypertension Treatment Study (Budenz et al 2006) reported that subjects with optic disc rim haemorrhage were twice as likely to progress to glaucoma as those without.

The Early Manifest Glaucoma Treatment Trial (Leske, Heijl, Hyman et al 2004) reported that those with optic disc rim haemorrhage were more likely to progress, with a strong relationship being reported between frequency of optic disc rim haemorrhage and risk of progression. Optic disc rim haemorrhage is an evanescent finding and is clearly visible for approximately six weeks after formation. A notch or nerve fiber defect may be left after the resolution of the acute haemorrhage. This can be an indicator of development or progression of glaucoma to a health care provider examining the eye.

OTHER STRONGLY ACKNOWLEDGED RISK FACTORS

Other risk factors for POAG that have been reported in the literature include the following:

- Low ocular perfusion pressure
  - Causes alteration in blood flow to the optic nerve
  - Ocular perfusion pressure value of less than 50 is associated with higher prevalence of POAG
  - A modifiable risk factor

- Systemic factors
  - Low diastolic blood pressure, hypotension, sleep apnea, thyroid disease, migraine, vasospasm, and Raynaud's phenomenon

- Genetic link
  - The role of genes in the pathogenesis is unclear – optineuron may play a neuroprotective role by reducing retinal ganglion cell susceptibility to apoptosis. One study found that over-expression of this variant compromises mitochondrial membrane integrity, increasing the susceptibility to death
  - Inherited as a complex trait – interaction of multiple genes and environmental factors
  - Currently 14 chromosomal loci for POAG listed by HUGO (GLC1A-N)
  - 3 genes within these loci have been identified: myocilin/TIGR (GLC1A), optineuron (GLC1E) and WDR36 (GLC1G)

SUMMARY OF RISK FACTORS

The risk factors shown in Table 10.2 are from randomized control studies.

STUDY	PURPOSE	RESULTS	RISK FACTORS
Ocular Hypertension Treatment Study (OHTS)	Evaluate safety and efficacy of topical ocular hypotensive medications in preventing or delaying onset of visual field loss and/or optic nerve damage in patients with ocular hypertension (IOP between 24-32 mm Hg)	Topical hypotensive medication delayed or prevented the onset of POAG	– Age (> 55) – Vertical c/d ratio (> 0.5) – Thin CCT – PSD (Visual field index) > 1.9 dB – IOP at baseline > 22 mm Hg
Early Manifest Glaucoma Trial (EMGT)	Compare immediate lowering of IOP with observation in progression of newly diagnosed open angle glaucoma	Progression risk halved by treatment Every 1 mm Hg decrease = 10% decrease in risk of progression	– No treatment – Age – Higher IOP – Exfoliation – Greater initial visual field loss – Bilateral glaucoma

Table 10.2: *Glaucoma risk factors*

Baseline risk factors for developing glaucoma (OHTS) are shown in Table 10.3.

The increases and decreases shown in Table 10.3 are **changes from baseline**.

Risk Factor	For every:	Relative Risk Factor for Glaucoma
		5 year risk of development to glaucoma increased by:
Age	10 year increase	22%
IOP	1 mm increase	10%
CCT	40 um decrease	71%
Vertical C/D ratio	0.1 increase	32%
PSD	0.2dB increase	27%

Table 10.3: *Relative risk for glaucoma*

Significant baseline predictive factors from multivariate proportional hazard models (OHTS) are shown in Figure 10.3.

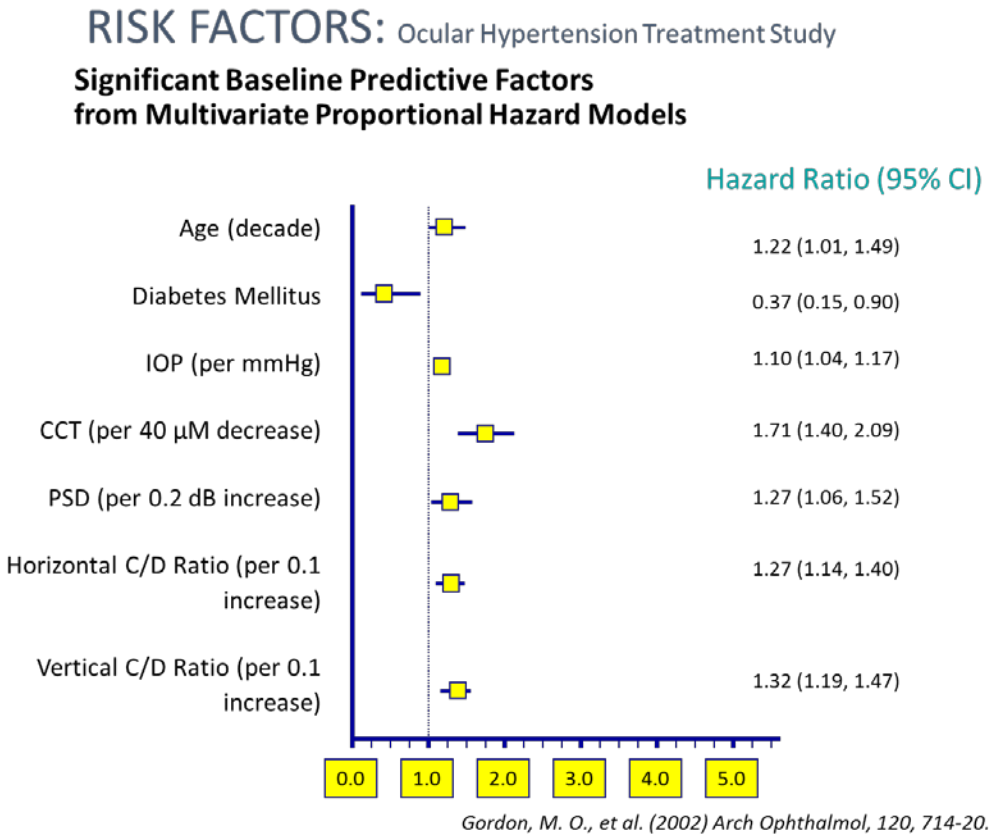

Figure 10.3: *Baseline predictive factors for glaucoma*

The prediction of OHTN patients developing glaucoma within 5 years are shown in Table 10.4. These predictions are based on the OHTS-EGPS study results.

Baseline Predictor	**Points for Baseline Predictor**				
	0	**1**	**2**	**3**	**4**
Age (yrs)	<45	45-<55	55-<65	65-<75	≥ 75
Mean IOP (mmHg)	<22	22-<24	24-<26	26-<28	≥ 28
Mean CCT (um)	>600	576-600	551-575	526-550	≤ 525
Mean vertical C/D	< 0.3	0.3-<0.4	0.4-<0.5	0.5-<0.6	≥0.6
Mean PSD (dB)	<1.8	1.2-<2.0	2.0-2.4	2.4-<2.8	≥ 2.8
Sum of Points	**0-6**	**7-8**	**9-10**	**11-12**	**>12**
Estimated **5 year risk**	≤ 4.0%	10%	15%	20%	≥33%

Table 10.4: *Prediction for developing glaucoma*

This prediction model is to be used with caution by the clinician. It is not a replacement for clinical judgment and the clinician always needs to consider all risk factors and the clinical picture when making management decisions.

OCULAR RISK FACTORS FOR ANGLE CLOSURE GLAUCOMA

REFRACTIVE ERROR AND AXIAL LENGTH

- Shorter axial lengths result in hyperopia
- Both refractive error and axial length have been identified as risk factors for the development of ACG

ANTERIOR CHAMBER DEPTH

- Shallow anterior chamber depths are associated with ACG

CRYSTALLINE LENS THICKNESS

- The risk of ACG increases with an increase in thickness of the crystalline lens. With age, the lens increases in thickness and this may explain the increased risk of ACG in older individuals