Epidemiology clinical trials in glaucoma

Pinakin Davey OD, PhD, FAAO
Professor and Director of Research

Western University of Health Sciences
College of Optometry

Disclosures

- None

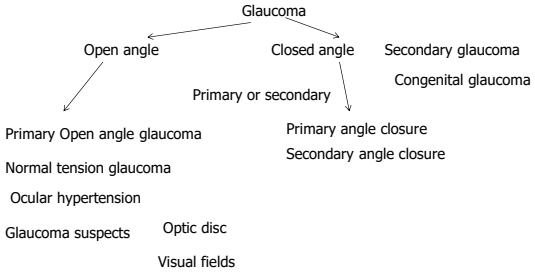
Definitions

- Epidemiology
  - A branch of medical science that deals with the incidence, distribution, and control of disease in a population.
- Prevalence
  - The number of instances of a given disease or other condition in a given population at a designated time.

What is glaucoma?

- Definition:
  - "Ocular tissue damage at least partially related to intraocular pressure"
  - Where glaucoma is concerned agreement is limited among clinicians and scientists.

Types of glaucoma



Prevalence of POAG in Caucasians

Study	Age range	Prevalence %
Roscommon	Over 50	1.9
Beaver Dam	43-84	2.1
Rotterdam	Over 55	1.1
Dalby	55-69	0.9
Blue Mountain	Over 49	2.4
Barbados Caucasians	40-84	0.8
Baltimore Caucasians	Over 40	1.3

Prevalence studies

- Prevalence in different studies varies
  - Different populations
  - Different methods used to obtain a sample
  - Definition of glaucoma

Prevalence of POAG in African American & African Caribbean

Study	Age range	Prevalence %
Barbados	40-84	7.1
Baltimore	Over 40	4.2
St Lucia	Over 30	8.8
London African-Caribbean	Over 35	3.9

Prevalence summary

- Prevalence of POAG is Caucasians over 40 years of age 2% and in African American and African Caribbeans is "four times" that.

Age and prevalence of glaucoma

- Age: Major effect; prevalence increases with increase in age
- Example: Baltimore eye study

	Age range	% Prevalence
Caucasians	40-49	0.92
	Over 80	2.16

Other studies also show the same trend!

Gender and POAG

- Unclear
- Blue mountain Women>Men
- Barbados Men>Women
- Rotterdam Men 3 times greater prevalence than women
- Other studies no difference

Prevalence of OHT in Caucasians

- Roscommon 3.6 %
- Blue Mountain 3.7 %
- Beaver Dam 25% of POAG had IOPs less than 21 mmHg.

Prevalence of angle-closure, narrow angles in Caucasians

Study	Age range	Prevalence %
Roscommon	Over 50	.09
Beaver Dam	43-84	.04
Blue Mountain	Over 49	.30
Baltimore Caucasians	Over 40	.40
Baltimore African-Americans	Over 40	.90

Asian population and angle-closure glaucoma

- Japanese population 0.31%*
- Chinese population Angle closure glaucoma 3 times more common than POAG**

- * Shiose et al A collaborative glaucoma survey for 1988 in Japan
- ** Quigley Number of people with glaucoma worldwide BJO 1996

Incidence of glaucoma

- Incidence: The number of instances of illness commencing, or persons falling ill, during a given period in a specified population.
- Very difficult to ascertain.
  - Early glaucoma needs to be followed for a long period of time.

Incidence of glaucoma -2

- Bedford Survey 0.048%
- Armaly et al 0.025%

- Incidence raises with age!
- .08/1000 at age 40 to 1.46/1000 at 80 yrs of age

Risk Factors

- Risk Factor: Aspect of personal behavior or life style, an environment exposure or an inborn or inherited characteristic which on the basis of epidemiological evidence is known to be associated to health conditions important to prevent.

Risk factors for glaucoma examined in population based studies

- Demographic
  - Age
  - Gender
  - Race
- Ocular
  - IOP
  - Optic nerve head
  - Myopia
  - Hypermetropia
- Systemic
  - Diabetes
  - Systemic hypertension
- Genetic
  - Family history
- Other
  - Cigarette smoking
  - Alcohol intake
  - Socio economic factors

Age & Gender

- Age; definite risk factor: Major
- Gender ? Overall unlikely
  - Barbados and Rotterdam Males> Females
  - Dalby Females > Males
  - Baltimore, Beaver Dam & Roscommon no association

Ethnic origin

- Higher prevalence of POAG among black racial groups and onset of disease is at a younger age.

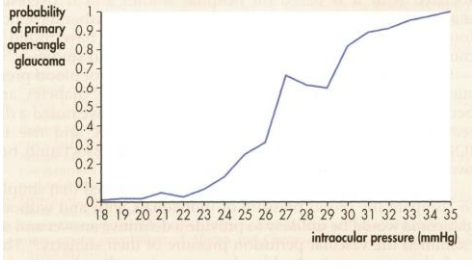
Ocular risk factors

- Intraocular pressure
- Optic nerve head
- Myopia
- Hypermetropia
- Central corneal thickness?

Intraocular pressure

- Major risk factor
  - Not as fundamental as once thought.
- Prevalence increases with increase in IOP
- Visual field loss slows down with decrease in IOP
- Even if both eyes have IOP lower than 21. The eye with greater IOP will lose field quicker.

Probablity of POAG relative to IOP



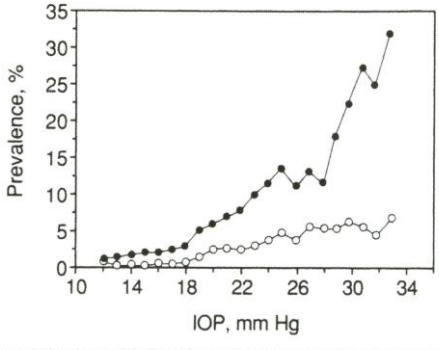
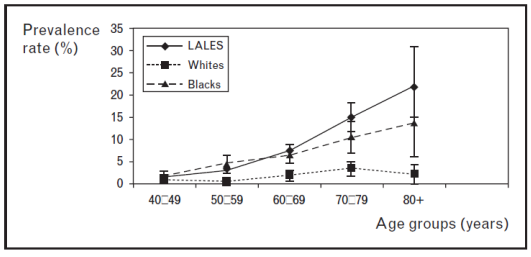


Figure 1. Prevalence of primary open-angle glaucoma in relation to screening IOP. NOTE: The curve is smoothed using a running mean with window width of 7 mm Hg. Caucasian American subjects, n = 5,700 eyes (open circles); African American subjects, n = 4,674 eyes (closed circles).

Figure 2 Comparison between the Los Angeles Latino Eye Study (LALES) and the Baltimore Eye Study (blacks and non-Hispanic whites) in age-specific prevalence of open-angle glaucoma



Prevalence of OAG in LALES

Age group (years)	Number who received on examination	Total	
		n (%)	95% CI
40–49	2363	31 (1.32)	0.90–1.86
50–59	1853	54 (2.92)	2.18–3.80
60–69	1195	88 (7.36)	5.90–9.08
70–79	584	86 (14.72)	11.78–18.18
≥80	147	32 (21.76)	14.90–30.72
Total	6142	291 (4.74)	4.22–5.30

Optic nerve head

- Important marker of presence and advancement of glaucoma.

Refractive errors

- Myopia : Associated with an increase in risk of POAG for a long time in hospital based population.
  - However hospital based studies are not ideal
- Hypermetropia: High degree of hypermetropia associated with acute types.

Diabetes and glaucoma

- Diabetes has been associated with glaucoma for a long time.
  - Hospital-based studies bias!
- The population based studies show no effect or much lesser effect.
- In studies like the Baltimore eye study show a protective effect!

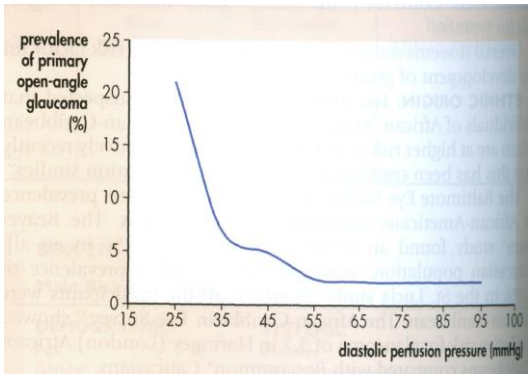
Diabetes and glaucoma

- Better to err on the side of caution and screen for glaucoma.
- Quigley's Baltimore eye study and OHTS study may have arrived at the conclusions due to bias in recruiting subjects!

Systemic hypertension and glaucoma

- Blood pressure and pathogenesis of glaucoma
  - Hospital based study
- Baltimore Eye Survey examined perfusion pressure
- Ocular Perfusion pressure= Blood pressure-IOP

(Systolic or Diastolic or mean pressure)



Tielsch et al Hypertension perfusion pressure and primary open angle glaucoma Arch ophthalmol 1995

Genetic factors

- Positive family history
- Bias:
  - + ve Family history makes a person have frequent check ups
  - Recall bias
    - Sibling with glaucoma odds ratio 3.69
    - Parents with glaucoma odds ratio 2.67
    - Children with glaucoma odds ratio 1.12

Other risk factors?

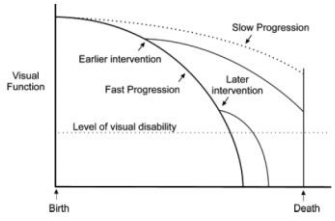
- Smoking
  - Katz and Sommer- Yes
  - Bever Dam- No
- Alcohol intake
  - Katz and Sommer -yes
  - Bever Dam- No
- Socio economic factors-Income, education, socio-economic status will have an effect.
  - Zip code effect!

Blindness and Glaucoma

- Major cause of irreversible blindness
- Approximately 6.7 million people are blind from glaucoma
- 120,000 blind in USA
- 10% will face blindness despite treatment
- 2% at 40-50 years of age have glaucoma
- 8% over 70 years of age have glaucoma

Blindness and 3

- Only 50% of patients are known.
- Rate of blindness is greater in African origin 6-8 times more than Caucasians.
- Third major cause of blindness in USA
- Most common cause of blindness registration among African-Americans



J Caprioli; A Visual Field Index for Calculation of Glaucoma Rate of Progression
American Journal of Ophthalmology, Volume 145, Issue 2, February 2008, Pages 343-353,

- Early diagnosis

Treat patients

Slow progression

Save sight and prevent blindness

- Any questions?

TREATMENT VERSUS NO TREATMENT

Collaborative normal tension glaucoma study

- OAG with normal IOP
- Patients had disc damage and field damage
- Progression was confirmed
- Fields confirmed 3 times.
- Evaluate rate of progression
- Effect of 30% drop in IOP on progression rate
- Meds, laser trabeculoplasty or trabeculectomy

- N= 230
- Treated vs Controls (approx equal sample size)
- Follow-up 5-7 years

Outcome

- Progression
  - 12% treated group vs 35% control group
- Cataract
  - 38% treated group vs 14% controls
  - Cataracts greater for surgical group vs meds or laser

Collaborative normal tension glaucoma study -outcomes

- Lowering IOP retards the progression rate of visual field loss compared with untreated eyes.
- Treatment effect was only obvious after removal of effect of cataract.
- **Some patients that progressed may have an IOP independent disease or IOP reduction was not enough**

Early Manifest Glaucoma Trial

- Newly diagnosed POAG
- Aims:
  - Compare treatment versus no treatment to evaluate effectiveness of IOP reduction in early previously untreated OAG
  - Secondary aims
    - Factors related to glaucoma progression
    - Natural history of disease

EMGT cont…2

- Population based screening in Sweden
- 44,243 screened
- 316 eyes of 255 patients recruited.
- Betaxolol and ALT vs obeservation
- Follow-up 6 years

Study details

- Every 3 months, IOP and perimetry (30-2)
- Every 6 months fundus photos
- Primary outcome measure
- VF loss in 3 consecutive fields
- Or disc damage change interpreted by masked observers.

Summary of results

- Mean untreated IOP 20.6 mmHg
- Progression rates were highly variable
- Progression 62% vs 45% untreated vs treated
- Risk of progression increased with higher baseline IOP compared to lower IOP
- More nuclear cataract in treated group vs controls
- VF identified progressors more readily than optic disc*

EMGT - Outcomes

- Treated group experience less and later progression than observation group (45% vs 62 %)
- Some patients showed no signs of progression despite no treatment.
- Results not applicable to high IOP or advanced glaucoma

EMGT Results cont…

- Pseudoexfoliation independent risk factor
- Post-hoc analysis
  - Thin CCT a risk factor in POAG
  - Low blood pressure risk factor in NTG
- IOP fluctuations was not a risk factor*
- Quality of life not different in treated vs untreated.

OHT VS POAG

- Differentiating OHT from early POAG may be very difficult.
- Look for signs of early damage
- SWAP and FDT may aid in early diagnosis of POAG

- In eyes with signs of early damage of optic disc the diagnosis of POAG should be considered and treatment initiated.
- Change if recorded can be diagnostic of early POAG

Ocular Hypertension Treatment Study

- Efficacy of topical hypotensive medications in delaying or preventing onset of glaucoma in ocular hypertensive patients.
- Medication versus observation
- N = 1636
- Follow-up 5 years
- Patients with IOP 24 to 32 mmHg one eye
- Other eye between 21 and 32 mmHg
- Randomly assigned to either treatment or observation group

Treatment goal

- IOP < 24 mmHg and at least 20% less than baseline
- Primary outcome
  - Development of POAG
    - As seen by VF abnormality
    - Or by disc abnormality

OHTs summary of results

- Mean IOP reduction was 22.5%
- Control group IOP decrease was 4% (why did control group decrease?)
- 4.4% of treated group progressed
- 9.5% of observation group progressed
- Treatment definitely shows a reduction of risk of glaucoma in OHT.
- Cataract formation was greater in treated group

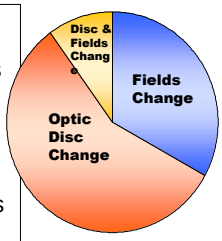
OHTS outcomes

- Baseline factors that predict onset of POAG
- Older age
- Larger vertical or horizontal CD ratio
- Greater PSD
- Higher IOP
- Strongest association was CCT
- Disc hemorrhage – increased risk of POAG development

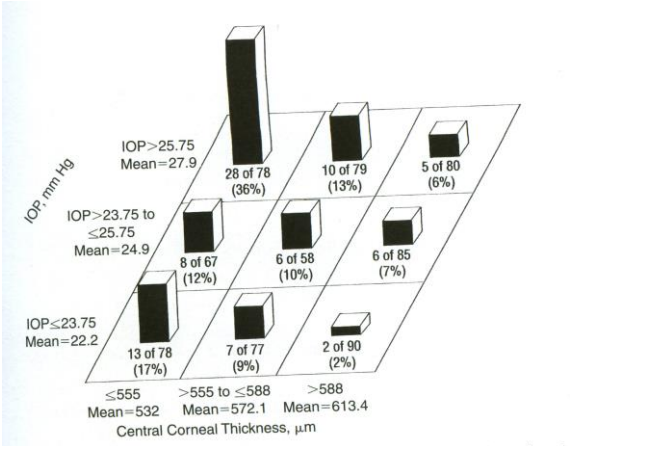
OHTS outcomes cont…

- However most untreated group did not deteriorate after 5 year of follow-up
- But the difference in treated versus untreated convertors increased with time.
- Both VF and disc evaluation is important; why?

- OHTS reports 55% of subjects reached endpoint (POAG) based on changes in the optic disc only.
- A further 10% of subjects had concurrent optic disc and visual field changes.
- Only 35% of glaucoma was found by visual field changes.



Kass et al., Arch Ophthalmol. 2002;120:701-703

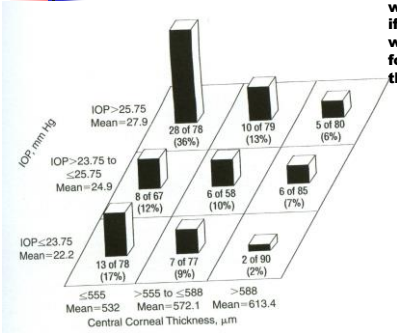


CCT and OHTS

- 40 micron decrease in CCT increased the risk of glaucomatous damage by 70%

Alternate explanation to OHTS reults

50% of OHTS patients will have normal IOP if correction factor was used to correct for central corneal thickness.



European glaucoma prevention study

- Similar to OHTS
- Efficacy of Dorzolamide in preventing ore delaying POAG in ocular hypertensive patients.
- IOP between 22 and 29 mmHg
- Main outcome VF and optic disc changes

Summary

- 1081 patients 120 developed POAG
- Duration of follow-up 55.3 months
- Mean IOP reduction
- 15% after 6 months
- 22% after 5 years — treatment group
- 9% after 6 months
- 19% after 5 years — control group

(because of regression to mean)

Results summary

- Same factors as OHTS predicted conversion to POAG
- Study failed to detect statistical significance between chosen treatment and placebo in either IOP lowering effect or in rate of conversion.

STUDIES COMPARING TREATMENTS

Clinical trials in glaucoma

Scottish glaucoma trial

- New POAG
- Medical therapy versus Trabeculectomy
- 116
- Mean follow-up 4.6 years

Scottish glaucoma trial- outcomes

- Trabeculectomy reduced IOP greater than medicine!
- Treated group showed greater deterioration in visual field when compared to trabeculectomy group

- Jay and Allan Eye 1989

Moorfields Primary Treatment Trial

- New POAG
- Medicine vs laser trabeculoplasty VS trabeculectomy
- N = 168
- Mean follow-up > 5 years

Moorfields Primary Treatment Trial -outcomes

- Lowering IOP
  - Trabeculectomy > Trabeculoplasty& medicine
- VF deterioration
  - Trabeculectomy < Trabeculoplasty& medicine

Glaucoma Laser Trial

- New POAG
- Medicine vs Laser trabeculoplasty
- N= 271
- Follow-up 2.5 to 5.5 years

Glaucoma Laser Trial - Outcomes

- Laser tabeculoplasty is at least as effective is medicine (timolol maleate)

Advanced Glaucoma Intervention Study -AGIS

- POAG after medical treatment failure
- No previous surgery
- Laser trabeculoplasty vs trabeculectomy
- N = 591 (789 eyes)
- Follow-up 4-7 years

AGIS outcomes

- Initially acuity loss was greater with trabeculectomy
- At 5 years VF loss was lesser with trabeculectomy in Caucasians
- Black patients had less progression with laser trabeculoplasty
- Dose-response relationship between IOP and VF progression likely

Collaborative Initial Glaucoma Treatment Study- CIGTS

- New POAG
- Medicine vs trabeculectomy
- N= 607
- Follow-up 5 years

CIGTS- Outcomes

- Outcomes very similar
- Surgical group had slightly more ocular symptoms early in the study

Overall picture based on all studies

- IOP reduction benefit is seen in POAG and OHT of various stages.
- Lower IOP means better protection but greater IOP reduction may not benefit all patients.
- IOP lowering treatment may not benefit all
- 20% IOP reduction in OHT patients may not prevent progression.
- Measurement of CCT in OHT and POAG patients must be done.

Overall picture continued….

- Large IOP reduction 40-50% may be required in patients at risk of vision loss threatens quality of life.
- All forms of treatment increase risk of cataract, especially glaucoma surgery.
- Disease progression increases with time