Recognised risk factors for glaucoma now include elevated intraocular pressure, age, race, family history, myopia and corneal thickness. In this article, Drs James Li Yim and Donald Montgomery discuss these risk factors such as the effect of diabetes and systemic hypertension, which may be protective of the optic nerve in some patients while posing a threat in others.

Glaucoma is the term applied to a group of optic neuropathies characterised by progressive retinal ganglion cell loss with corresponding visual field loss and optic nerve head tissue remodelling. Raised intraocular pressure (IOP) has long been recognised as a major risk factor for the development of these conditions.

In this article we will review the risk factors for glaucoma that are widely accepted and also those whose role is more speculative. We will give particular attention to the possible role of systemic hypertension as a potentially modifiable risk factor as this has been one of the more contentious issues with a number of population studies yielding conflicting results1-6.

**Intraocular pressure**

Elevated IOP is recognised as the most important risk factor for the development and progression of primary open angle glaucoma (POAG). In the population based Barbados Eye Study, participants with IOP greater than 21mmHg had more than eleven times the likelihood of having POAG than those with IOP of 21mmHg or less1. The Early Manifest Glaucoma Trial (EMGT) subsequently showed that the hazard ratio for progression of POAG was increased by 11 per cent for every 1mmHg of elevation of IOP2.

The Advanced Glaucoma Intervention Study (AGIS)3, Ocular Hypertension Treatment Study (OHTS)4, Collaborative Normal Tension Treatment Study (CNTTS)5, and EMGT6 have each convincingly shown that lowering of IOP reduces the progression of POAG. IOP can be lowered both by medical therapy and filtering surgery. The Collaborative Initial Glaucoma Treatment study (CIGTS) confirmed that either modality can effectively reduce IOP, being equally effective in reducing visual field progression at five years7.

**Age**

POAG is predominantly a disease of the elderly and population studies clearly show that increasing age is associated with an increased risk of development of the disease. The Blue Mountains Study reported prevalence increasing exponentially from 0.4 per cent at under 60 years to 11.5 per cent at over 80 years2 while in the Rotterdam study13 prevalence increased from 1.4 per cent between the ages of 55 to 59 years to 2.6 per cent at 80 years and older (p<0.001). Other studies have shown prevalences ranging from 0.2 per cent to 2.7 per cent in the 50 to 59 year old age group and ranging from 1.6 per cent to 12.8 per cent in over 80 year olds14-18. Ocular blood flow reduces with age and this evidence may favour a vascular/ischaemic theory for the progression of glaucoma19,20.

**Sex**

Studies of the relationship between sex and POAG have yielded conflicting results. Some found men to be at higher risk27; some found women to be at higher risk21 while some found no significant difference in risk between the sexes18.
Race
Epidemiological studies have shown that people of African descent have an increased risk of visual impairment from glaucoma compared with their white counterparts. In addition to a greater prevalence of glaucoma they tend to experience an earlier onset of the disease, which is more advanced at presentation and responds less well to treatment, contributing to a higher risk of blindness. In the Barbados Eye study involving 4,709 patients between the ages of 40 and 84 years, the prevalence of POAG was found to be seven per cent amongst blacks and 0.8 per cent amongst whites. Similarly, the Baltimore study found the prevalence of POAG was three to four times as high in blacks as in whites.

Family history
In a population-based study Wolfs et al. demonstrated that the prevalence of glaucoma was much higher in siblings and offspring of patients with glaucoma than in relatives of controls. The lifetime risk of glaucoma was almost 10 times higher. A similar finding was observed in the Baltimore Eye Survey. It is very important that first degree relatives of patients with glaucoma receive regular eye checks in order to detect glaucoma at an early stage. Glaucoma represents a heterogeneous group of optic neuropathies and we can be certain that many genes are implicated in their pathogenesis. In the future it is very likely that genetic testing will be used to facilitate diagnosis and target specific therapies for glaucoma.

Myopia
The Blue Mountains Eye Study confirmed a strong relationship between glaucoma and myopia in an older white population sample. Myopic patients had a two to threefold increased risk of glaucoma compared with that of non-myopic participants independent of other glaucoma risk factors and IOP.

Central corneal thickness
It has long been known that normal variation in central corneal thickness (CCT) can have a very significant impact on the accuracy of IOP measurement by tonometry and correction factors have been proposed ranging from 1.1 to 3.5mmHg for every 10 per cent variation in CCT. Interest in this area has been reignited by the finding in OHTS that central corneal thickness (CCT) was a strong predictor for the development of POAG in patients with ocular hypertension. Patients with a CCT of 555μm or less had a threefold increased risk of developing POAG compared with those with a CCT of 588μm or more. Whether this relates simply to the fact that intraocular pressure was being underestimated in eyes with thin corneas or whether eyes with thin corneas truly have an increased vulnerability to glaucoma remains open to debate. Interestingly, CCT has not been shown to be a useful index in assessing the risk of progression in established glaucoma.

Diabetes
Whether or not diabetes represents a significant risk factor for glaucoma remains controversial. The population-based Beaver Dam and Rotterdam studies respectively appeared to demonstrate a doubling and tripling of the presence of POAG amongst diabetic subjects; however, a more recent Scottish study failed to confirm any firm association between diabetes and POAG and ocular hypertension. As diabetic patients tend to undergo regular fundoscopy it might be expected that asymptomatic glaucoma would be more likely to be detected than in subjects not undergoing regular examination. In epidemiological studies this type of detection bias can easily give rise to an apparent causal association where none exists or overemphasise any genuine association.

Blood pressure
The Blue Mountains Eye Study reported a 50 per cent higher risk of POAG in hypertensive patients when compared to normotensives, independent of IOP and other risk factors. In contrast, the Barbados Eye Study reported that hypertension halved the relative risk (RR) of incident POAG at four years. Between these two extremes, the Egna-Neumarkt Study noted a weak tendency towards an association between systemic hypertension and POAG prevalence, while the Baltimore study showed a modest positive association between systemic hypertension and POAG prevalence, with a stronger association among older subjects.

In attempting to reconcile these disparate findings it may be helpful to consider the vascular/ischaemic hypothesis of glaucoma that postulates that the condition is the result, at least in part, of inadequate perfusion of the optic nerve head. Increased blood pressure early in the course of systemic hypertension, before the onset of small vessel damage, could result in increased blood flow or greater hydrostatic resistance to closure of small vessels and therefore
Raised IOP on its own does not constitute the disease of glaucoma.

Ocular blood flow has been shown to reduce with age and this may favour a vascular/ischaemic theory for the progression of glaucoma.

In the future it is very likely that genetic testing will be used to facilitate diagnosis and target specific therapies for glaucoma.

Some studies have found a positive correlation between the presence of systemic hypertension and POAG while others have reported contradictory findings.

Several studies reported a strong association between lower diastolic perfusion pressure and a higher prevalence of POAG.

Care must therefore be taken to avoid overtreating systemic hypertension in patients with glaucoma as this may exacerbate nocturnal hypotension and result in further embarrassment of the optic nerve head.

Key points

- Raised IOP on its own does not constitute the disease of glaucoma.
- Ocular blood flow has been shown to reduce with age and this may favour a vascular/ischaemic theory for the progression of glaucoma.
- In the future it is very likely that genetic testing will be used to facilitate diagnosis and target specific therapies for glaucoma.
- Some studies have found a positive correlation between the presence of systemic hypertension and POAG while others have reported contradictory findings.
- Several studies reported a strong association between lower diastolic perfusion pressure and a higher prevalence of POAG.
- Care must therefore be taken to avoid overtreating systemic hypertension in patients with glaucoma as this may exacerbate nocturnal hypotension and result in further embarrassment of the optic nerve head.

Conclusion

Elevated IOP, age, race, family history, myopia and corneal thickness are now well accepted risk factors for glaucoma. Debate continues over whether diabetes and systemic hypertension should be regarded as posing additional risk. There does, however, seem to be compelling evidence that low ocular perfusion pressure, as a function of diastolic blood pressure and IOP, is associated with the development of POAG. There is also evidence that nocturnal hypotensive episodes, possibly compounded by optic nerve head vascular dysregulation, can lead to progression of glaucoma. Care must therefore be taken to avoid over treating systemic hypertension in patients with glaucoma as this may exacerbate nocturnal hypotension and result in further embarrassment of the optic nerve head. Patients with glaucoma and a history of vasospastic conditions such as migraine or Raynaud's phenomenon may be particularly vulnerable in this regard. They should be viewed by the ophthalmologist as being possibly a higher risk group warranting more regular monitoring and possibly earlier intervention.

Conflict of interest: none declared.
References


