

Although there are several [types](#) of glaucoma we will limit our focus here to primary open angle glaucoma. Primary Open-Angle Glaucoma (POAG) is the second leading cause of irreversible blindness in the United States. It is generally characterized by a clinical triad: (1) elevated intraocular (eye) pressure ; (2) development of [optic nerve atrophy](#); and (3) loss of peripheral [field of vision](#), ultimately impairing central vision. The term 'Glaucoma' as used in these pages refers to 'Primary open-angle glaucoma (POAG)'. Historically, glaucoma has been viewed as a disease caused by increased eye pressure. The current view is that glaucoma represents a common end stage clinical presentation of several different diseases. To understand this view, think of heart failure - which is not a disease but a clinical end stage because of many diseases like high blood pressure, coronary artery disease etc. Glaucoma is similarly regarded as a final common end stage pathway of a number of different conditions. While high eye pressure is the most important risk factor for the development & progression of glaucoma, it is still only a risk factor and not the disease itself.

Over the years, numerous investigators have studied the characteristics of individuals who have glaucoma, and based on those studies it became possible for them to identify several factors that seem to occur more frequently in glaucoma patients. Since there is a greater likelihood of these factors being present in someone with glaucoma, it is reasonable to assume that these be considered as risk factors for glaucoma. Any individual who has these risk factors should be screened for the possibility of glaucoma. It is estimated that approximately 10 patients per 1000 patients with glaucoma risk factors will develop glaucoma per year. This prompted Medicare to announce a [Glaucoma screening benefit](#) in January 2002. (View [video](#) of NEI glaucoma public service announcement)

Patients with glaucoma risk factors are followed as 'Glaucoma suspects'. How strong is the suspicion? That depends upon the number of risk factors present. In order to identify and determine whether you are a 'glaucoma suspect' or have other eye problems, the American Academy of Ophthalmology has suggested a [screening schedule](#). Eye examinations conducted at the suggested intervals are more likely to identify 'glaucoma suspect' eyes. If the screening tests identify you as having risk factors for glaucoma, then a more rigorous [follow-up schedule](#) is needed. In general this means establishing a baseline (visual fields, optic nerve pictures) and eye pressure measurements 3 to 4 times a year. Your physician will decide the follow-up interval based on the strength of the suspicion for glaucoma. Serial examinations and continuity of care are critical for glaucoma diagnosis and management. One-time examinations do not have the same value.

## **Risk Factors for Glaucoma**

### **Strong Risk Factors**

- High Intraocular (Eye) Pressure
- Aging

- Positive family history of glaucoma in a first degree relative
- Race (Blacks)
- Suspicious optic nerve appearance (cupping > 50% or asymmetry)
- Central corneal thickness less than 555 microns (0.5 mm)



### **Possible Risk Factors**

- High Myopia (near sightedness)
- Diabetes
- Hypertension
- Eye Injury or Surgery
- Other Risk Factors
  - History of steroid use
  - Migraine headache and peripheral vasospasm
  - Sleep-related breathing disorder
  - Gender: Male

### **Intraocular (Eye) Pressure and Glaucoma**

The generally accepted normal mean eye pressure (intraocular pressure - IOP) value is 15.5 mmHg with a standard deviation of 2.5 mmHg. The normal pressure can range from 10 to 21 mmHg. The eye pressure has a non-gaussian distribution with a skew towards higher pressures (meaning in many people pressure above the 21 mmHg level is not abnormal). It is well recognized that some eyes undergo extensive glaucoma damage even when the pressure is in the 'normal' range, while others suffer no damage with pressure well above 21 mmHg. Despite this, the value of 21 mmHg has been historically accepted as a good way to separate the 'normal' eye pressure from a pressure level which should be viewed with suspicion for glaucoma. The distribution of eye pressure in glaucoma patients was analyzed in the Baltimore Eye Survey. The likelihood that an eye with glaucoma will have a pressure of more than 22 mmHg was 8.6 times more than the likelihood of it having a pressure of less than 21 mmHg.

You must understand however, that just because you have eye pressure above 21 mmHg does not mean that you have glaucoma. What it does mean is that you are at a higher risk of developing glaucoma. If in addition you have some of the other strong risk factors, then reducing the eye pressure with eyedrops may be reasonable to lessen your chances of developing glaucoma in the future. If there are no other risk factors then it seems reasonable to follow you closely without any pressure reducing treatment. The **Ocular Hypertension Treatment Study (OHTS)** showed that if the high eye pressure is lowered (by approximately 20%), then the probability of developing glaucoma over a period of 5 years is about 4%. If the eye pressure is not lowered, the probability of developing glaucoma is about 9% - i.e twofold more than if treated (read more about this study in NIH [News Release](#)). After potential side effects of eyedrops and cost of treatment are factored in, it seems that even the OHTS trial favors treating high eye pressure only when other strong risk factors are present. In this study the highest risk patients were identified as having: 1) Eye pressure more than 27 mmHg; 2) cup to disc ratio more than 0.5; 3) Central corneal thickness less than 555 microns.

Of course, if you have field of vision defects in addition to high eye pressure, then you will be deemed as having glaucoma and will need treatment to lower the eye pressure rightaway. The results of the **Early Manifest Glaucoma Trial (EMGT)** show that immediately treating people who have early stage glaucoma can delay progression of the disease. In this trial, 49% of patients had progression of visual field defects if the eye pressure was not lowered, but fewer than 30% had glaucoma progression if the eye pressure was immediately lowered by 25% to a mean eye pressure of 15.5 mmHg (read more about this study in NIH [News Release](#)).

Accepting that lowering eye pressure is beneficial for glaucoma patients, a fundamental question is how much should it be lowered? Establishing a 'target pressure' provides an answer to this question. An appropriate target pressure can be considered to be the highest pressure level at which there is no further glaucoma damage. The initial 'target pressure' should be 20% to 30% lower. Additional lowering beyond 30% is justified by the number and severity of additional risk factors for the development of optic nerve damage, such as family history and race. The initial target pressure is an estimate and a means toward the ultimate goal of protecting the optic nerve. The adequacy and validity

of the target pressure are periodically reassessed by comparing optic nerve status (by optic nerve appearance and visual field tests) with previous (including baseline) examinations.

## Race and Glaucoma

In a study funded by the National Eye Institute, researchers at The Johns Hopkins University reported that glaucoma is three to four times more likely to occur in Blacks than in Whites. In addition, glaucoma is six times more likely to cause blindness in Blacks than in Whites.

In a study funded by the National Eye Institute called the **Advanced Glaucoma Intervention Study (AGIS)**, researchers found that black and white patients with advanced glaucoma respond differently to two surgical treatments for the disease (more about this study is in NEI [Press Release](#)). Blacks have thinner corneas than whites (by about 23 microns) and this may well be the factor that puts blacks at a higher risk for glaucoma progression (per EMGT study data).

## Family history and Glaucoma Genes

Glaucoma tends to run in families. In the Baltimore Eye Study, the risk of having glaucoma was approximately 3.7-fold higher for individuals who had a sibling with glaucoma (risk was slightly lower if a parent or children had glaucoma instead of a sibling). In the Rotterdam Eye Study, the risk of having glaucoma was 9.2-fold for individuals who had a relative with glaucoma. (Arch Ophthalmol 1998; 116:1640-5. Arch Ophthalmol 1994; 112:69-73. Surv Ophthalmol. 2002;47:547-61)

Although it is clear that genetics plays an important role in primary open angle glaucoma, details about the inheritance remain unclear. No single mode of inheritance can adequately describe glaucoma as a whole. It seems that glaucoma development depends not so much on a single gene but rather upon the interaction of several genes and possibly environmental factors too. However, a minor proportion of glaucoma (only about 3% of all open angle glaucoma) is caused by defects in single genes. The chromosomal locations of six genes that can independently cause glaucoma have been mapped. One of them is Myocilin gene. Many names for this gene have been coined as it was discovered independently by several laboratories. These names include TIGR (Trabecular-meshwork Induced Glucocorticoid Response), GLC1A, myocilin, and TIGR/myocilin.

The discovery of glaucoma genes provides a method for early detection of glaucoma. Genetic testing is capable of identifying those at highest risk for developing glaucoma. Such patients would include family members of patients with known glaucoma gene defects and members of families with a strong history of inherited glaucoma. However only about 3% of all primary open angle glaucoma patients have the glaucoma gene defect. This implies that the prevalence of glaucoma gene defects in the general population is very low. This makes routine screening tests of whole populations unviable. Even so, glaucoma gene testing of those who are at extremely high risk for developing glaucoma may be of value. The glaucoma gene test is commercially available (**Ocugene test**).

## Aging and Glaucoma

Everyone over age 60 has an increased risk for glaucoma. Other groups at increased risk include Blacks over age 40.

## Central corneal thickness and Glaucoma

The National Eye Institute supported Ocular Hypertension treatment study (OHTS) has identified corneal thickness as a strong risk factor for developing glaucoma. Patients with a corneal thickness less than 555 microns have a three fold greater risk of developing glaucoma as compared with those who's cornea are more than 588 microns thick. This surprising new information is expected to make corneal thickness measurement (pachymetry) an important part of the glaucoma work-up.

## High myopia (Near Sightedness) and Glaucoma

Nearsighted patients have a twofold to threefold increased risk of glaucoma compared with those who are not nearsighted. This association is weak for eyes with low myopia (Odds ratio, 2.3) but is stronger for eyes with moderate-to-high myopia (Odds ratio, 3.3) (Mitchell. Ophthalmology 1999; 106:2010-5).

## Diabetes and Glaucoma

Most studies support a weak association between Diabetes and Glaucoma. The odds ratio is a number

that shows the strength of association between diabetes and glaucoma. It can vary from 0 to infinity. If the odds ratio is one, there is no association. If it is more than 1, it means there is an association. For glaucoma and diabetes odds ratio in different studies has ranged from 1.03 to 3.11. Although present, this is not a strong association. The question whether or not diabetes is a significant risk factor for glaucoma remains controversial. Nevertheless, it is recommended that diabetics be screened for glaucoma and effective January 2002, Medicare has started to cover glaucoma screening examination in diabetics. (Ellis. Br J Ophthalmol 2000;84:1218-24, Mitchell. Ophthalmology 1997;104:712-18, Dielemans Ophthalmology 1995;102:54-60, Klein Ophthalmology 1994;101:1173-7)

### **High Blood Pressure and Glaucoma**

Several studies have shown that increase in systemic blood pressure produces a slight increase in eye pressure (IOP). Increases in eye pressure in response to 10-mmHg increase in systolic and diastolic blood pressures are only 0.24 and 0.40 mmHg, respectively. Therefore although real, the increase in eye pressure is of such modest proportions as to be of no clinical importance in the pathogenesis of Glaucoma. At best this finding is of theoretical interest. We can conclude that based on data available from several studies, hypertension produces eye pressure effects that are too slight to be regarded as a risk for glaucoma.

In contrast, the diastolic perfusion pressure of the ocular tissues is an important factor in the development of glaucoma damage. Lower diastolic perfusion pressure is associated with a marked, progressive increase in the frequency of glaucoma. Ocular (eye) diastolic perfusion pressure is calculated as follows: Diastolic blood pressure minus eye pressure. Therefore if your blood pressure is 120/80 and the eye pressure is 16, then the diastolic perfusion pressure will be 80 (diastolic pressure) minus 16 (eye pressure), in this case equal to 64 (80 minus 16). On the basis of data from several studies we may conclude that there is an increased risk of glaucoma damage when the ocular diastolic perfusion pressure is less than 55 mmHg. Reduced diastolic perfusion pressure is only one of the mechanisms whereby optic nerve damage can occur but it is probably not the most important in terms of frequency.

In general vascular diseases (systemic hypertension, atherosclerosis or vasospasm) play a greater role in normal-tension glaucoma (NTG) than primary open angle glaucoma (POAG). In hypertension, increase in peripheral vascular resistance (as opposed to increase in eye pressure) may contribute to glaucoma damage.

It is important to maintain an adequate balance between blood pressure and the eye pressure. The optic nerve can be compromised if it does not get enough blood supply and the eye pressure (IOP) remains high. This can happen in the following two situations:

1. If there is an aggressive lowering of blood pressure with medications. If the mean arterial pressure falls and the eye pressure due to Glaucoma remains high then blood supply to the optic nerve may fall below a critical level causing damage.
2. If the blood pressure control is good but you start taking Glaucoma eyedrops that also cause lowering of blood pressure (Timoptic, Betoptic etc).



The care of a patient with systemic hypertension and Glaucoma should be coordinated between the primary care physician and the ophthalmologist. (Bonomi. Ophthalmology 2000;107:1287-93, Tielsch. Arch Ophthalmol 1995;113:216-221, Dielemans Ophthalmology 1995;102:54-60, Leske Arch Ophthalmol 1995;113:918-924)

### **Sleep-Disordered Breathing and Glaucoma**

Sleep-disordered breathing (SDB) characterized by snoring, excessive daytime sleepiness and insomnia and is accompanied by large swings in blood pressure and repetitive hypoxic periods during sleep. Patients with Glaucoma have more sleep-disordered breathing. Chronic hemodynamic changes and recurrent severe hypoxia resulting from SDB may contribute to anoxic optic nerve damage, implicated in glaucoma. Normal-tension glaucoma patients constitute a high-risk population for sleep apnea syndrome. Therefore, they should be screened for sleep apnea syndrome and SDB with polysomnography, and, if necessary, be treated to avoid late cardiovascular and neurological sequelae. We recommend obtaining a sleep history from patients with Glaucoma and performing polysomnography in those patients with sleep disturbance symptoms. (Onen Acta Ophthalmol Scand 2000; 78:638-41. Mojon Ophthalmologica 2002; 216:180-4)

### **Gender (Male) and Glaucoma**

The relation between primary open-angle glaucoma and gender is still controversial. In the Baltimore Eye Survey (JAMA 1991;266:369-74), the Beaver Dam Eye Study (Ophthalmology 1992;99:1499-504), and the Blue Mountains Eye Study (Ophthalmology 1996;103:1661-9), no significant difference was found between prevalence of primary open-angle glaucoma in men and women. However, in the Framingham Eye Study (Am J Epidemiol 1977;106:17-32), the Barbados Eye Study (Arch Ophthalmol 1994;112:821-9), and the Rotterdam Study (Invest Ophthalmol Vis Sci 2000;41:3309-21), up to a twofold higher prevalence was found in men. If it is true that glaucoma occurs more often in men, then it makes sense to assume that female sex hormones have a possible protective effect on glaucoma. Indeed, Rotterdam study data was analyzed again recently to uncover the finding that women who achieved menopause prior to 45 years of age had a higher likelihood of developing glaucoma (Am J Epidemiol 2001;154:138-44).

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