

**REVIEW ON RISK FACTORS IN GLAUCOMA**

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**ABSTRACT**

Glaucoma, “the silent thief of sight”. It is a neurodegenerative syndrome characterized by a progressive optical atrophy that is the result of the retina ganglion cell death by apoptosis as a consequence of a combination of different components such as oxidative stress, ischemia, mitochondrial damage, and proteome alterations. Increased intra ocular pressure is mainly due to a backup of the aqueous humor circulates through the front of the eye. When determining the potential benefit of intra ocular pressure lowering, so consider the relationship between intra ocular pressure and the loss of retinal ganglion cells. There are many risk factors governing the development of glaucoma, for many years several epidemiological studies have been conducted to analyses the risk factors. As lots and lots of risk factors have been

identified it was hard to analyses their individual and collective effects on a patient. In inspecting the important diagnostic contribution of a patient, this review consider age, effect of gender, race, family history, injuries to the eye, blood pressure, hyperlipidemia, diabetes, depression and anxiety, and most of all drug induced glaucoma.

**KEYWORDS:** Glaucoma, Intraocular Pressure, Ocular Hypertension, Retinal Ganglion Cell.

**INTRODUCTION**

Glaucoma is a combination of diseases that leads to the irreversible loss of vision by destruction of eye’s optic nerve. The proper detection and treatment, can protect eyes from loss of vision.<sup>[1]</sup> After cataract it was found that glaucoma is the second largest cause of blindness worldwide. In 2013 number people affected with glaucoma was 64 million. This

will be increasing to 80 million by 2020.<sup>[1]</sup> Glaucoma is mainly caused by death of retinal ganglion cell (RGC) by apoptosis due to optical atrophy. Elevated intraocular pressure (IOP) is a significant risk of glaucoma.<sup>[2]</sup> Age, race, some diseases and some drugs are also induce glaucoma. There are seven types of glaucoma Primary Open-Angle Glaucoma, Normal Tension Glaucoma, Angle-Closure Glaucoma, Acute Glaucoma, Pigmentary Glaucoma, Exfoliation Syndrome and Trauma-Related Glaucoma. Most probably above 45 aged people were more prone to glaucoma, and have a family history. When consider the racial factors Africans have more chance. Patient who have any one of the following disease also show high prevalence, Diabetes, Myopia, Regular, long-term Steroid/Cortisone use and a previous eye injury. The early detection must decrease the severity of glaucoma. Medical diagnosing of glaucoma is mainly by using Tonometer, Visual Field Test and Ophthalmoscopy. Coming to the treatment part, first choice should be eye drop mainly prostaglandin analogs. But treatment methods varying from patients to patients with their severity. Other main treatment methods are pills, laser surgery and the final method is the eye operation, but it done only in extreme conditions. In initial stage commonly monotherapy is done, but in most of cases combination therapy give more positive result. In both mono and combination therapy thae main aim to reduce the IOP, so eye drop like medication have duration of 6 hours. Commonly pilocarpine, timolol, epinephrine and prostaglandin analogs are used in eye drops for glaucoma treatment. In case of pills carbonic anhydrase inhibitors like acetazolamide and methazolamide are used. But nowadays laser treatment gets more importance and priority.<sup>[3]</sup> Identification of risk factors of glaucoma is mainly done by population based study. There are lots of studies conducted in community level, as population based cohort studies. From all these studies there are some common factors that influence glaucoma especially in IOP, like gender, race, age, drugs and diseases.<sup>[4]</sup> Here we discuss and evaluate the risk factors of glaucoma on basis of studies conducted in population.

## **RISK FACTORS**

### **Age**

Age and incidence of glaucoma is directly proportional. Commonly glaucoma related with many age bonded diseases such as macular degeneration, vascular diseases, obstructive sleep apnea, pigmentary dispersion syndrome and pseudoexfoliation syndrome. Assessment of glaucoma at different age depends on different health conditions such as diabetes, hypertension, migraine, hypotension, cataracts, obstructive sleep apnea syndrome and drug

induced. As taking age as a risk factor to glaucoma, presence of so many other health issues can rise with the susceptibility. Glaucoma also has a high chance in a weaker young adult.<sup>[4]</sup>

### **Gender**

Eye disease is considered less affectively by patient sex as compared to the other diseases. The possible reason includes the presence of few morphological differences in eyes between men and women and few eye diseases that manifest with specific sex-based differences.<sup>[2]</sup>

Out of males and females, the prevalence of having Ocular Hypertension Treatment (OHT) shows that the most common factor for the onset of POAG. A study done by using meta-analysis of Bayesian, gives a clear picture that men were having most chances to effect Open angle glaucoma. In case of closure angle glaucoma, females get more prone. All of those findings should be pertinent with population studies and also females are having more life span than men, which may rise their chance for having glaucoma and progressively blindness followed by it.<sup>[4]</sup>

### **Genetics and family history**

The offer of genetics and family history in glaucoma prediction chance has always been controlled due to less education of family history but most of the patients have less knowledge of their relatives suffering with glaucoma. More than 50% of cases are undiagnosed due to the non-reliability of family disease history. In recent studies, it is proved that a patient with family history of glaucoma shows a relative risk of 2.1 times than others having OAG. The risk of family history may change relating to the nearness and relationship to the patient. It has been proven that about 50% of all primary open angle glaucoma patients have a family history with their close relatives such as parents, siblings and children are having a 9 times more risk. Wolfs et al and co-authors in their study found that the first degree close relatives have a 22% life-time chance of glaucoma when compared to other distant relatives. In most of studies, 10.4% patients were having a glaucoma diagnosed siblings but which is 0.7% in the siblings of normal. About 60% of glaucoma patients having glaucomatous relatives.<sup>[4]</sup>

### **Eye Conditions, Injuries, or Surgeries**

Many ophthalmic accidents such as injuries direct on eye, such as trauma and sports accidents or any history of injuries and having multiple eye surgeries for many complicated eye diseases. In blunt trauma, the sink system of eye is disturbed or it can cause inflammation

in the eye which leads to and rise chances of cause glaucoma. Another cause is inflammation that occurs in the eye after surgery, but usually this inflammation is rare and may cause only minimal alteration to the anatomy of the drainage system of the eye. However, in some very rare cases, the reoccurrence of inflammation and damage to the drainage system can lead to increased risk for developing glaucoma.<sup>[5]</sup>

### **Races**

Glaucoma is second largest cause of blindness all over the world after cataracts, glaucoma was found to be the common cause of loss of vision among Africans, Americans and people who were of African resident. The ratio of developing glaucoma was found to be 6-8 times more in African Americans than in Caucasians.<sup>[3]</sup>

When considering the people of Asian descent it was found that they were appeared to be having increased risk of developing angle But closure angle glaucoma have only for lower than 10% in all of observed cases of glaucoma. For citizens of Japanese it was found that they were at a more risk of having.<sup>[1]</sup>

### **From ocular hypertension to open angle glaucoma**

People affected with ocular hypertension (OHT) are mainly identified by increases in IOP (>21mmHg), difference in visual field and optic disc which should be normal by definition. The occurrence of OHT in those people older than 40 years in the US population may vary between 4-7%, and the chances of developing open angle glaucoma increases in people having ocular hypertension. Ocular hypertension have been studied extensively for evaluating whether it is possible to prevent the progress of Open angle glaucoma and to assess its risk factors and history associated with the occurrence of OAG. Mainly two large trials have been done in the past years – First one is Ocular Hypertension Treatment Study (OHTS) and the European Glaucoma Prevention Study (EGPS). Both those studies OHTS and EGPS give relevant information about both the baseline factors that relates with the progression of Open angle glaucoma (baseline predictive factors) and the factors that were noted during the follow-up of the study and both these factors were associated with the outcome intercurrent factors.<sup>[6]</sup>

### **BP and IOP**

BP is one of the numerous metabolic systems that shows a circadian rhythm. BP show variation in single day with time, lowest at around 3 AM, little bit increased in the early

morning hours especially before waking, then reaching a peak value at mid-morning. This variation leads to the decrease in sympathetic activity and circulation of catecholamine. In human's body levels of plasma epinephrine and norepinephrine shows endogenous circadian rhythmicity, at during the middle of the biological day with a broad peak, but the BP rise in morning is independent to this mechanism. So many studies are conducted to determine the relationship of IOP with this mechanism; normally IOP is generally higher in the morning. But this phenomenon is questioned today to find specification for glaucoma patients. The average IOP was significantly higher night period than day-wake period. So we can conclude that a nocturnal IOP elevation is independent with body posture. Another study showed that there were no significant changes in IOP at any time point.

Low blood pressure and increased IOP can cause the lowering of ocular perfusion pressure which leads to cause decrease in blood flow to the eye and ischemic oxidative stress damage to the axons and atrophy to the retinal ganglion cells. Several other studies showed that increase in BP is associated with elevated IOP which then leads to glaucoma, this also may lead to microangiopathy which can cause retina and optic nerve damage, the excessive lowering of BP in glaucoma patients can lead to decrease in ocular perfusion pressure which may further lead to ischemic injury. The current treatment for open angle glaucoma is lowering the IOP value but there is no findings to support the increase in BP as a therapy of open angle glaucoma. So both high and low BP can be harmful for patients having progressive glaucoma without controlled IOP so special monitoring should be done for these patients.<sup>[7]</sup>

### **Diabetes and Intraocular Pressure**

Diabetes is a metabolic disorder that has elevated blood glucose or HbA1c levels which have direct relationship with high level of IOP. The correct physiologic mechanism that relates diabetes and higher IOP is unknown. According to that HbA1c levels were related with IOP value irrespectively, and long term diabetes may leads changes in IOP. This is mainly related to the accumulation glycation end (AGE) products. AGE products in turn encourage cellular senescence and causes apoptosis of human trabecular meshwork cells. With dysfunction of the trabecular meshwork, IOP may increase. Another assumption is the effects of TGF- $\beta$ . TGF- $\beta$  was observed with elevated level of aqueous humor and trabecular meshwork of eyes with diabetes or glaucoma. In animal studies, human TGF- $\beta$ 2 was found with lowered outflow of aqueous and elevate IOP in mice eyes.<sup>[8]</sup>

### **Hyperlipidemia and Glaucoma**

Hyperlipidemia is also a metabolic disorder, we found that individuals with hyperlipidemia shows reduction in chances for developing OAG. The exact reason for this phenomenon is unknown, but which has a potential positive impact on reduction in OAG. Mc Gwin et al found that patients who taking statins or other cholesterol-lowering drugs minimum of 23 months, its leads to reduction in risk of OAG. Main mechanism is that the trabecular meshwork cell culture model showed that statins can elevate aqueous outflow. Statins also show neuroprotective effects on ischemia in the brain in retina. Additional studies should be conducted to get better knowledge about the hyperlipidemia, cholesterol- lowering medications, and OAG.<sup>[9]</sup>

### **Depression and Anxiety**

Glaucoma is a second leading chronic, progressive eye disease in world, which dominate irreversible loss of vision and distinguished by optic nerve damage. It is found that, there is a strong relationship between anxiety and depression with glaucoma. Patient always curious, panic and tensed about Loss of vision, which gradually increases the chance of psychiatric disorders. In glaucoma Patients the chances of psychiatric disorder is high because of the blindness restricts the daily Routines and procedures of them. J. Rezapour et al conducted a population based study which is a self-reported one, in this study they found that glaucoma patients are to be more depressed or Anxious than others. There is a another important information that, in glaucoma patients rate of Obstructive sleep apnea syndrome is 1.67 times more than others.<sup>[10]</sup>

### **Drug induced glaucoma**

#### **1) Glucocorticoids**

Drugs may cause temporary or prolonged damage to the optic nerve and visual fields, without significant rise of IOP, parallel to normal-tension glaucoma. Different drugs have been reported to the National Registry of Drug-Induced Ocular Side Effects (Casey Eye Institute, Oregon Health Sciences University. Glucocorticoids act systemically and locally for their anti-inflammatory properties. Exogenous glucocorticoids, administered to the eye and the periocular tissues, intravenously, and in pill form or as inhalants, are the known cause to elevate IOP. Excess production of endogenous glucocorticoids as in Cushing's syndrome can leads to elevated IOP level. Inhaled glucocorticoids are becoming a mainstay of treatment for respiratory disorders.<sup>[11]</sup>

### **Mechanism of Increased IOP**

Glucocorticoids can lead to drainage of aqueous humour through the trabecular meshwork/Schlemm's canal system by mechanisms other than angle closure frequently by inducing structural and functional changes in the trabecular meshwork system commonly to that of POAG.

### **Clinical Signs**

Decreased vision, elevated IOP, enlarged oedematous and cloudy corneas, photophobia, tearing, blepharospasm and damage to the optic disc. In elder children, adults and geriatrics, the clinical presentation is same as to POAG, with elevated IOP.

### **2) Adrenergic Agonists**

Phenylephrine drops are intended to induce pupillary dilation for ophthalmic fundus and may cause glaucoma in non-selected patients. Epinephrine (adrenaline) is common drug for choice for the treatment of anaphylactic shock, ventricular fibrillation, and allergic reactions. Adrenergic agonists lead to pupillary dilation results in glaucoma in susceptible patients.<sup>[12]</sup>

This effect can be managed by discontinuing the medication and controlling the increased IOP and glaucoma with medication.<sup>[11]</sup>

### **3) Salbutamol (Albuterol)**

It's a nebulized  $\beta_2$ -specific adrenergic agonist having a bronchodilating action in patients with asthma and chronic obstructive pulmonary disease (COPD). salbutamol is mainly entered into the cornea and conjunctiva by absorption, this causes dilation of partial area of the pupil which stimulate the pupillary block mechanism in circulatory pathway of the aqueous humors which extends to the posterior chamber to anterior chamber, this leads to the pushing forward of the iris against the trabecular meshwork. This may lead to Increased IOP which can be managed by using cells of properly fitted masks and hand-held nebulizers which can decrease absorption of salbutamol in the cornea and conjunctiva. Protective eyewear can offer an additional benefit for this problem.<sup>[11]</sup>

### **4) Anticholinergic agents**

Commonly used anticholinergic agents are tropicamide, ipratropium bromide, atropine. Tropicamide is mainly applied for inducing pupil dilation for fundus inspection, Ipratropium bromide is an anti-muscarinic drug usually given with combination with salbutamol, it is

suspected that  $\beta$ 2-adrenergic agents and ipratropium bromide escapes from the face mask and causes pupil dilation by diffusing into the cornea which may lead to glaucoma.<sup>[12]</sup>

Atropine induces anticholinergic action by relaxing the ciliary muscles and dilating the pupil it is used to treat bradycardia related to general anesthesia. Many post-operative glaucoma was reported in patients which had undergone facial, endoscopic, orthopedic surgeries.<sup>[11]</sup>

### **5) Histamine H1 and H2 receptor antagonist**

Chlorpheniramine, Brompheniramine, Dexbrompheniramine, Dexchlorpheniramine are the common H1 antagonists used in treatment for allergies and cimetidine, ranitidine are H2 antagonist used for gastric problems such as gastroesophageal reflux, both H1 and H2 are having frail anticholinergic adverse effects so it can lead to mydriasis and glaucoma.<sup>[11]</sup>

### **6) Anticoagulants**

After an anticoagulant therapy for choroidal or subretinal hemorrhage the complication for having a glaucoma is rare, the main risk factors are continuous therapy with anticoagulants, age related macular degeneration. The commonly used anticoagulants such as heparins and low molecular weight heparins example enoxaparin and warfarin can cause or increase the risk of having glaucoma.<sup>[12]</sup>

The only way manage this condition is to discontinue the anticoagulant treatment and decrease intra ocular pressure. Peripheral iridotomy well not effective in the management due to the reason that there is no pupillary block mechanism. Surgical procedure is the only method to drain the hemorrhage.<sup>[11]</sup>

### **CONCLUSION**

Glaucoma is one of the most common and dangerous eye disease, characterized by loss of vision due to the damage of optic nerve. Commonly in treatment reduce IOP of eye by using various drugs. Early detection can decrease severity and must consider all risk factors like gender, age, racial, family history, drug induced and other diseases induction.

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