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# Effects of Sex Hormones on Ocular Blood Flow and Intraocular Pressure in Primary Open Angle Glaucoma: A Review

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**Précis:** This review explores the relationship between glaucoma and gender, showing the results of studies investigating the effects of sex hormones on intraocular pressure and ocular blood flow.



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**ABSTRACT**
Primary open-angle glaucoma (POAG) is a multifactorial optic neuropathy characterized by progressive retinal ganglion cell death and visual field loss. Some speculate that gender plays a role in the risk of developing POAG and that the physiologic differences between men and women may be attributed to the variable effects of sex hormones on intraocular pressure (IOP), ocular blood flow, and/or neuroprotection. Estrogen, in the form of premenopausal status, pregnancy, and post-menopausal hormone therapy is associated with increase in ocular blood flow, decrease in IOP and neuroprotective properties. The vasodilation caused by estrogen and its effects on aqueous humor outflow may contribute. On the other hand, although testosterone may have known effects in the cardiovascular and cerebrovascular systems, there is no consensus as to its effects in ocular health or POAG. With better understanding of sex hormones in POAG, sex hormone-derived preventative and therapeutic considerations in disease management may provide for improved gender-specific patient care.
KEYWORDS: glaucoma, estrogen, testosterone, ocular blood flow, intraocular pressure, neuroprotection
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**INTRODUCTION**: Certain demographic and co-morbidity related risk factors affect the development and progression of primary open-angle glaucoma (POAG), a multifactorial optic neuropathy characterized by progressive retinal ganglion cell death and visual field loss.[1] Intraocular pressure (IOP) is the best defined and only currently modifiable risk factor of POAG.[1] However, high IOP does not always lead to or accelerate glaucomatous progression.[2] Other factors including ocular blood flow, aqueous humor dynamics and physiological influence of gender should be taken into consideration to clearly understand the pathogenesis of POAG.[2] Recent evidence supports blood flow disturbances as a risk factor for glaucoma.[3] Many large population-based studies have reported low ocular perfusion pressures in eyes with glaucoma.[2-4] Some individuals may be at increased risk for glaucoma possibly through varying hemodynamic processes and impaired ocular circulation.[3,4] The contribution of ischemic damage in glaucoma may be local (confined within the retina and anterior optic nerve), or may represent only one aspect of a more generalized ischemic process.[3] It is well established that aqueous humor dynamics in glaucoma patients is different from healthy, age-matched cohorts.[1] Trabecular outflow facility is reduced, thus leading to an increase in IOP. Reduced outflow facility is an indicator of pathological changes in the trabecular meshwork, which may also mirror defects in the lamina cribrosa and consequently damage to retinal ganglion cell axons.[1] It is speculated that gender plays a role in POAG risk and pathogenesis and that the physiologic differences between men and women may be attributed to the influence of sex hormones on ocular blood flow, IOP, and aqueous humor dynamics.[2]

This review explores the link between glaucoma and sex hormones, IOP, and ocular blood flow. Articles from PubMed published between 1985 and 2018 were identified by searching the keywords: estrogen, progesterone, testosterone, gender, hormonal status, ocular blood flow, intraocular pressure, glaucoma, neuroprotection, retina, optic nerve, aqueous humor dynamics, and outflow facility.

**SEX DIFFERENCES IN POAG**: Conflicting data exists on the prevalence of POAG among men and women. Two studies reported women to be disproportionately affected by POAG.[5,6] However, in the largest most recent meta-analysis describing and predicting the global prevalence of glaucoma through the year 2040 among 37 pooled studies, men were more likely to develop POAG than women with an odds ratio of 1.36.[7] Another meta-analysis also found that POAG was more prevalent in men than women.[8] A five-year incidence of POAG stratified by age and gender with 3271 participants found that men had higher incidence rates of POAG than women in the 5th, 6th, and 7th decades, but by the 8th decade they were similar.[9] The reasons behind these gender related differences in POAG may also be related to ethnic background, genetic predisposition, anatomical and physiological differences, and environmental factors to name a few.

Structural differences of the eye between men and women may explain part of this discrepancy. There have been recent advances in imaging of the living eye, such as optical coherence tomography (OCT). These OCT images have found that men have thicker corneas, and women have more steeply curved corneas.[10,11] Although thicker corneas may alter IOP measurements, the link between anatomical differences between sexes and POAG has not yet been made.

**OCULAR BLOOD FLOW**: Numerous differences in ocular blood flow among men and women exist. In a study using Laser Speckle Flowgraphy, the mean blur rate (MBR), a measure of relative blood flow velocity in the optic nerve head (ONH), and the resistivity index (RI) were higher in females compared to males.[12] However, no difference in choroidal MBR was found between sexes and the blowout time (BOT) was higher in men. A high BOT indicates that the blood flow remained at a high level for an extended period of time between heartbeats and that

the peripheral vasculature received sufficient amounts of blood.[12] In another study, in response to therapeutically reduced IOP, peak systolic velocity (PSV) increased in women in the central retinal artery (CRA) and decreased in the ophthalmic artery (OA) and posterior ciliary arteries (PCAs).[13] In this same study, PSV and end diastolic velocity (EDV) decreased in all three vessels in men. These findings are not without controversy. One study reported no difference in ocular blood flow parameters between sexes in all three of these vessels.[14]

The increased ocular blood flow seen in female patients may be related to lower rates of atherosclerosis in females compared to males, yet difference in autoregulatory systems, especially in retinal capillaries, may better explain the disparity.[15] In response to fluctuations in blood pressure, the ocular vasculature will auto regulate to maintain constant perfusion over a wide range of pressures. Thus, dysfunction of autoregulation may contribute to pathogenesis of POAG and lead to ischemic damage of the ONH. In female POAG patients, inferior retinal capillary flow was positively correlated with ocular perfusion pressure (OPP), whereas in male POAG patients, superior and inferior retinal blood flow were negatively associated with OPP.[2] Previously our laboratories have shown differences in retinal blood flow following perturbation between superior and inferior regions of the retina; although no differences were reported between genders. This may be an important consideration as regional glaucomatous defects might be linked to reduced perfusion to the localized corresponding structural tissues. In women, estrogen may have a positive overall effect on retinal autoregulation as increased blood flow was correlated with increased OPP, an indication of healthy regulatory mechanisms.[2]

In a retrospective data analysis of POAG patients within the Department of Ophthalmology at Indiana University School of Medicine, female POAG patients had a positive association between mean arterial pressure (MAP), systolic blood pressure (SBP), diastolic blood

pressure (DBP) and inferior retinal blood flow, whereas male POAG patients had a negative association between these variables (unpublished data). However, the association between OA EDV and SBP, DBP, and MAP was positive in males and negative in females (unpublished data). These associations between retinal and retrobulbar flow could illustrate differences in autoregulatory mechanisms between male and female POAG patients. Gender may affect vascular reactivity in response to changes in BP, leading to long-term discrepancies in disease progression. These differences between men and women also stress the importance of understanding the effects of sex hormone on the pathogenesis of POAG.

The effects of estrogen and testosterone on ocular blood flow and regulatory mechanisms in POAG may explain the difference in prevalence of POAG between sexes. There is growing evidence linking changes in ocular blood flow and glaucoma.[2-4,16] Furthermore, the association between sex hormones and IOP may be significant as IOP is the only controllable factor in managing POAG in the clinical setting. A review of the literature suggests that estrogen increases ocular blood flow, decreases IOP, and provides neuroprotection in the retina. The effect of testosterone on these variables is less clear and this complexity provides an additional reason to warrant further investigation.

**SEX HORMONES: ESTROGEN:** Increased estrogen exposure, in the form of pre-menopausal status, pregnancy, and postmenopausal hormone therapy (PMHT), is associated with a reduced risk of POAG.[17] However, oral contraceptive (OC) use is associated with increased risk of POAG according to Pasquale et al. and Wang et al.[18,19] Another recent study of the Korean National Health and Nutrition Examination Survey in 2018 found no association between OC use and POAG, yet demonstrated early menopause was associated with an increased risk of POAG.[20] Protective effects of estrogen may be due to its vasodilatory properties systemically and specifically its effects in the cerebrovascular system.[21,22] Estrogen regulates vascular tone by

modulating endothelial cell production and release of vasoactive substances such as nitric oxide. The relation of nitric oxide synthase 3 (NOS3) single nucleotide polymorphisms (SNPs) to POAG depended on age at menarche and parity, where these associations were modified by estrogen exposure history.[23] Similarly, interactions have been observed between NOS3 SNPs and postmenopausal hormone use in relation to POAG, further supporting the potential protective vasodilatory role of estrogen.[24] However, menopausal hormone therapy has been well-documented in the literature and clinical practice to be associated with systemic adverse effects of ischemic stroke and venous thromboembolism.[25] Women using PMHT have increased thrombin, a key protein in the clotting cascade catalyzing the conversion of fibrinogen to fibrin, compared to those not using PMHT. Yet this causal effect is seen with oral administration and not with transdermal administration of PMHT.[26] Estrogen's hypercoagulable effects in the eye and their relation to route of administration require further investigation before considering the therapeutic potential of PMHT in POAG.

Vasoactive properties of estrogen have been postulated to improve blood flow. Estrogen in the form of PMHT reduces the vascular resistance of the CRA in postmenopausal women due to vasodilation.[27] Furthermore, the pulsatility index of the CRA varies at differing phases of the menstrual cycle, demonstrating increased pulsatility with phases associated with estrogen surge (mid-luteal phase) and antagonized by phases dominated by progesterone influences (mid-follicular and periovulatory phase).[28] Inferotemporal retinal (ITRA) blood flow also increased in postmenopausal women on PMHT, which included estrogen and progesterone in combination therapy or estrogen therapy alone.[29] Although the estrogen therapy group had a slightly higher ITRA blood flow than the combination therapy group, the difference was statistically insignificant. This lends credibility to the hypothesis of the antagonistic effects of progesterone

towards estrogen.[28,29] Menopausal status is also highly correlated with choroidal circulation. Using Laser Doppler Flowmetry, young premenopausal women (<40 years) demonstrated higher choroidal submacular flow than women over the age of 40, and these differences were not seen in males of similar age.[30] The results of these studies combined strongly associate increased estrogen exposure with increased retinal, retrobulbar, and choroidal blood flow. This suggests that the vasoactive properties of estrogen could help combat ischemic damage seen in POAG.

The relationship between estrogen and IOP has been thoroughly investigated over the years. Multiple studies have confirmed significantly lower IOP in postmenopausal women undergoing PMHT when compared to those who are not.[31-34] Other studies have failed to find such an effect in postmenopausal women undergoing PMHT consisting of estrogen, progesterone, and tibolone.[35,36] A study from the Women's Health Initiative, representing a post hoc analysis of a randomized control trial of PMHT in the treatment of age-related macular degeneration, also found reductions in IOP in an estrogen-only treatment group.[37] Estrogen may work to reduce IOP via a variety of mechanisms which include reducing aqueous production and episcleral venous pressure or by increasing aqueous humor outflow.[37] One contradictory study found no significant reductions in IOP in response to PMHT or estrogen-only treatments.[38]

Reductions in IOP also have been reported in pregnant women. Interestingly, women with twin pregnancies had greater reductions in IOP than women with singleton pregnancies most likely due to their higher levels of estrogen and progesterone.[39] The reduction in IOP may result from increased outflow facility and decreased episcleral venous pressure.[40,41] Elevated levels of progesterone during pregnancy may block the ocular hypertensive effect of endogenous corticosteroids.[42] One study of lions found higher IOP in luteal lionesses than in non-luteal lionesses, associating elevated progesterone levels with increased IOP.[43] More research is needed

to better understand the mechanism underlying the effects of estrogen on IOP and to understand the relationship between progesterone and IOP.

The neuroprotective capacity of estrogen has also been widely established. The Rotterdam Eye Study established a link between decreased estrogen levels and glaucoma progression; the conclusion being that women who entered menopause early, before the age of 45 years, had 2.6-fold increased odds ratio risk of developing POAG.[44] The Nurses' Health Study also demonstrated that entering menopause at age greater than or equal to 54 years was associated with reduced risk of POAG compared with entering menopause at age 50 to 54.[45] Several mechanisms for the protective properties of estrogen against glaucomatous progression have been proposed. One study reported that estrogen increased retinal blood flow and protected the retinal nerve fiber layer (RNFL) as a result of its vasomotor properties.[29] A study in rats found that topical estrogen decreased retinal ganglion cell (RGC) loss caused by high IOP.[46] In a similar rat model study, estrogen eye drops significantly increased estrogen concentration in the retina and produced structurally and functionally measurable neuroprotective measures including reduced RGC loss and preservation of vision.[47] Interestingly, there may be a "critical period" for estrogen's beneficial effect in the brain. If hormone therapy is initiated in non-healthy neurons or after a significant period of time following menopause, the beneficial effects of estrogen, such as reducing RGC loss, is not observed.[48] Glaucomatous progression is characterized by RGC loss and RNFL damage; these studies demonstrate estrogen's protective features in POAG and that there is a temporally undefined critical window during which this process occurs.[48]

**SEX HORMONES: TESTOSTERONE:** The role of testosterone in ocular health and cerebral vasculature was originally studied in the early 1980s, however the lack of recent investigation demonstrates a gap in understanding and consensus on its role in POAG. As critical testosterone levels are not linked to direct reproductive milestones as seen with estrogen levels, testosterone's

influence on risk factors and pathophysiologic processes of the eye has been difficult to measure. The literature demonstrates that testosterone has vasodilatory effects on vascular beds through increasing the expression of endothelial nitric oxide synthase.[49] Additionally, testosterone has exhibited anti- inflammatory properties in animal studies.[49] Testosterone may be protective against cardiovascular dysfunction and atherosclerosis through these mechanisms, yet less is known about the effect of testosterone in the eye.[49,50]

The effects of testosterone appear to be antagonistic towards those of estrogen in regards to ocular blood flow. In premenopausal women, serum levels of estrogen have been positively correlated with OA PSV and EDV, whereas serum testosterone was negatively correlated with CRA PSV and EDV.[51] Contradicting these results, a study in men found that testosterone had an independent, protective effect on retinal vasculature through inducing a vasodilatory response in retinal resistance vessels, indicating a beneficial role in vascular dynamics.[52] In addition, studies on the effect of testosterone on cerebral blood flow may parallel its effects in the eye. Gonzalez reports that male rodents have increased vascular tone in the middle cerebral arteries (MCA) compared to female rodents on average.[53] In humans, chronic treatment with testosterone resulted in increased vascular tone in MCA compared to controls. Although acute effects of testosterone are dilatory in nature, long term effects may enhance other endothelium-dependent vasoconstrictor pathways in the cerebral vasculature including those involving thromboxane, a potent vasoconstrictor.[53]

Conflicting results are seen with the relationship between testosterone and IOP. Topical administration of testosterone to rabbit and human eyes did not significantly alter IOP.[54,55] Androgen replacement therapy was found to also have no effect on IOP in patients with idiopathic hypogonadotropic hypogonadism.[56] Interestingly, a study of post-menopausal women

found that higher testosterone was associated with increased IOP.[38] More recently in the Nurses' Health Study, higher testosterone levels in postmenopausal women was also associated with higher IOP and higher POAG risk. [57] It has been suggested that the relationship between intracranial pressure (ICP) and IOP may also play a fundamental role in glaucoma. Recent studies have demonstrated that ICP is lower in patients with POAG when compared to nonglaucomatous control subjects.[58,59] A decreased ICP could result in an increased trans lamina cribrosa pressure difference (IOP minus ICP) and lead to glaucomatous damage within the optic nerve head.[58] As androgen receptors are found in the choroid plexus, it is hypothesized that testosterone may directly stimulate cerebrospinal fluid (CSF) production.[60] Increased CSF production increases ICP, thus demonstrating that testosterone may be protective against glaucomatous progression.[60]

The neuroprotective effects of testosterone on the central nervous system have been investigated, providing clues to its functionality within the eye. In a study of rats, testosterone reduced neuronal damage following sciatic nerve crush, indicating that testosterone may be neuroprotective to lumbar spinal neurons.[61] These neuroprotective mechanisms of testosterone may work directly through androgen receptors and connecting pathways.[62]

Role of testosterone in POAG is unclear, however it is evident that sex hormones have particular influences on ocular blood flow and IOP. As these factors are important in POAG, developing an understanding of their relationship is necessary. Most of the studies regarding estrogen and testosterone discussed in this review were cross-sectional in nature, leaving a gap in our understanding that could be filled by longitudinal studies on the influence of sex hormones on POAG parameters. Furthermore, the published studies represent a variety of methods of measuring ocular blood flow, ranging from Heidelberg Flowmetry to Laser Doppler Flowmetry.

Future studies utilizing new OCT angiography modalities may further expand our current knowledge and provide a single more readily available platform to normalize blood flow measurements across studies.[63]

**SUMMARY:** Overall, this review of the literature suggests that estrogen increases ocular blood flow, decreases IOP, and provides neuroprotection. The effect of testosterone on these variables is less clear with conflicting results or lack of consistent associations. As we move towards improved individualized medical care, there is a need for more study on the influences of sex hormones on POAG risk. With further understanding of the physiological influence of sex hormones in the context of POAG risk, our ability to accurately assess risk factors and individualize management plans may be further realized allowing for improved patient care.

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