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Estrogen deficiency accelerates aging of the optic nerve

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Abstract

Objective—To provide a comprehensive review on hormone-based pathophysiology of aging of the optic nerve and glaucoma.

Methods—A literature review and expert opinions.

Results—Glaucoma, a group of intraocular pressure-related optic neuropathies, is characterized by the slow progressive neurodegeneration of retinal ganglion cells and their axons resulting in irreversible visual sensitivity loss and blindness. Increasing evidence suggests that glaucoma represents the accelerated aging of the optic nerve and is a neurodegenerative disease of the central nervous system. This review highlights the high burden of glaucoma in elderly women and the importance of understanding the hormone-related pathophysiology of optic nerve aging and glaucoma in women.

Conclusions—Strong epidemiological, clinical, and experimental evidence supports the proposed hypothesis that the early loss of estrogen leads to premature aging and increased susceptibility of the optic nerve to glaucomatous damage. Future investigations into the hormone-related mechanisms of aging and glaucoma will support the development of novel sex-specific preventive and therapeutic strategies in glaucoma.

Keywords

Aging; Glaucoma; Sex difference; Estrogen; Blindness

The optic nerve undergoes an aging process that results in a decreased number of retinal ganglion cells and their nerve fibers, which subsequently leads to reduced visual sensitivity.^{1–3} Specifically, histopathological and clinical evidence demonstrates the age-related thinning of the retinal nerve fiber by ~0.2% or 0.2 μm per year.^{3–5} Similarly, glaucoma, a group of intraocular pressure (IOP)-related optic neuropathic conditions, is characterized by the slow progressive neurodegeneration of retinal ganglion cells and their axons resulting in irreversible visual sensitivity loss and blindness.⁶ Growing evidence supports the hypothesis that glaucomatous optic neuropathy represents accelerated aging of the optic nerve and is a neurodegenerative disease of the central nervous system.^{7–9} Due to the aging world population, the burden of glaucoma is rising.¹⁰ Women carry the greatest burden of this disease because they comprise the majority of the aging population affected by glaucoma, and they have a higher rate of visual impairment than males with glaucoma.^{10, 11} Therefore, investigations into the sex-specific mechanisms of glaucoma are

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needed to develop novel preventive and therapeutic interventions. This review highlights the importance of understanding the hormone-based pathophysiology of the optic nerve in the aging process and glaucoma. It further summarizes the evidence supporting our proposed central hypothesis that the early loss of estrogen leads to the premature aging of the optic nerve and increased susceptibility of the optic nerve to glaucomatous damage.

High burden of glaucoma in the aging population and in elderly women

Globally, more women are affected by glaucoma than men. This sex difference is related to the fact that glaucoma is a strongly age-related condition and women live longer than men. Glaucoma is the leading cause of permanent blindness worldwide, with primary open-angle glaucoma (POAG) the most common type, comprising 74% of all glaucoma cases.¹⁰ In addition, the total number of people with glaucoma has been predicted to increase from 60.5 million in 2010 to 79.6 million in 2020.¹⁰ In addition, we calculated the predicted number of persons with POAG, aged 40 years and older in the US from 2011–2050, by applying the prevalence rates of POAG from published population-based studies to population estimates and projections based on the 2000 census. Our 40-year forecast predicted a 270% increase in the number of POAG cases in the US, from 2.71 million in 2010 to 7.32 million in 2050, whereas the overall US population will increase by only 150% over the same period.¹² Currently, there are 11% more women with POAG than men. Furthermore, the majority of the current caseload is found in the elderly population, especially elderly women aged 70 years and older. Although POAG demonstrates no clear sex predilection, the current high caseload among women reflects their greater longevity alluded to above (life expectancy, 75.7 years in men vs. 80.7 in women).¹³ This women-to-men case number discrepancy will continue for the next few decades. During this period, the difference will slowly decline due to the increasing life expectancy of men, and there will be ~1% more women affected by POAG than men in the US by 2050.

It is of particular interest that, at present, 90% of the worldwide population of centenarians are women.¹⁴ Different theories have been proposed for this sex difference in longevity, including the protective effect of estrogen, the superior immune system of women, and the compensatory effect of the second X chromosome in women.¹⁴ In addition, it is believed that menstruation during the reproductive period might be beneficial. Specifically, women are relatively iron deficient due to menstruation, and this lower iron load could reduce oxidative stress in tissues.¹⁵ The study of sex differences in aging and longevity is still evolving; however, further investigations into the sex- and hormone-based mechanisms of aging will lead to a better understanding of these differences. Interestingly a popular hypothesis among researchers is that oxidative stress, a pillar of deleterious aging, affects the outflow pathway and optic nerve and contributes to glaucoma pathogenesis.¹⁶

In addition to the higher number of glaucoma cases in women compared to men, women self-report a higher rate of visual impairment by glaucoma and yet are less likely to be treated. The 2002–2005 National Health Interview Survey (NHIS) revealed that women have higher self-reported visual impairment from all causes (odds ratio (OR), 1.31; 95% confidence interval (CI), 1.19–1.45) and a trend toward higher prevalence of self-reported visual impairment from glaucoma (OR, 1.20; 95% CI, 0.99–1.45) compared to men.¹⁷ In addition, a national preventive initiative supported by the US Department of Health and Human Services, Healthy Vision 2010, highlighted the higher rate of visual impairment from glaucoma in women than in men (1.53% vs. 1.12%, respectively).¹⁸ The report however did not comment if the difference was statistically significant. Of note, both reports were based on the NHIS. Specifically, the following question was used to classify visual impairment from glaucoma: Do you have trouble seeing, even when wearing glasses or

contact lenses? This indicates that the visual impairment assessed was a subjective decrease in acuity.

There is a gender disparity in the treatment of glaucoma. For instance, women in some parts of the world have limited access to healthcare.¹⁹ In addition, even in developed countries such as the US, women are 24% less likely to be treated for glaucoma.²⁰ As a result, targeting glaucoma prevention in women will decrease the overall burden of glaucoma and the caseload of glaucoma-related visual impairment.

Aging increases the susceptibility of the optic nerve to glaucoma

The pathophysiology of POAG is unclear; however, 2 main theories have been proposed: the mechanical and vascular theories. According to the mechanical theory, damage is thought to occur at the level of the lamina cribrosa (a connective tissue strut that supports retinal ganglion cell axons as they exit the eye and enter the orbit and course toward the brain) from mechanical stress caused by increased IOP.⁶ The vascular theory suggests that ischemia/decreased perfusion or vascular dysregulation of the optic nerve leads to neurodegeneration.^{6, 21, 22} Other proposed mechanisms of glaucomatous optic neuropathy include abnormal immunity and dysfunctional supporting tissues such as glial cells.^{6, 7, 23} These abnormalities may trigger oxidative stress, which in turn could further damage retinal ganglion cells.

The risk for glaucoma increases with age.^{11, 24–32} Aged optic nerves are more vulnerable to glaucomatous damage for several reasons (Fig. 1A). For example, the aged optic nerve is more susceptible to mechanical stress from increased IOP.^{33, 34} Specifically, the change in elastin and the increasing stiffness of type I collagen with age reduce the flexibility of the lamina cribrosa, thereby decreasing support to the axons of the retinal ganglion cells in the presence of elevated IOP.^{34, 35} Additionally, the aged vascular system makes the optic nerve and retinal ganglion cells prone to the vasculopathy of POAG. Aging of the vascular system also results in decreased perfusion to the optic nerve.³⁶ Changes in systemic blood pressure with age may also further diminish circulation to the optic nerve, retinal ganglion cells, retinal nerve fiber, and their supporting tissues. Furthermore, aged glial tissue provides less protection to neurons.^{6, 7, 23} In particular, the age-related dysfunction of the immune regulatory system induces oxidative stress and promotes retinal ganglion cell injury.^{6, 7, 23} Finally, the age-related decrease in the number of retinal ganglion cells and their axons provides a reduced reserve and decreased redundancy of the neuronal network; therefore, the aged optic nerve is prone to functional loss from glaucomatous damage. Previous histopathological reports demonstrated an age-related thinning of 0.2–0.3% per year for retinal nerve fibers and 0.5–0.6% per year for retinal ganglion cells.^{1, 4, 5}

In summary, the aged optic nerve is susceptible to glaucomatous damage; therefore, identifying the factors that accelerate aging of the optic nerve, such as estrogen deficiency, will support the development of novel preventive and therapeutic strategies for glaucoma.

An early decline in female sex hormones accelerates aging of the optic nerve and increases the risk for glaucoma

Evidence supports the hypothesis that estrogen deficiency is involved in the pathophysiology of optic nerve aging and glaucomatous neurodegeneration through several mechanisms (Fig. 1B). In accordance with the mechanical theory, estrogens may regulate IOP by influencing the aqueous production and outflow systems through receptors in the ciliary epithelium.^{37, 38} For instance, hyperestrogenemia during pregnancy has been found to be associated with a 10% decrease in IOP and an increase in central corneal thickness

(CCT). Of note, IOP measurement can be affected by changes in CCT. Specifically, non-edematous thick CCT causes falsely high IOP reading, whereas edematous thick CCT can lead to falsely low IOP reading. Although it was unclear if increased CCT during pregnancy is related to edema, IOP was found to decrease during pregnancy despite a concomitant increase in CCT. The exact mechanisms for the ocular hypotensive effect are not well understood. It has been postulated that pregnancy-related IOP reduction is a result of increased outflow facility and decreased venous pressure.^{39–43} Furthermore numerous studies document higher IOP in postmenopausal women³⁷ and a reduction in IOP of 1–4 mmHg after postmenopausal hormone (PMH) use in women with and without POAG.^{37, 44–47} In support of the vascular theory, estradiol (E2) regulates smooth muscle tone and vascular resistance and augments the activity of endothelial-based nitric oxide synthase (NOS3).^{48, 49} Specifically, E2 may influence perfusion of the optic nerve, retinal ganglion cells, and their supporting structures. This effect has been demonstrated in animal models and clinical studies.^{36, 50} A 22–45% increase in perfusion to the retina was reported in ovariectomized rats treated with E2 compared to control ovariectomized rats treated with vehicle.⁵⁰ In humans, aging and age-related decreases in female sex hormones negatively affect ocular blood flow,⁵¹ while PMH use has been shown to enhance ocular blood flow.^{36, 37, 52–54}

Visual function is also sensitive to sex hormones. Previous studies showed decreased mean visual sensitivity thresholds during the luteal phase (low estrogen state), when compared to a follicular phase (high estrogen state) in normal menstruating women with an averaged age of 35.6 years.⁵⁵ Of interest, the difference was only found with a visual field test that specifically measures a group of ganglion cell in the koniocellular pathway (ganglion cells that are sensitive to blue-yellow color).

Additionally, the neuroprotective effect of E2 in glaucoma animal models is likely mediated through estrogen receptors in retinal ganglion cells.^{50, 56, 57} In support of this possibility, the systemic administration of E2 prevented the retinal ganglion cell loss induced by acute IOP in rats,⁵⁶ and E2 pellet implantation after ovariectomy preserved the retinal ganglion cells and retinal nerve fibers in DBA2J mice, a murine model for glaucoma.⁵⁷ In addition, in an animal experiment, the effect of E2 was blocked by intraperitoneal injection of Tamoxifen, an estrogen receptor inhibitor.⁵⁷ Finally, PMH use has been shown to preserve retinal nerve fibers in postmenopausal women. Estrogen deficiency may accelerate the aging of the optic nerve, as evidenced by decreased retinal nerve fiber thickness in women who did not use PMH compared to women who did.⁵⁰ As a result, postmenopausal women who do not use PMH may be prone to functional loss from glaucoma due to the loss of neuroprotection and decreased reserves of retinal nerve fibers. In addition to clinical evidence and animal models, epidemiologic studies have demonstrated an association between decreased estrogen exposure and the risk for developing glaucoma later in life.^{58–62} Surrogates for lifetime decreased estrogen exposure were measured by several population-based studies that revealed a role for a late menarche, early menopause, and/or duration from menarche to menopause. The Rotterdam group was the first to show that early menopause (before age of 45) was associated with a 2.6-fold increased risk of POAG.⁵⁸ Later, the Blue Mountain Study reported 2-fold increased risk of POAG in women with late menarche (after age of 13).⁶¹ In addition, the Nurses' Health Study (NHS) showed that a 50% reduced risk of POAG was seen among women older than 65 who entered menopause after age 54 years. In contrast, the Aravind Comprehensive Eye Survey did not find significant associations between reproductive factors and risk of POAG.⁵⁹ Notably, the mean age of participant in this study was 10 years younger than the participants mentioned in other studies.⁶² Furthermore NHS investigators reported that oral contraception use, which may interfere with normal menstrual cycling, was associated with a 25% increased risk of POAG.⁶⁰ In this report, the type of oral contraceptives was not collected.⁶⁰ The evidence further suggests a

protective effect of female sex hormones and the benefit of PMH use in women.^{58, 60, 61, 63} In brief, there was significant risk reduction of POAG among PMH users.^{58, 61} Furthermore, a significant reduction in risk for POAG has been demonstrated in women who are at risk for developing glaucoma, defined as women with ocular hypertension.⁶⁰ This substantial evidence supports our hypothesis that early estrogen deficiency could accelerate the aging of the optic nerve and predispose the optic nerve to glaucomatous damage.

Estimated number of women at risk and clinical implications

Six percent of women enter the menopause before 45 years.^{64–66} Accordingly, we estimate that ~9.42 million women in the US may be at risk for early estrogen deficiency. Of those, 1.38 million women aged 65 years and older may be at risk for early aging of the optic nerve and glaucoma. In addition, increasing evidence indicates a higher risk for premature menopause in women who underwent hysterectomy or uterine artery embolization at a younger age.⁶⁶ Specifically, the average age of menopause in women who underwent hysterectomy was 45.4 ± 4.0 years, compared to 49.5 ± 4.0 years in women who did not undergo surgery.⁶⁷ Compromised ovarian blood flow after hysterectomy has been hypothesized to cause early estrogen deficiency. Furthermore, women with medical conditions such as cancer, which is associated with long-term anti-estrogen treatment, may also be predisposed to early aging of the optic nerve. These at-risk women will benefit from screening for signs of early optic nerve aging and glaucoma. Although some evidence suggests that PMH use may be beneficial, randomized clinical trials have not yet been conducted and PMH use is contraindicated in certain populations of at-risk women (e.g., those with cancer) and is not readily accessible worldwide. Nevertheless, targeted approaches to maintain optimal perfusion to the optic nerve and decrease oxidative stress to neurons could be implemented. Specifically, topical congeners that supply estrogen locally might have some role in preventing or treating POAG in women.

Future directions: sex differences in gene-environment interactions

Sex differences in single nucleotide polymorphisms (SNPs) at the estrogen receptor beta (*ESR2*) locus have been reported in POAG.^{48, 68, 69} Specifically, the Rotterdam study demonstrated that the SNPs rs1256031 and rs4986938 in *ESR2* were significantly associated with an increased risk of incident POAG (regardless of the IOP at diagnosis) in men, but not in women.⁶⁸ Interestingly, in a Japanese population, these SNPs were associated with increased IOP with the high tension variant of POAG, in women but not in men.⁶⁹ The reason for this difference in sex dimorphism is not clear. It may be due to different genetic makeup in the two populations or the inherent differences in the type of open-angle glaucoma assessed.

In addition, sex differences in a SNP at the *NOS3* locus have been reported in POAG patients. In a case-control study from the Nurses' Health Study and the Health Professionals' Follow-up Study, the *NOS3* SNP rs3918188 was significantly inversely associated with POAG and high IOP in women, but not in men.⁴⁸ Furthermore, the *NOS3* SNP, female sex, and PMH use in women with high-tension POAG demonstrated significant interactions.⁴⁸ For instance, PMH use was inversely associated with high-tension POAG in women with the *NOS3* genotype (TT genotype at T-786C), which is associated with reduced nitric oxide production.^{48, 70, 71}

On the basis of the hormone-based pathophysiology of glaucoma, new genes associated with POAG have recently been identified.⁷² For instance, SNPs between caveolin 1 (*CAV1*) and caveolin 2 (*CAV2*) were associated with POAG mostly in white women in the US.⁷³ This finding suggests that phenotype stratification and data analysis based on molecular

pathways, such as NOS3 and estrogen interactions, may lead to the successful discovery of genes for POAG.⁷³

Estrogen-based therapy may benefit men and women. In men, non-reproductive tissue such as local neurons, glial cells, and vascular tissue can generate E2 de novo and/or via the conversion of circulating testosterone to E2 by aromatization.^{74, 75} As a result, estrogen plays an important role in the male brain and vasculature. Sex differences in the responses to estrogen in the central nervous system and cardiovascular system have been demonstrated.^{74–76} Growing evidence supports the link between sex differences in estrogen and hormone-related glaucoma pathophysiology. Future studies examining sex differences in gene-sex and hormone-environment interactions may lead to the development of sex-specific hormone-based interventions for POAG that will benefit women and men.

Conclusions

Women bear a greater burden of glaucoma than men in light of the higher caseload, higher rates of visual impairment, and disparity in treatment observed in women. Investigations into sex-specific risk factors for glaucoma and the hormone-based pathophysiology of aging of the optic nerve and glaucoma are critical to improve care for glaucoma in women. Progress in these areas of research will serve as a foundation for personalized medicine and lead to the development of novel preventative measures and therapies for glaucoma that will benefit women and men.

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Fig 1.

Fig 1A. The relationship between aging and glaucoma pathophysiology. Abbreviations: RGC, retinal ganglion cells; RNFL, retinal nerve fiber layer; IOP, intraocular pressure.

Fig 1B. The potential protective effects of female sex hormones on glaucoma pathophysiology. Abbreviations: RNFL, retinal nerve fiber layer; IOP, intraocular pressure; PMH, postmenopausal hormone.