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Is Estrogen a Therapeutic Target for Glaucoma?

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Abstract

Objective—To provide an overview of the association between estrogen and glaucoma.

Methods—A literature synthesis of articles published in peer review journals screened through May 05, 2015 using the PubMed database. Key words used were “estrogen and glaucoma,” “reproductive factors and glaucoma,” “estrogen, nitric oxide and eye.” Forty three journal articles were included.

Results—Markers for lifetime estrogen exposure have been measured by several studies and show that the age of menarche onset, oral contraceptive (OC) use, bilateral oophorectomy, age of menopause onset and duration between menarche to menopause are associated with primary open angle (POAG) risk. The Blue Mountain Eye Study found a significantly increased POAG risk with later (>13 years) compared with earlier (≤12 years) age of menarche. Nurses' Health Study (NHS) investigators found that OC use of greater than 5 years was associated with a 25% increased risk of POAG. The Mayo Clinic Cohort Study of Oophorectomy and Aging found that women who underwent bilateral oophorectomy before age 43 had an increased risk of glaucoma. The Rotterdam Study found that women who went through menopause before reaching the age of 45 years had a higher risk of open-angle glaucoma (2.6-fold increased risk) while the NHS showed a reduced risk of POAG among women older than 65 who entered menopause after age 54 years.

Increased estrogen states may confer a reduced risk of glaucoma or glaucoma related traits such as reduced intraocular pressure (IOP). Pregnancy, a hyperestrogenemic state, is associated with decreased IOP during the third trimester. Though the role of post-menopausal hormone (PMH) use in the reduction of IOP is not fully conclusive, PMH use may reduce the risk of POAG.

From a genetic epidemiologic perspective, estrogen metabolic pathway single nucleotide polymorphisms (SNPs) were associated with POAG in women and polymorphisms in endothelial nitric oxide synthase, a gene receptive to estrogen regulation, are associated with glaucoma.

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Conclusions—Increasing evidence suggests that lifetime exposure to estrogen may alter the pathogenesis of glaucoma. Estrogen exposure may have a neuroprotective effect on the progression of POAG but further studies need to confirm this finding. The role of sex-specific preventive and therapeutic treatment may be on the horizon.

Keywords

glaucoma; optic nerve degeneration; reproductive hormones; estrogen; post-menopausal hormones; sex differences

Introduction

Glaucoma is the second leading cause of blindness worldwide¹ and is considered to be a slowly progressing neurodegenerative disease characterized by gradual loss of retinal ganglion cells (RGCs)² leading to vision loss.³ Women have a significantly lower incidence of primary open angle glaucoma (POAG) compared to their male counterparts until age 80 at which time the incidence of POAG equalizes.⁴ Such a finding has prompted investigation into the role of reproductive hormones in POAG pathogenesis. Furthermore, there are currently 11% more women with POAG than men.⁵ In particular, the majority of the current burden of POAG is found in the elderly population, especially elderly women.⁵ As such, exploring the role of reproductive hormones on the development of POAG may shed light on these findings.

Parameters used in the diagnosis of POAG, visual function and optic nerve head analysis, have been found to be sensitive to reproductive hormone variation.^{6,7,8} Akar et. al. showed decreased mean visual sensitivity using short-wavelength automated perimetric (SWAP) analysis during the low estrogen state (luteal phase), when compared to the high estrogen states (follicular phase) in normal menstruating women.⁶ Confocal scanning laser ophthalmoscopy has identified differences in neuroretinal rim area during the menstrual cycle and these differences have been correlated with fluctuating hormone levels.⁷ These findings have suggested the possibility that reproductive hormones, estrogen in particular, may have a role in optic nerve structure and function.

Estrogens are steroid hormones that exist in three major naturally occurring forms: 17- β -estradiol (E2), estrone (E1) and estriol (E3). All three are formed from the androgens testosterone and androstenedione through enzymatic aromatization.⁹ In premenopausal women, large amounts of estrogens are synthesized in the ovaries, but these hormones are also produced in many other tissues. This intracrine synthesis occurs in both females and males and is mediated by the action of steroidogenic enzymes on dehydroepiandrosterone (DHEA).^{10,11} As such, a number of steroidogenic enzymes have been identified in the retina.^{12,13,14} The extra-ovarian synthesis of estrogen is the only source of this hormone in postmenopausal women.¹⁰

The effects of estrogens are mediated by specific nuclear receptors, the estrogen receptor (ER) α and β types that act as hormone-inducible transcription factors.¹⁵ E2 binds equivalently to ER α and ER β , whereas E1 prefers ER α and E3 binds preferentially to ER β .^{16,17} Depending upon the cell and tissue, the expression of these receptors may be

regulated by estrogens and vary according to sex, the menstrual cycle, and age.¹⁸ These estrogen receptors are abundantly expressed throughout the eye, and in particular the retina.^{19,20} In fact, retinal ganglion cells have been found to express estrogen receptors ER α and ER β ²¹ yet the precise role of such receptors in retinal ganglion cell (RGC) homeostasis remains unknown. Estrogen effects are also mediated through membrane estrogen receptors (mER) via a non-classical pathway.^{22,23,24,25,26} This pathway induces rapid changes in membrane fluidity, the activity of neurotransmitter receptors, and the regulation of transcription factors. The role of mERs in ocular tissues, in particular RGCs, has yet to be elucidated.

Menopause, defined by a decline in estrogen sufficient to halt menses, and POAG are both age-related conditions characterized by declining estrogen. Elucidating the relationship between female reproductive aging and POAG may provide greater understanding regarding the pathogenesis of disease, in particular the role of estrogen in the development of POAG. This article will review reproductive health factors, from menarche to menopause to the post-menopausal period, as they relate to POAG and POAG related traits such as intraocular pressure (IOP).

Methods

Original English language articles published in peer-reviewed journals were included. An exploratory search in PUBMED was performed on May 05, 2015 using the following search criteria:

1. “Estrogen and glaucoma” (n=88 articles)
2. “Reproductive factors and glaucoma” (n=16 articles)
3. “Estrogen, nitric oxide and eye” (n=12 articles)

Abstracts identified were reviewed and included if they addressed the role of estrogen in the development of POAG. Abstracts that did not focus on POAG, POAG-related traits such as IOP or did not mention the role of estrogen or its metabolic intermediates in the pathogenesis of POAG were excluded. A total of 43 articles were identified using these selection criteria.

Results

There is a growing body of evidence supporting lifetime estrogen exposure as having a role in the pathogenesis of POAG. Studies have been inconclusive regarding the effect of the menstrual cycle on IOP trends over the short term.^{27,28,29} Over the long term, markers for lifetime estrogen exposure have been measured by several studies and show that late menarche, oral contraceptive (OC) use, early menopause and a shorter duration between menarche to menopause affect POAG risk. The Blue Mountain Eye Study found a significantly increased POAG risk with later (>13 years) compared with earlier (≤12 years) age of menarche.³⁰ Researchers using data from the Nurses' Health Study (NHS) found that oral contraceptive (OC) use of greater than 5 years was associated with a 25% increased risk of POAG.³¹ The authors of the study postulate that OCs prevent the secondary estrogen

surge that occurs during ovulation, thus reducing a women's lifetime exposure to estrogen.³¹ One limitation of this study is that the type of OC used was not described (progesterone only vs combined estrogen-progesterone) which may introduce confounding variables when interpreting this result. Analysis of Rotterdam Study data found that women who went through menopause before reaching the age of 45 years had a higher risk of open-angle glaucoma (2.6-fold increased risk).³² Furthermore, the NHS showed a reduced risk of POAG among women who entered menopause after age 54 years.³³ Interestingly, this finding was significant for those women older than 65 years of age.³³ This finding may shed light on the contrary findings of the Aravind Comprehensive Eye Survey. This survey found no statistically significant relationship between POAG and the age of onset of menarche, the onset of menopause and the duration of estrogen exposure.³⁴ Of note, the average age of the women in this study was 51 years of age – over one decade younger than the women in the above mentioned studies.

Other surrogates for lifetime estrogen exposure, or lifetime reduced estrogen exposure, can be found in studies assessing the risk of POAG in patients who have undergone bilateral oophorectomies as these individuals have decreased circulating estrogens. Using the Mayo Clinic Cohort Study of Oophorectomy and Aging, Vajaranant et. al. found that women who underwent bilateral oophorectomy before age 43 had an increased risk of glaucoma.³⁵ This finding is consistent with the above mentioned epidemiologic studies showing that early loss of female sex hormones confers an increased risk of glaucoma.

If decreases in estrogens increase glaucoma risk, then increased estrogen could lead to a decreased risk of glaucoma or glaucoma related traits such as IOP. During pregnancy, a hyperestrogenemic state, lower IOP can be found, especially during the third trimester despite increased central corneal thickness.^{36,37,38,39,40} The exact mechanism of this IOP reduction is unknown but is thought to be multifactorial in nature, possibly resulting from increased outflow facility and decreased venous pressure.^{39,41}

Yet another factor that alters a lifetime estrogen exposure is that of post-menopausal hormone (PMH) use. Several studies (Table 1) show that PMH use is associated with reductions in intraocular pressure (IOP).^{42,43,44,45, 46,47,48} Interesting, there are a few studies that show PMH use has no effect on IOP.^{49,50,51}

The literature also suggests that PMH use may reduce the risk of POAG.^{35, 52} In particular, Newman-Casey et. al. found that of PMH users, women prescribed estrogen had a 0.4% per month reduction in POAG and those prescribed estrogen and progesterone had a 0.6% per month reduction in the development of POAG.⁵³ These findings support the notion that there is a strong association between increased estrogen exposure and reduced risk of POAG. It is interesting that Vajaranant et. al. did not find a decreased risk of glaucoma in the patient group with early oophorectomy and OAG who were treated with PMH.³⁵ This may be attributed to fact that only a small sample size of patients (11%) were treated.

From a genetic epidemiologic perspective, Pasquale et. al. found an association between estrogen metabolic single nucleotide polymorphisms (SNP) and POAG using data from the National Eye Institute Glaucoma Human Genetic Collaboration (NEIGHBOR)

consortium.⁵³ This study found estrogen metabolic pathway SNPs were associated with POAG in women but not men and this association was stronger with high pressure glaucoma than in normal pressure glaucoma.⁵⁴ Interestingly, the catechol-o-methyltransferase (COMT) gene showed a strong association with both high pressure and low pressure glaucoma in women.⁵⁴ The COMT enzyme catalyzes estradiol into two inactive derivatives thus reducing the functional availability of estradiol.⁵⁴

Another enzyme implicated in POAG pathogenesis is endothelial nitric oxide synthase (*NOS*). Endothelial *NOS* forms nitric oxide that in turn mediates vascular tone and modulates blood flow to the optic nerve.⁵⁵ It has been established that compromised blood flow to the optic nerve and endothelial dysfunction play a role in the pathogenesis of POAG.^{56,57} Polymorphisms in *NOS3* in particular are associated with glaucoma.^{58,59,60,61,62,63,64} Interestingly, estrogen has been found to upregulate *NOS3*.⁶⁵ After nitric oxide is generated it binds to soluble guanylate cyclase to mediate smooth muscle relaxation. Interestingly, the soluble guanylate cyclase $\alpha 1$ -deficient mouse model demonstrates features of POAG including modest increase in IOP (~2 mm Hg), abnormal retinal vasoreactivity to nitric oxide donors and optic nerve degeneration.⁶⁶ It is interesting that gene association studies suggest the relation between endothelial *NOS3* SNPs and high pressure POAG is stronger in women than men.⁶³ Also, for women with age of menarche <13 years, the rs3918188 *NOS3* SNP was associated with a reduced risk of POAG.⁶⁷ Furthermore, for women with certain *NOS3* variants, POAG risk was inversely associated with high pressure POAG among PMH users.⁶³ All of these studies point towards reproductive hormones contributing to POAG pathogenesis.

Discussion

From a translational perspective, the question of whether estrogen is a feasible therapeutic target for POAG is important to consider.

Using the DBA/2J mouse model – an experimental model with age-related increases in IOP, Zhou et. al. found subcutaneous implantation of 17- β -estradiol pellets reduced retinal ganglion cell death.⁶⁸ Furthermore, Tatrai et. al. found that topical 17- β -estradiol protects the retinal ganglion cell layer and preserves visual function in a rodent model of glaucoma where IOP is increased by sclerosing the episcleral veins with hypertonic saline.⁶⁹ These studies suggest that estrogen could have a protective effect in animal models of glaucoma. Though Tatrai et. al. found topical administration of 17- β -estradiol lead to systemic side effects in the animal model studied,⁴⁹ further investigations may lead to the development of topical preparations with specific vehicles of delivery that may avoid systemic issues. Furthermore, such estrogen therapy may have protective effects on other ocular pathology such as age related cataract,⁷⁰ diabetic retinopathy⁷¹ and age-related macular degeneration.⁷² However, estrogen-only hormone replacement therapy has shown an increased risk of developing dry eye syndrome.⁷³

The protective effect of estrogen in other neurodegenerative diseases has been well documented. In particular, estrogen therapy has found to decrease a woman's risk of other neurodegenerative conditions including Alzheimer's disease and Parkinson's disease.^{74,75,76}

The time at which this therapy is administered is crucial and has given rise to the “critical period hypothesis.”⁷⁷ This hypothesis suggests the timing of hormone therapy, in regard to the onset of menopause, is vital. That is, when administered in the perimenopausal period, estrogen could provide neurological, and cardiovascular benefits. However, if hormone therapy is delayed until after menopause allowing a period of long-term estrogen deprivation, estrogen may become detrimental by increasing risk of venous thromboembolism, ischemic stroke and multi-infarct dementia.⁷⁷

The Women’s Health Initiative (WHI) ten-year follow-up study supports the critical period hypothesis as the global index of chronic diseases was decreased in women aged 50–59, suggesting that PMH may provide benefits in perimenopausal women.⁷⁸ This is in contrast to the initial WHI study that was stopped prematurely as it found an increased risk of ischemic stroke in women taking PMHs.⁷⁹ In the initial WHI trial, the average age of the menopausal women enrolled was 63.3 years. Since the median age of onset of natural menopause is 51, these women were more than a decade past the onset of menopause and had already been estrogen deficient for many years before the WHI began. Therefore, the negative findings of the initial WHI may not be applicable to women who are currently experiencing or have recently completed the menopausal transition.⁸⁰

Although beyond the scope of this review, the opposite perspective is of interest. Specifically, if estrogen has a protective effect on the pathogenesis of POAG, then does estrogen blockade have a deleterious effect on the development of POAG? This question has multiple practical applications as patients with certain breast and gynecological cancers are treated with estrogen antagonists and aromatase inhibitors⁸¹ thereby decreasing their exposure to estrogen. Using a population based case control study model, Paganini-Hill et al found patient’s undergoing tamoxifen therapy did not have an increased prevalence of glaucoma as determined via a self-reported survey.⁸² This result may be confounded by the wide age range of surveyed patients (ages 57–75), lack of stratification of glaucoma prevalence by age range, and type of glaucoma.

Studies have shown that bilateral risk reduction mastectomy and salpingo-oophorectomy (RRSO) may decrease the risk of breast cancer in *BRCA-1/2* mutation carriers due to reduction in estrogen exposure.⁸³ What are the visual consequences of such treatment? Should patients undergoing such treatment be monitored closely with regards to their ophthalmologic health? These are questions for future investigations.

Conclusion

Epidemiologic and genetic studies report an association between estrogen exposure and the risk of glaucoma. Though research regarding the role of PMH therapy and IOP reduction remains inconclusive, further investigations may reveal new sex-specific prevention and therapeutic options that may be tailored for individual treatment. Furthermore, future investigations may lead to the development of viable ocular delivery options that take advantage of the neuroprotective effect of estrogen while minimizing systemic side effects.

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Table 1

Postmenopausal hormone (PMH) use and intraocular pressure (IOP)

	Study Design	Number of treated patients/ control patients	IOP associated with no PMH use (Mean $\pm$ STD) mm Hg	IOP associated with PMH use (Mean $\pm$ STD) mm Hg	Change in IOP (mm Hg)	Months on PMH therapy	Type of PMH
Affinito ⁴²	Prospective controlled randomized study	25/25	16.1 $\pm$ 2.3	14.1 $\pm$ 2.0	-2	3	E+P
Altintas ⁴³	Prospective study with age matched controls	20/24	16.2 $\pm$ 2.3	12.3 $\pm$ 1.8	-3.8	2	E or E+P
Cocksuef ⁴⁴	Prospective	34/0	14.1 $\pm$ 2.8	13.4 $\pm$ 2.7	-0.7	6	E+P
Sator ⁴⁵	Prospective study	25/0	16.2 $\pm$ 2.4 OS 15.3 $\pm$ 2.3 OD	14.0 $\pm$ 2.0 OS 13.8 $\pm$ 1.9 OD	-2.2 OS -1.5 OD	3	E+P
Tint ⁴⁶	Prospective cross sectional study	91/172	13.3 $\pm$ 2.9	11.85 $\pm$ 2.65	-1.7		E or E+P
Treister ⁴⁷	Prospective	15/15	-	-	-2.0 -1.8	6	E E+P
Uncu ⁴⁸	Prospective study	30/0	14.6 $\pm$ 0.8	12.6 $\pm$ 0.68	-2.0	12	E or E+P
Abramov ⁴⁹	Prospective controlled cross sectional study	107/107	15	16	-1	12	E or E+P
Guaschino ⁵⁰	Prospective controlled randomized study	40/40	14.8 $\pm$ 3.2	14.9 $\pm$ 4.3	-0.1	12	E+P
Toker ⁵¹	Retrospective cohort study	30/32	13.3 $\pm$ 2.3	13.6 $\pm$ 2.5	-0.3	48 (average)	E+P

Abbreviations used: E = estrogen, E+P = combined estrogen and progesterone; STD = standard deviation