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Gender and glaucoma: what we know and what we need to know

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Abstract

Purpose of review—With growing aging populations and an increase in cases of glaucoma and glaucoma blindness worldwide, aging populations are particularly at higher risk of glaucoma and glaucoma blindness. Awareness of the gender differences might increase attention towards populations at risk.

Recent findings—Women not only outlive men, but also outnumber men in glaucoma cases worldwide. Women are at higher risks for angle closure glaucoma, but there is no clear gender predilection for open angle glaucoma. Of interest, there is some evidence suggesting that female sex hormones might be protective of the optic nerve. In addition, it is hypothesized that decreased estrogen exposure is associated with increased risk for open angle glaucoma, yet population-based studies present inconsistent results. Presently, there is insufficient evidence to support hormonal replacement therapy use in glaucoma prevention. In addition, it appears that women carry a larger burden of glaucoma blindness due to longevity and disadvantages in socioeconomics/health beliefs.

Summary—Current evidence suggests that older women are at risk for glaucoma and glaucoma blindness. Further interdisciplinary research involving investigators, specialized in glaucoma, women's health and health disparities, will lead to better understanding of gender health disparities in glaucoma and better targeting populations at risk.

Keywords

gender difference; glaucoma; women health; female sex hormone; blindness

Introduction

“Does sex matter in glaucoma?” A thought-provoking editorial piece by Higginbotham in 2004 provides an excellent overview for gender and glaucoma. [1] The author presented a line of evidence supporting that sex does matter in glaucoma. First, the Rotterdam Study demonstrated increased risk of primary open angle glaucoma (POAG) in women with early

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menopause. [2] Second, women are at higher risk for primary angle closure glaucoma (PACG) likely due to anatomical predisposition. [3–4, 5*, 6]. Third, female sex was found to be a risk factor in normal tension glaucoma. [7] Lastly, the changes in the level of female sex hormones may influence intraocular pressure (IOP) as well as vascular resistance that might effect the optic nerve head circulation. As women go through cycles of hormonal changes, this might potentially influence the onset and the course of the disease. [1] Accordingly, gender and/or changes in sex hormone levels should be taken into consideration in the care of patients with glaucoma.

It is estimated that glaucoma cases worldwide will increase from 60 million in 2010 to 80 million in 2020 due to increased aging population. [6] Women bear a larger burden than men because not only do women outlive men, but women also outnumber men and represent 60% of all glaucoma cases combined. [6, 8–9] As such, awareness of the gender differences might increase attention towards populations at risk. This article provides a comprehensive review of the following topics; gender predilection for glaucoma; gender difference in visual impairment due to glaucoma; the potential protective effect of female sex hormones on glaucoma; and gender disparity in glaucoma.

Gender predilection for glaucoma: who is at risk for developing glaucoma?

Previous studies demonstrated that women are at higher risk for PACG (Table 1). In addition, the risk is particularly high among Asian and Alaskan Native populations. [6, 10–14] In contrast, there is no clear consensus on gender predilection for POAG (Table 2). In whites, the Baltimore Eye Survey and the Beaver Dam Eye Study showed no difference in prevalence by gender. [15, 16] In contrast, the Framingham Eye Study and the Rotterdam Study showed an increased prevalence among males, whereas the Blue Mountains Eye Study showed an increased prevalence among females. [17–19] In contrast, 5-year incidence rates for women were non-significantly higher in women compared to men in the Rotterdam Study, which was exclusively white (odds ratio (OR): 1.3; 95%confidence interval (CI), 0.9–2.0). [20] In blacks, the risk appears higher in men. [15, 21, 22] For instance, the Barbados Eye Study showed age-adjusted prevalence ratio of 1.4 in men. In Hispanics, the Proyecto VER showed no gender difference; whereas the Los Angeles Latino Eye Study suggested 1.73 time risk in men (OR: 1.73; 95%CI, 1.30–2.30). [23–25]

These inconsistencies among population-based studies may result from an inadequacy in the study power necessary to answer this question. [26] In addition, results may be influenced by different criteria and different populations. Based on a Bayesian meta-analysis, Rudnicka et al. determined variation in POAG prevalence with age, gender, race, year of publication and survey methods. [26] The authors demonstrated that blacks had the highest POAG prevalence at all ages, but whites had the steepest increase in the POAG prevalence with age. Based on 61, 267 participants from 25 studies, POAG prevalence among men was higher than women (OR, 1.37; 95% credible interval (CrI), 1.22–1.53). In contrast, the Eye Diseases Prevalence Research Group did not find any significant gender difference in the POAG prevalence by race. [27] Rudnicka et al. noted that the two meta-analyses used different database, and Friedman et al. had access to unpublished data on gender difference which allowed them to include additional information that were not available in original

studies. In addition, Rudnicka et al, included additional studies from outside the US for the black populations in their meta-analysis, After combining the two meta-analyses, Rudnicka et al. found that the OR was changed to 1.23 (95%CrI, 1.06–1.42), and men still had higher risk for POAG compared to women.

In summary, women are at risk for PACG but the gender predilection for POAG is unclear. Based on the largest meta-analysis, the age-adjusted prevalence of POAG might be higher in men, especially more evident in blacks.

Gender difference in glaucoma blindness: who is at risk for glaucoma blindness?

Reducing glaucoma blindness has been identified as a major goal in Healthy Vision 2010, a national prevention initiative supported by the US Department of Health and Human Services. [28*] According to Healthy Vision 2010, the rate of visual impairment from glaucoma was higher in women (1.53% vs 1.12%). Based on the US database, the 2002–2005 National Health Interview Survey (NHIS), women had a higher self-reported visual impairment for all causes (OR: 1.31; 95%CI, 1.19–1.45) and higher prevalence of self-reported visual impairment from glaucoma (OR: 1.20; 95%CI, 0.99–1.45). [29*]

Besides the NHIS report, there was little data from the population-based studies that addressed gender difference in glaucoma blindness. For example, age-adjusted odds for monocular blindness due to glaucoma was higher in the US Hispanic women (OR: 1.73; 95%CI, 0.47–6.39), however this was based on a small number of cases. [30] Most studies presented overall (non-cause specific) prevalence of visual impairment and blindness. For example, a report from the World Health Organization and other reports suggest that the risk for visual impairment for all causes is twice as high in women than men in every region of the world. [6, 29, 31, 32] Of all causes of blindness, glaucoma is the second leading cause, accounting for 12% of cases of blindness in the world. In addition to the higher risk, women comprise two-third of the world's population of visually impaired and blind individuals and this number is higher, even after age-adjustment. [31, 33*] Additionally, the Eye Diseases Prevalence Study Group suggested that the risk for blindness might be different in different ethnicity. In whites, the blindness prevalence was higher in women, although it was not significant after age adjustment. In contrast, a higher age-adjusted prevalence of blindness was found among black men. [34]

Approximately, 10% of POAG and 25% of PACG cases are bilaterally blind. [6] The blindness cases are estimated to be 4.5 million for POAG and 3.9 million for PACG in 2010, rising to 5.9 and 5.3 million in 2020, respectively. [6] Who is at risk for glaucoma blindness? This matter is more complex as risk of blindness might be influenced by multiple factors such as biological predisposition, sociocultural factors, as well as racial and gender disparities. It appears that women have a higher risk for blindness for all causes worldwide. Given the higher number of glaucoma cases and the potential higher risk for glaucoma blindness in women, increased awareness and attention toward the care for glaucoma in this vulnerable group is recommended.

The effect of sex hormones on glaucoma: what have we learned from population-based studies?

Table 3 summarizes results from previous studies investigating the effect of female sex hormones on POAG development. The Rotterdam Study, a landmark study investigated the effect of female sex hormones on glaucoma. [2] Specifically, women who entered menopause before age of 45 had a 2.6-fold increased risk for POAG, compared with those who entered menopause after age of 50. This finding is supported in part by other studies. For instance, the Blue Mountains Eye Study suggested that shorter estrogen exposure might be associated with POAG. [35] The authors observed higher risk for glaucoma in women with late menarche and increased parity. In addition, there was a non-significant increased risk for glaucoma in women with early menopause (OR: 1.7; 95%CI, 0.7–3.8) and with history of shorter exposure of endogenous estrogen (< 30 years; OR: 1.8; 95%CI, 0.6–5.3). More recently, the Nurses' Health Study, a 22-year longitudinal cohort study, investigated the association between female sex hormones and POAG incidence. [36**] In this study, Pasquale et al. made a notable observation. Specifically, the authors demonstrated the relationship between lower incidence of POAG in women who reported late menopause, but this association was only statistically significant in a group of women older than 65 years of age (Risk ratio (RR): 0.53; 95%CI, 0.32–0.89). This observation could perhaps explain conflicting results from the Aravind Comprehensive Eye Survey reporting no significant association between POAG and the female reproductive factors including the onset of menarche, the onset of menopause and the duration of estrogen exposure. [37] However, as Pasquale et al. commented, the mean age of the Aravind Study was more than a decade younger than those of other previous studies with positive associations.

If estrogen protects women from developing glaucoma during the reproductive period, could hormone replacement therapy (HRT) reduce risk for glaucoma in post-menopausal women? Table 4 summarizes results from previous reports studying the association between the use of female sex hormones and POAG. The Rotterdam Study and the Blue Mountains Study demonstrated non-significant risk reduction for POAG in women who reported HRT use. [2, 35] In contrast, the Los Angeles Latino Eye Study showed no association between sex hormone use and POAG. [25] Of note, these aforementioned studies were not originally designed to answer this particular question and therefore, data on the type of hormone use, onset and duration of HRT and/or birth control use might not be available for analyses. Later, the Nurses' Health Study, a 22-year longitudinal cohort study, evaluated the potential effect of the female sex hormones on the development of POAG. [36**] The investigators not only evaluated different types of hormone use, but also looked at the incidence of POAG in women at risk, characterized by IOP elevation greater than 21 mmHg. They found significant risk reduction of POAG in women with ocular hypertension who used a combination of estrogen and progestin, and found non-significant risk reduction in this group of women who used estrogen only. The effect of HRT and/or sex hormones on glaucoma development/risk reduction is perhaps similar to the risk and benefit of HRT for cardiovascular risk reduction in post-menopausal women. [38] This topic is multifaceted and complex since it depends on not only the type and age of initiation of HRT, but also on individual susceptibility for the particular diseases. Based on the evidence, it is possible the

age-related declines in female sex hormones might place women at greater risk for developing glaucoma; however, there presently is insufficient evidence to support HRT use in glaucoma prevention.

The effect of sex hormones on glaucoma: why might female sex hormones be protective?

Higher IOP was demonstrated after menopause. [39] In addition, a significant 1–4 mmHg IOP reduction has been demonstrated after HRT initiation in both women with and without glaucoma. [39–41] This observation could be explained by the fact that 17β estradiol augments the activity of endothelial-based nitric oxide synthase (NOS) and therefore could regulate smooth muscle tone and vascular resistance. As receptors are located in the ciliary body and the outflow system, it might potentially influence IOP by regulating both aqueous production and aqueous outflow. [39, 42]

In addition, sex hormones have been shown to affect ocular hemodynamics. As opposed to testosterone, estrogen enhances ocular blood flow. [43] It has been demonstrated that aging and age-related declines in female sex hormones negatively affect ocular blood flow. [43, 44] Even after adjusting for age, post-menopausal women demonstrated lower blood velocity and higher vascular resistance, compared to pre-menopausal women. [43] In addition, it was suggested HRT could improve ocular blood flow in post-menopausal women. For instance, post-menopausal women with HRT had similar vascular resistance distal to the ophthalmic artery, compared to that of young women. [45]. In addition, HRT was shown to reduce vascular resistance in the central retinal artery and posterior ciliary artery. [39, 46] Although to a lesser degree, another study also showed the benefit of HRT on ocular blood flow in post-menopausal women with glaucoma. [47] The results were however inconsistent when other investigators compared different groups of post-menopausal women with HRT and without HRT. One report showed lower vascular resistance in women with HRT, but others showed no difference between the two groups. [39, 45, 48]

Furthermore, prior investigations using animal models demonstrated neuroprotective effects of female sex hormones. Specifically, 17β estradiol prevented retinal ganglion cell (RGC) loss induced by an acute IOP elevation in rats and preserved RGC in DBA/2J, a glaucoma mouse model after oophorectomy. [49**, 50**] The neuroprotective effect of 17β estradiol was thought in part to be mediated through estrogen receptors located in the RGC. [49**, 50**]

Lastly, estrogen may be protective, yet hormonal effects are complex since the effects of estrogen on cell type could vary depending on the ratio between α - and β -type estrogen receptors within the tissue. [39] More recently, the Rotterdam Study investigated the association between polymorphism in estrogen receptor genes and POAG risk. They found that estrogen receptor β , and not α polymorphisms, were associated with increased incidence of POAG. Of interest, this association was only significant in men, but not in women. [51**] Further investigation may provide better understanding of this gender difference in the effect of estrogen.

Gender and glaucoma: is there gender difference and/or disparity?

As stated, women outnumber men in rapid-growing aging populations. [9] In addition, women outnumber men in the total number of cases for glaucoma combined. Although there is no clear evidence of gender predilection in POAG, overall, women are likely to become visually-impaired due to glaucoma. There are several factors that could influence this discrepancy. These include biological and non-biological factors (eg. socioeconomic, cultural, health beliefs and access to health care). [52*]

Concerning biological factors (gender difference), women are at risk for PACG, but there is no clear predilection for POAG. Of particular interest, it is possible that female sex hormones might provide some protective effect to the optic nerves. After menopause, women may lose this protective effect and therefore their risk for POAG reaches that of men. This observation interestingly seems to mimic cardiovascular risks in post-menopausal women. [38]

Concerning non-biological factors (gender disparity), women in some parts of the world have less access to health care. [32] In addition, a review of United Healthcare database suggested that women were 24% less likely to be treated for glaucoma. [53] This observation is consistent with previous studies showing lower treatment rates in the intensive care unit and in cardiovascular diseases for women. Considering all factors, older women are particularly at risk and therefore attention should be placed to improve the care for this growing group.

Conclusion

With growing aging populations and an increase in cases of glaucoma and glaucoma blindness worldwide, older women are particularly at higher risk of glaucoma and glaucoma blindness. Furthermore, women carry a larger burden of glaucoma blindness due to longevity and disadvantages in socioeconomic/health beliefs. Of interest, female sex hormones may be protective against glaucoma. Since issues surrounding gender disparity are complex; further interdisciplinary research involving investigators who specialize in glaucoma, women's health and health disparities is necessary. Increased awareness and understanding of gender health disparities in glaucoma will lead to better targeting populations at risk and better use of available resources to improve care for our glaucoma patients.

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Table 1

Prevalence and Incidence of PACG by Race/Ethnicity and Gender

Race/ Ethnicity and Author	Study, Location (Sample Size)	Age (yr)	Prevalence of PACG in Percent (95% CI)			Gender Predilection	Adjusted Odds Ratio OR (95%CI) [#]
			All	Men	Women		
Asian Lavanya 2008	Singapore (n = 2042)	50+	19.3 ^a	n/a	n/a	Women	1.4 (1.1–2.0) [*]
Casson 2009	The Kandy Eye Study, Sri Lanka (n = 1375)	40+	4.7 ^b (1.1–9.4) 0.6 ^c (0.0–1.2)	n/a	n/a	Women	9.2 (2.8–31.3) ^{***}
American Indian/Alaskan Native Van Rens 1988	Alaska (n = 368)	40+	3.8	2.1	5.5	n/a	n/a
Caucasian Mitchell 1996	Blue Mountains Eye Study (n = 3654)	49+	0.3	n/a	n/a	n/a	n/a
Klein 1992	Beaver Dam Eye Study (n = 4926)	43+	0.1	n/a	n/a	n/a	n/a
Black Tielsch 1991	Baltimore Eye Survey (n = 5308)	40+	0.9 ^d	n/a	n/a	n/a	n/a
Hispanic Quigley 2001	Proyector VER (n = 4774)	40+	0.1	n/a	n/a	n/a	n/a [§]
Race/ Ethnicity and Author	Study (Sample Size)	Age (yr)	Incidence Rate of PACG (per 100,000; 95% CI)			Gender Predilection	Adjusted Odds Ratio OR (95%CI)
			All	Men	Women		
Asian Seah 1997	As Island-Wide Survey, Singapore (n = 1555100) ¹	30+	12.2 (10.5–13.9)	7.4	20.4	Women	2.4 (1.8–3.4) ^{§§}
Caucasian Teikari 1987	Finland (n = 1796) ²	n/a ²	3.8	2.0	5.3	Women	2.6 [¶]

[#] OR = adjusted odds ratio between men and women

¹ Based on the 1994 census and reported cases during 1-year study period;

² Retrospective review of a national computerized discharge registry during 10-year period, minimal age not defined.

^a A cross-sectional study recruited from a primary care clinic;

^b Overall prevalence including primary angle closure suspect, primary angle closure, and primary angle closure glaucoma;

^c Primary angle closure glaucoma;

^d Based on a personal communication, cited in Klein 1992

- * Adjusted for age, gender, axial length, intraocular pressure and race;
- ** Adjusted for age, gender, lens opacity, anterior chamber depth;
- § 3 out 5 were women;
- §§ Relative risk, not stated if adjusted for other variables;
- ¶ Adjusted for age

Table 2

Prevalence and Incidence of POAG by Race/Ethnicity and Gender

Race/ Ethnicity and Author	Study (Sample Size)	Age (yr)	Prevalence of POAG in Percent (95% CI)			Gender Predilection	Adjusted Odds Ratio OR (95%CI) [#]
			All	Men	Women		
White Tielsch 1991	Baltimore Eye Survey (n = 5308)	40+	1.3 (0.8–1.8)	2.7	2.4	No*	n/a
Klein 1992	Beaver Dam Eye Study (n = 4926)	43+	2.1	2.0	2.2	No	n/a
Leibowitz 1980	Framingham Eye Study (n = 2631)	52+	1.9	2.5	1.4	Men	1.8
Dielemans 1994	Rotterdam Study (n = 3062)	55+	1.1 (1.1–1.1)	1.9	0.6	Men	3.6
Mitchell 1996	Blue Mountains Eye Study (n = 3654)	49+	3.0 (2.5–3.6)	n/a	n/a	Women**	1.6 (1.0–2.3)
Black Tielsch 1991	Baltimore Eye Survey (n = 5308)	40+	4.7 (3.8–5.7)	2.7	2.4	No*	n/a
Leske 1994	Barbados Eye Study (n = 4709)	40+	6.7 (6.3–7.8)	8.3 (7.1–9.7)	5.7 (4.9–6.7)	Men [§]	1.4
Hispanic Quigley 2001	Proyecto VER (n = 4774)	40+	2.0 (1.6–2.4)	n/a	n/a	No	1.1 (0.7–1.7) ^d
Varna 2004	Los Angeles Latino Eye Study (n = 6142)	40+	4.7(4.2–5.3)	5.4 (5.0–6.4)	4.4 (3.6–5.0)	No	n/a
Doshi 2008	Los Angeles Latino Eye Study (n = 6142)	40+	n/a	5.6	4.4	Men ^{§§}	1.7 (1.3–2.3)
Race/ Ethnicity and Author	Study (Sample Size)	Age (yr)	Incidence Rate of POAG (per 1,000; 95% CI)			Gender Predilection	Adjusted Odds Ratio OR (95%CI)
			All	Men	Women		
White Voodg 2005	Rotterdam Study ¹ (n = 3842)	55+	1.2 (0.8–1.7)	1.5 (0.9–2.4)	1.0 (0.6–1.7)	No	1.3 (0.9–2.0)
Black Leske 2008	Barbados Eye ² Study (n = 3222)	40+	4.4 (3.7–5.2)	4.9 (3.8–6.4)	4.1 (3.2–5.1)	No	1.2 (0.8–1.7) ^b

[#] OR = adjusted odds ratio between men and women; CI = confidence interval¹ 5-year incidence;² 9-year incidence risk ratio

* Adjusted for race and age;

** Adjusted for age;

[§] age-adjusted prevalence ratio;

^{SS}Based on logistic regression including age, gender, marital status, smoking, and family history, with adjustment for intraocular pressure

^a men as a reference;

^b women as a reference

Table 3

Female Reproductive Factors and POAG

Resources (Sample Size)	Mean age (yr)	Female reproductive factors significantly associated with glaucoma			Comments
		Onset of menopause	Onset of menarche	Duration of estrogen exposure ^I	
Rotterdam Study 2001 (n = 3078)	68.8	yes	n/a	n/a	- Increased risk (OR: 2.6; 95%CI, 1.5–4.8) in women with early menopause, compared to later menopause (< 45 yr vs. > 50 yr)*
Blue Mountains Study 2003 (n = 2072)	66.4	no	yes	no	- Increased risk (OR: 2; 95%CI, 1–3.9) in women with late menarche (> 13 yr) - Non-significant increased risk (OR: 1.7; 95%CI, 0.7–3.8) in women with early menopause (< 45 yr vs. 50 yr) - Non-significant increased risk (OR: 1.8; 95%CI, 0.6–5.3) in women with shorter duration of endogenous estrogen exposure (< 30 yr). - Parity significantly increased risk for glaucoma (p = 0.03) and decreased risk for ocular hypertension (p = 0.03).§
Aravind Comprehensive Eye Survey 2004 (n = 5150)	51.3	no	no	no	- Onset of menarche (OR: 1; 95%CI, 0.3–2.9; 14yr vs 13yr)§§ - Onset of menopause (OR: 1.1; 95%CI, 0.1–16; 45 yr vs 50yr)§§ - Duration of estrogen exposure (OR: 1.6; 95%CI, 0.1–23; < 30yr vs 35yr)§§ - Parity was not associated with glaucoma risk.§§ - Relatively younger population
Nurses' Health Study 2007 (n = 56703)	60.7	yes	n/a	n/a	- 22-year longitudinal cohort study - Decreased risk (RR: 0.53; 95%CI, 0.32–0.89) in women older than 65 with late menopause (< 54 yr)¶

OR = odds ratio; CI = confidence interval

^I Number of years between reported age at menarche and menopause

* Adjusted for age, hypertension, diabetes and use of hormone replacement therapy;

** Adjusted for age, history of diabetes, hypertension, myopia, pseudoexfoliation, and family of glaucoma, excluded women with hysterectomy;

§ Adjusted for age, history of diabetes, hypertension, myopia, pseudoexfoliation and family history of glaucoma;

§§ Adjusted for age, diabetes, pseudoexfoliation and myopia;

¶ Adjusted for age, period at risk, family history of glaucoma, African-American heritage, hypertension, diabetes, body mass index, smoking, alcohol intake, physical activity, caffeine intake

Table 4

The Use of Hormones and POAG

Resources (Sample Size)	Mean Age (yr)	Type of hormone		Comments
		HRT	OCP	
Rotterdam Study 2001 (n = 3078)	68.8	no	n/a	- Non-significant decreased risk (OR: 0.54; 95%CI, 0.17–1.74) in women who had used HRT*
Blue Mountains Study 2003 (n = 2072)	66.4	no	no	- Non-significant decreased risk (OR: 0.5; 95% CI, 0.2–1.2) in women with HRT**
Nurses' Health Study 2007 (n = 56703)	60.7	yes	n/a	-22-year longitudinal cohort study evaluating different types of HRT combinations and looking at POAG incidence in women at risk [§] - Decreased risk (RR: 0.58; 95%CI, 0.36–0.94) in users of estrogen with progestin combination - Non-significant risk reduction (RR: 0.93; 95%CI, 0.63–1.35) in users of estrogen only
Los Angeles Latino Eye Study 2008 (n = 1916)	54.9	no	no	-No types of hormone noted. ^{§§}

HRT = hormonal replacement therapy, OCP = oral contraceptive pill

OR = odds ratio, RR = risk ratio; CI = confidence interval

* Adjusted for age, hypertension, diabetes;

** Adjusted for age, history of diabetes, hypertension, myopia, pseudoexfoliation, and family history of glaucoma;

[§] women at risk characterized by intraocular pressure > 21 mmHg, adjusted for age, period at risk, family history of glaucoma, African-American heritage, hypertension, diabetes, body mass index, smoking, alcohol intake, physical activity, caffeine intake;

^{§§} Adjusted for age and gender