The association of estrogen-signaling pathways and susceptibility to open-angle glaucoma

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Abstract

Background: Glaucoma is a complex multivariate disorder characterized by retinal ganglion cell (RGC) loss and optic nerve degeneration. Evidence suggests the role of estradiol (E₂) and the etiology of glaucoma. Therefore, this present study evaluates the association between estrogen-signaling pathways and the risk of open-angle glaucoma (OAG).

Results: Meta-analysis was performed from available studies that investigated intraocular pressure (IOP) in patients treated with or without hormone replacement therapy (HRT) and studies that evaluated the associations between estrogen receptor (ER) polymorphisms and the risk of OAG. The pooled result showed that HRT had a positive effect in lowering IOP. Moreover, ERβ polymorphisms showed a significant association with the risk of OAG.

Conclusion: This report supports the notion that estrogen-signaling pathways play a pivotal role in the development of OAG.

Keywords: Estradiol, Estrogen receptor, Polymorphisms, Hormone replacement therapy, Intraocular pressure, Open-angle glaucoma

1 Background

Glaucoma is a complex multivariate disease characterized by retinal ganglion cell (RGC) loss and optic nerve degeneration [1]. A high intraocular pressure (IOP) is observed in the glaucomatous eye as a result of trabecular meshwork (TM) outflow resistance [2]. It is well known that open-angle glaucoma (OAG) is the most common type of glaucoma [3]. Several risk factors have been identified and associated with the etiology of glaucoma including elevation of IOP, immune and inflammatory mediators, and oxidative stress [4]. The number of people with glaucoma worldwide is projected to be 111.8 million in 2040, particularly in the Asian and African populations [5]. Further, the prevalence of OAG is likely observed in men and linearly increases with age [6], suggesting that female sex steroid hormones contribute to the development of OAG.

Estradiol (E₂) is a predominant form of estrogen and is considered as the major female sex steroid hormone. E₂ biosynthesis is catalyzed from testosterone by the rate-limiting enzyme aromatase, encoded by the cyp19a gene [7–10]. E₂-mediated effects are mainly modulated by two types of estrogen receptor (ER), ERα and β. Because estrogen signaling is dependent on its receptor, subtle changes in the DNA sequence (polymorphism) of ER genes may result in different responses to E₂ [11]. Therefore, understanding ER genes polymorphisms are necessary in regard to their role in glaucoma pathogenesis.

Previously, it has been reported that ERβ is predominantly expressed in the central nervous system (CNS) [7]. Interestingly, in the retina, the expression of ERβ is strongly localized in the ganglion cell layer (GCL) [12]. Furthermore, the administration of E₂ suppresses ganglion cell loss and improve contrast sensitivity in glaucoma model [13–16], implying that E₂ exerts a neuroprotective effect on the retina and optic nerve and possibly is becoming an important approach for glaucoma treatment.
A number of studies have been showing a positive impact of hormone replacement therapy (HRT) in lowering IOP and the prevalence of glaucoma in post-menopausal women [17, 18], although the correlation between $E_2$ and glaucoma has been studied to some extent. Interestingly, however, genotypic distributions of ER and the effect of HRT among various glaucoma patients vary across studies and have not been systemically analyzed. Thus, this report will highlight how estrogen plays an important role in the pathophysiology of OAG.

2 Methods
A literature search was conducted from major international databases until September 2019.

2.1 Effect of HRT in lowering IOP
To evaluate the efficacy of HRT in lowering IOP, the selection criteria were as follows: (1) comparing the IOP of HRT-treated patients with controls, (2) patients were female in a menopausal period, (3) a case-control design, and (4) pre-post treatment evaluation. Pooled standardized mean difference (SMD) with 95% confidence interval (CI) was used to assess the IOP between patients with HRT and controls. Heterogeneity among studies was evaluated using $Q$ test and $I^2$ statistic. Subgroup analysis based on the methodological design was performed to investigate if heterogeneity existed. Begg’s funnel plots and Egger’s regression test were used to assess publication bias. An analysis with $P < 0.05$ is considered statistically significant.

2.2 Association of ER polymorphism and glaucoma
To analyze the association of ER polymorphism and glaucoma, the selection criteria were as follows: (1) evaluating the associations between ER polymorphisms and the risk of OAG, (2) glaucoma patients and control subjects were a combination of male and female, and (3) a case-control design. The genotypic frequency for the ER polymorphisms was tested by Hardy–Weinberg equilibrium (HWE). The associations between the ER polymorphisms and OAG risks were estimated by calculating the pooled odds ratio (OR) and 95% CI. Heterogeneity was evaluated with $Q$ test and $I^2$. Begg’s funnel plots and Egger’s regression test were used to evaluate publication bias. The value of $< 0.05$ was indicative of statistical significance.

3 Results
Aromatase, encoded by the $cyp19a1$ (cytochrome P450 19A1) gene, is a rate-limiting enzyme for $E_2$ biosynthesis [7–10]. The expression and activity of $cyp19a1$ are significantly decreased in menopausal women [19]. At some point, a previously published article reviews the role of HRT in regulating IOP [18]. However, a meta-analysis was not performed. In this current study, 10 studies included in this meta-analysis measured the IOP from menopausal women with or without HRT (Table 1). A meta-analysis of IOP in patients with HRT and the controls were shown in Fig. 1a. The pooled results indicated HRT-treated patients had lower IOP than controls or pre-treatment (SMD = −0.39, 95% CI = −0.52 to −0.26, $P < 0.00001$). There was a significant heterogeneity ($I^2 = 84\%$, $P < 0.00001$) in pooled studies. Duration treatment was of considerable effect on heterogeneity ($b = 0.162$; $P = 0.041$). Begg’s funnel plot (Fig. 1b) and Egger’s test showed that there was a Publication bias between studies ($P = 0.001$), which is possibly caused by the heterogeneity of studies. Therefore, a trim and fill method was carried out but did not leverage the results and the outcome remains similar, indicating that it was not affected by publication bias.

Estrogen-mediated effects are modulated by ER [7]. Two studies investigating the associations between ER polymorphisms and the risk of OAG were evaluated. Two and four polymorphisms occurred in the ERα and ERβ genes, respectively (Table 2). All of the polymorphisms complied with the HWE ($P > 0.05$). The pooled results showed that there was no significant association between ERα gene polymorphisms with the risks of OAG. A significant association was observed between ERβ gene polymorphisms with the risk of OAG (indicated by an asterisk in Table 3). Compared to the TC/CC genotypes, the TT genotype of ERβ rs1256031 showed a 36% decrease in the odd’s ratio (OR = 0.64, 95% CI 0.47–0.88, $P = 0.006$). Moreover, the TT genotype of ERβ rs1256031 also significantly decreased the risk of OAG by 39% compared to the TC genotype (OR = 0.61, 95% CI 0.44–0.86, $P = 0.005$), indicating that the C allele increased the risk of OAG. On the other hand, the G allele of ERβ rs4986938 was associated with the risk of OAG (OR = 1.37, 95% CI 1.04–1.82, $P = 0.03$), while the A allele was protective. No publication bias was observed for the association of the ER polymorphisms and the OAG risks ($P > 0.05$).

4 Discussion
In this present study, it showed that HRT act as an IOP-lowering agent in menopausal women. Indeed, a low level of $E_2$ has been suggested to be associated with an increased IOP [6]. Moreover, a high IOP and degenerated RGCs are observed in female $cyp19a1$ knockout mice [32], thereby suggesting that estrogen is necessary for regulating aqueous humor dynamics. Currently available treatments for glaucoma are to control and maintain the IOP. However, most of the drugs are reducing IOP by modifying aqueous dynamic [33], but not necessarily treat the underlying mechanisms of high IOP, which is mainly caused by TM outflow resistance [2]. It
has been reported that an increase in aqueous outflow resistance is closely associated with fibrotic changes in TM [34]. Thus, drugs targeting IOP with anti-fibrotic properties may be useful for treating glaucoma.

Fibrotic changes in OAG patients are characterized by extracellular matrix (ECM) deposition in TM, which was mediated by transforming growth factor-β (TGF-β) 1 and 2, with levels significantly elevated in the aqueous humor of patients with OAG [35–37]. On the other hand, the administration of E2 has been reported to suppress TGF-β-induced activation of Smad and MAD-related protein 3 (Smad3) activity [38]. Further, E2 prevents cardiac fibrosis through the ERβ signaling pathway by inhibiting the effects of angiotensin II (AngII) and endothelin-1 (ET-1)-induced pro-fibrotic signaling in female mice [39]. Therefore, a combination of drugs lowering IOP with estrogen replacement therapy seems promising in targeting normal IOP for menopausal women with glaucoma.

It was showed that ERβ rs1256031 and rs4986938 polymorphisms were associated with OAG risks, but not ERα. A study from Pasquale et al. was not included in this meta-analysis because genotype frequency was not provided. However, they reported that both ERα and ERβ play an important role in high-tension glaucoma (HTG) and normal-tension glaucoma (NTG) among

| Author          | Country    | Mean age (year) | Duration of treatment | Type                                      | IOP (mmHg) |
|-----------------|------------|-----------------|-----------------------|-------------------------------------------|------------|
| Abramov et al. 2005 (a) [20] | Israel     | 66.45           | 12 months             | NA (RO)                                  | 107 15.2   |
| Abramov et al. 2005 (b)         |            |                 |                       | NA (LO)                                  | 107 15.3   |
| Affinito et al. 2003 (a) [21]  | Italy      | 53.7            | 3 months              | Estradiol + medroxyprogesterone acetate   | 24 14.1    |
| Affinito et al. 2003 (b)        |            | 53.7            | 6 months              | Estradiol + medroxyprogesterone acetate   | 24 14.1    |
| Altıntaş et al. 2004 (a) [22]  | Turkey     | 46.1            | 2 months              | NA                                       | 20 12.33   |
| Altıntaş et al. 2004 (b)        |            |                 |                       |                                           | 20 12.33   |
| Coksuer et al. 2011 [23]       | Turkey     | 45–60*          | 6 months              | Estradiol + drospirenone                 | 34 13.4    |
| Guaschino et al. 2003 [24]     | Italy      | 59.9            | 12 months             | Estradiol + dydrogesterone               | 40 14.8    |
| Özcan et al. 2017 (a) [25]     | Turkey     | 49.9            | 6 months              | NA                                       | 61 13.94   |
| Özcan et al. 2017 (b)           |            |                 |                       |                                           | 61 13.94   |
| Sator et al. 1997 (a) [26]     | Turkey     | 55.7            | 1 week                | Estradiol + medroxyprogesterone acetate (RO) | 25 14.9    |
| Sator et al. 1997 (b)           |            |                 |                       | Estradiol + medroxyprogesterone acetate (LO)| 25 15.2    |
| Sator et al. 1997 (c)           |            |                 | 1 month               | Estradiol + medroxyprogesterone acetate (RO)| 25 14.4    |
| Sator et al. 1997 (d)           |            |                 | 3 months              | Estradiol + medroxyprogesterone acetate (LO)| 25 14.2    |
| Sator et al. 1997 (e)           |            |                 |                       | Estradiol + medroxyprogesterone acetate (RO)| 25 13.8    |
| Sator et al. 1997 (f)           |            |                 |                       | Estradiol + medroxyprogesterone acetate (LO)| 25 14.2    |
| Tint et al. 2010 (a) [27]       | Scotland   | 59.35           | NA                    | Estradiol only                           | 33 11.81   |
| Tint et al. 2010 (b)            |            |                 |                       | Combined                                  | 58 11.87   |
| Toker et al. 2003 [28]         | Turkey     | 52.4            | 1.5 months            | NA                                       | 30 13.29   |
| Vajaranant et al. 2016 (a) [29] | USA        | 71.875          | 5 ± 1 years           | Estradiol (RO)                           | 808 15.4   |
| Vajaranant et al. 2016 (b)      |            |                 |                       | Estradiol + progestin (RO)               | 1397 15.6   |
| Vajaranant et al. 2016 (c)      |            |                 |                       | Estradiol (LO)                            | 808 15.3   |
| Vajaranant et al. 2016 (d)      |            |                 |                       | Estradiol + progestin (LO)               | 1397 15.7   |

n and SD represented the number of samples and standard deviation of IOP, respectively
NA not available, RO right ocular, LO left ocular
*Data presented as range
Fig. 1  

(a) Forest plot of the pooled studies evaluating IOP in HRT-treated patients and controls.  
(b) Begg’s funnel plot to evaluate publication bias

Table 2  
Characteristics of individual studies for the associations between ER polymorphisms and the risk of OAG

| Author                   | Country | Polymorphism | Type | Gender (f/m)a | Ageb | Genotype distributionc | PHWE d |
|--------------------------|---------|--------------|------|---------------|------|------------------------|--------|
|                          |         |              |      |               |      | Case                  | Control|
|                          |         |              |      |               |      | Total (95% CI)         |         |
| ERα                      |         |              |      |               |      | Heterogeneity: Tau² = 0.06; CH² = 94.83, df = 12 (P = 0.0001); I² = 87% |         |
| Kosior-Jarecka et al. 2019 [30] | Poland | rs12154178 | NTG  | 100/43        | 74/NA| 0.111733               | 0.410095|
| Kosior-Jarecka et al. 2019 | Poland | rs1884054 | NTG  | 100/43        | 74/NA| 0.111733               | 0.410095|
| Kosior-Jarecka et al. 2019 | Poland | rs2158656 | NTG  | 100/43        | 74/NA| 0.111733               | 0.410095|
| Kosior-Jarecka et al. 2019 | Poland | rs7159462 | NTG  | 100/43        | 74/NA| 0.111733               | 0.410095|
| Mabuchi et al. 2010 [31] | Japan   | rs1256031  | HTG  | 63/29         | 77.5/NA| 0.101595               | 0.001733|
| Mabuchi et al. 2010      | Japan   | rs4986938  | HTG  | 63/29         | 77.5/NA| 0.101595               | 0.001733|

NA not available, NTG normal-tension glaucoma, HTG high-tension glaucoma
aGender based on type of glaucoma
bThe mean age of case and control
c1 represents the common allele, while 2 represents the minor allele
dP for HWE equilibrium test in controls
women, respectively [40]. Interestingly, ER modulates cyp19a1 expression which turns to create a positive loop between estradiol-aromatase [7]. Thus, ER polymorphisms may affect the physiological functions of estrogen in regulating aromatase and its product which later contributes to the development of OAG. Another possibility is that cyp1b1 (cytochrome P450 1B1) is regulated by ER [41], and the downregulation of this gene is correlated with OAG and oxidative stress in TM [42, 43], although conflicting results regarding the role of polymorphism in cyp1b1 and the risk of OAG between studies were documented [40, 42, 44, 45]. However, the loss of function in cyp1b1 variants, particularly c.1064_1076del, p.(Arg355Hisfs*69), seems to be associated with an increased risk for OAG [45]. Moreover, it is possible to hypothesize that estrogen might be modulated by cyp1b1 in regulating IOP.

5 Conclusion
In conclusion, this report shows that estrogen-signaling pathways are associated with the risk of OAG. Screening of hormonal status might be useful for the early detection of OAG.

Abbreviations
A: Adenine; C: Cytosine; CI: Confidence interval; CNS: Central nervous system; cyp19a1: Cytochrome P450 19A1; cyp1b1: Cytochrome P450 1B1; E 2: Estradiol; ECM: Extracellular matrix; ER: Estrogen receptor; G: Guanine; GCL: Ganglion cell layer; HRT: Hormone replacement therapy; HWE: Hardy–Weinberg equilibrium; IOP: Intraocular pressure; OAG: Open-angle glaucoma; RGC: Retinal ganglion cell; Smad3: Sma and MAD-related protein 3; SMD: Standardized mean difference; T: Thymine; TGF: Transforming growth factor; TM: Trabecular meshwork

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Author's contributions
ZU designed, performed, analyzed, and wrote the manuscript. The author read and approved the final manuscript.

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Table 3 Meta-analysis for the association between ER polymorphisms and the risk of OAG

| Contrast | Number of studies | OR   | 95% CI   | I^2 (%) | P value |  |
|----------|-------------------|------|----------|---------|---------|--|
| ERα rs12154178 |                   |      |          |         |         |  |
| A vs C     | 2                 | 0.97 | 0.72–1.31 | 0       | 0.84    |  |
| AA vs AC/CC | 2                 | 0.98 | 0.70–1.38 | 0       | 0.92    |  |
| CC vs AA/AC | 2                 | 1.60 | 0.72–3.59 | 0       | 0.25    |  |
| CC vs AA   | 2                 | 1.58 | 0.70–3.58 | 0       | 0.27    |  |
| CC vs AC   | 2                 | 1.63 | 0.71–3.74 | 0       | 0.25    |  |
| ERα rs1884054 |                  |      |          |         |         |  |
| A vs C     | 2                 | 1.01 | 0.75–1.36 | 0       | 0.95    |  |
| AA vs AC/CC | 2                 | 1.02 | 0.72–1.42 | 0       | 0.93    |  |
| CC vs AA/AC | 2                 | 0.86 | 0.45–1.63 | 21      | 0.64    |  |
| CC vs AA   | 2                 | 0.85 | 0.41–1.77 | 32      | 0.67    |  |
| CC vs AC   | 2                 | 0.96 | 0.79–1.15 | 0       | 0.61    |  |
| ERβ rs1268656 |                  |      |          |         |         |  |
| T vs G     | 2                 | 1.49 | 1.01–2.21 | 0       | 0.05    |  |
| TT vs GT/GG | 2                 | 1.58 | 0.83–3.02 | 62      | 0.17    |  |
| GG vs TT/TG | 2                 | 0.73 | 0.49–1.08 | 1       | 0.11    |  |
| GG vs TT   | 2                 | 2.08 | 0.88–4.88 | 0       | 0.09    |  |
| GG vs GT   | 2                 | 1.66 | 0.67–4.11 | 0       | 0.27    |  |
| ERβ rs7159462 |                  |      |          |         |         |  |
| C vs T     | 2                 | 0.70 | 0.70–1.10 | 0       | 0.12    |  |
| CC vs CT/TT | 2                 | 0.66 | 0.42–1.05 | 0       | 0.08    |  |
| TT vs CT/CT | 2                 | 4.05 | 0.73–22.30 | 0       | 0.11    |  |
| TT vs CC   | 2                 | 4.27 | 0.77–23.55 | 0       | 0.10    |  |
| TT vs CT   | 2                 | 3.07 | 0.53–17.72 | 0       | 0.21    |  |
| ERβ rs1256031 |                  |      |          |         |         |  |
| C vs T     | 2                 | 1.20 | 0.99–1.46 | 0       | 0.07    |  |
| CC vs TC/TT | 2                 | 1.15 | 0.84–1.58 | 0       | 0.37    |  |
| TT vs CC/TC | 2                 | 0.64 | 0.47–0.88 | 0       | 0.006   |  |
| TT vs CC   | 2                 | 0.70 | 0.48–1.30 | 0       | 0.07    |  |
| TT vs TC   | 2                 | 0.61 | 0.44–0.86 | 0       | 0.005   |  |
| ERβ rs4986938 |                  |      |          |         |         |  |
| G vs A*    | 2                 | 1.37 | 1.04–1.82 | 0       | 0.03    |  |
| GG vs GA/AA | 2                 | 1.37 | 1.00–1.88 | 0       | 0.05    |  |
| AA vs GG/GA | 2                 | 0.51 | 0.21–1.24 | 0       | 0.14    |  |
| AA vs GG   | 2                 | 0.48 | 0.20–1.16 | 0       | 0.10    |  |
| AA vs GA   | 2                 | 0.63 | 0.25–1.59 | 0       | 0.33    |  |

*p < 0.05

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