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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 (E_2) 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 (E_2) is a predominant form of estrogen and is considered as the major female sex steroid hormone. E_2 biosynthesis is catalyzed from testosterone by the rate-limiting enzyme aromatase, encoded by the *cyp19a* gene [7–10]. E_2-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 E_2 [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 E_2 suppresses ganglion cell loss and improve contrast sensitivity in glaucoma model [13–16], implying that E_2 exerts a neuroprotective effect on the retina and optic nerve and possibly is becoming an important approach for glaucoma treatment.

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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

Table 1 Summary of the studies for the IOP between HRT-treated patients and the control subjects

Author	Country	Mean age (year)	Duration of treatment	Type	IOP (mmHg)					
					HRT			non-HRT/pre		
					n	Mean	SD	*n*	Mean	SD
Abramov et al. 2005 (a) [20]	Israel	66.45	12 months	NA (RO)	107	15.2	0.4	107	15.5	0.4
Abramov et al. 2005 (b)				NA (LO)	107	15.3	0.5	107	15.2	0.2
Affinito et al. 2003 (a) [21]	Italy	53.7	3 months	Estradiol + medroxyprogesterone acetate	24	14.1	2	24	16.6	2.3
Affinito et al. 2003 (b)			6 months		24	14.1	2.1	24	16.6	2.4
Altintaş et al. 2004 (a) [22]	Turkey	46.1	2 months	NA	20	12.33	1.76	24	14.66	1.71
Altintaş et al. 2004 (b)					20	12.33	1.76	20	16.16	2.32
Coksuer et al. 2011 [23]	Turkey	45–60*	6 months	Estradiol + drospirenone	34	13.4	2.7	34	14.1	2.8
Guaschino et al. 2003 [24]	Italy	59.9	12 months	Estradiol + dydrogesterone	40	14.8	3.2	40	14.9	4.3
Özcan et al. 2017 (a) [25]	Turkey	49.9	6 months	NA	61	13.9344	1.47	76	15.41	1.76
Özcan et al. 2017 (b)					61	13.9344	1.47	76	14.35	1.4
Sator et al. 1997 (a) [26]	Austria	55.7	1 week	Estradiol + medroxyprogesterone acetate (RO)	25	14.9	2	25	15.2	2.6
Sator et al. 1997 (b)				Estradiol + medroxyprogesterone acetate (LO)	25	15.2	2.4	25	15.9	2.6
Sator et al. 1997 (c)			1 month	Estradiol + medroxyprogesterone acetate (RO)	25	14.4	2.1	25	15.2	2.6
Sator et al. 1997 (d)				Estradiol + medroxyprogesterone acetate (LO)	25	14.2	2.3	25	15.9	2,6
Sator et al. 1997 (e)			3 months	Estradiol + medroxyprogesterone acetate (RO)	25	13.8	1.9	25	15.2	2.6
Sator et al. 1997 (f)				Estradiol + medroxyprogesterone acetate (LO)	25	14.2	2.3	25	15.9	2.6
Tint et al. 2010 (a) [27]	Scotland	59.35	NA	Estradiol only	33	11.81	2.91	172	13.25	2.85
Tint et al. 2010 (b)				Combined	58	11.87	2.51	172	13.25	2.85
Toker et al. 2003 [28]	Turkey	52.4	1.5 months	NA	30	13.29	2.28	32	13.56	2.5
Vajaranant et al. 2016 (a) [29]	USA	71.875	5 ± 1 years	Estradiol (RO)	808	15.4	3.2	860	15.8	3.3
Vajaranant et al. 2016 (b)				Estradiol + progestin (RO)	1397	15.6	3	1282	15.7	3.1
Vajaranant et al. 2016 (c)				Estradiol (LO)	808	15.3	3.1	860	15.9	3.2
Vajaranant et al. 2016 (d)				Estradiol + progestin (LO)	1397	15.7	3	1282	15.7	3

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

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 E_2 has been reported to suppress TGF-β-induced activation of Sma and MAD-related protein 3 (Smad3) activity [38]. Further, E_2 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

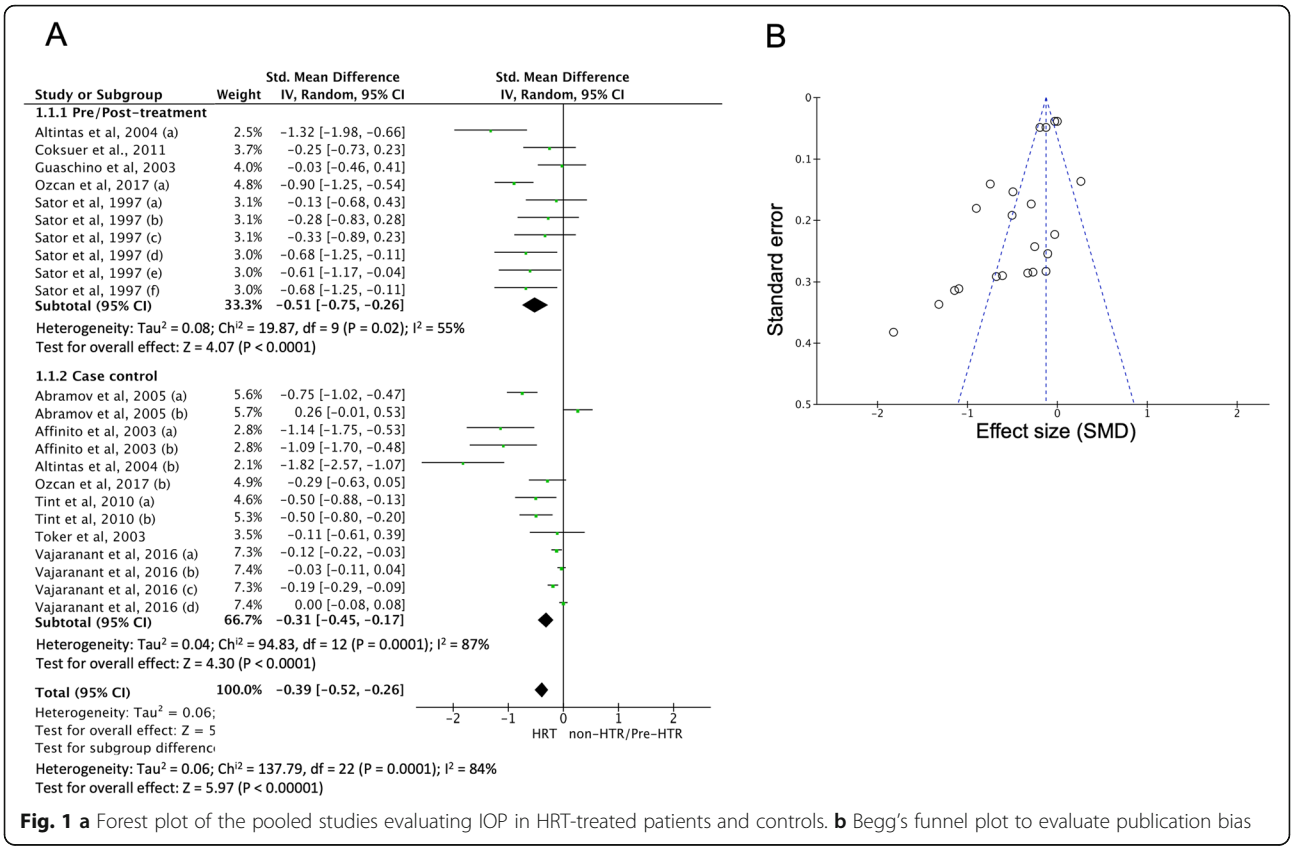

Fig. 1 a Forest plot of the pooled studies evaluating IOP in HRT-treated patients and controls. **b** Begg's funnel plot to evaluate publication bias

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]	Age[b]	Genotype distribution[c]						P_{HWE}[d]
						Case			Control			
						11	12	22	11	12	22	
ERα												
Kosior-Jarecka et al. 2019 [30]	Poland	rs12154178	NTG	100/43	74/NA	77	57	6	90	68	6	0.111733
Kosior-Jarecka et al. 2019	Poland		HTG	63/29	77.5/NA	50	36	7	90	68	6	0.111733
Kosior-Jarecka et al. 2019	Poland	rs1884054	NTG	100/43	74/NA	61	57	17	79	67	19	0.410095
Kosior-Jarecka et al. 2019	Poland		HTG	63/29	77.5/NA	46	36	6	79	67	19	0.410095
ERβ												
Kosior-Jarecka et al. 2019	Poland	rs1268656	NTG	100/43	74/NA	88	36	8	124	33	5	0.142854
Kosior-Jarecka et al. 2019	Poland		HTG	63/29	77.5NA	66	17	5	124	33	5	0.142854
Kosior-Jarecka et al. 2019	Poland	rs7159462	NTG	100/43	74/NA	102	25	5	142	22	1	0.883193
Kosior-Jarecka et al. 2019	Poland		HTG	63/29	77.5/NA	75	13	1	142	22	1	0.883193
Mabuchi et al. 2010 [31]	Japan	rs1256031	NTG	326/290	63.75/65.45	59	107	47	49	84	58	0.101595
Mabuchi et al. 2010	Japan		HTG	326/290	63.35/65.45	53	113	46	49	84	58	0.101595
Mabuchi et al. 2010	Japan	rs4986938	NTG	326/290	63.75/65.45	161	49	3	136	48	7	0.294793
Mabuchi et al. 2010	Japan		HTG	326/290	63.35/65.45	167	40	5	136	48	7	0.294793

NA not available, *NTG* normal-tension glaucoma, *HTG* high-tension glaucoma
[a]Gender based on type of glaucoma
[b]The mean age of case and control
[c]1 represents the common allele, while 2 represents the minor allele
[d]*P* for HWE equilibrium test in controls

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/GT	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	070–1.10	0	0.12
CC vs CT/TT	2	0.66	0.42–1.05	0	0.08
TT vs CC/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	0.48–1.03	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

*$P < 0.05$

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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