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Eye diseases in women

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Abstract

Although eye diseases are considered to be relatively less affected by patient sex, it is noteworthy
that the presence of hormone receptors have been confirmed in various ocular tissues, which were
considered to have few sex-based differences.

Female hormone levels are known to change because of menstruation, pregnancy, and meno-
pause. When female hormone levels markedly fluctuate in such situations, the disease state may
change.

The fluctuations in the levels of sex hormones affect the corneal thickness conditions of uveitis.

Estrogen may be a possible therapeutic option for glaucoma because it protects the eyes from dam-
age caused by glaucoma and reduces intraocular pressure; it is particularly promising in the treat-
ment of postmenopausal women with glaucoma.

Estrogen is considered to have a prophylactic effect against eye diseases. However, there is a re-
port that female sex is an independent risk factor for the progression of diabetic retinopathy, so it
may not always exert a prophylactic effect. Thus, caution should be exercised.

Based on recent progression of studies on this field, the importance of treatment according to gen-
der has been recognized in the treatment of eye diseases.

Key words: Eye disease, sex-based differences, female hormone

Introduction

Eye diseases are considered to be relatively less affected by patient sex as compared to other
diseases. Therefore, fewer articles have been published on sex-based differences in the field of oph-
thalmology than in other fields. The possible underlying reasons include the presence of few
morphological differences in eyes between men and women and few eye diseases that manifest with spe-
cific sex-based differences.

Although the eyes are smaller in proportion to the whole body, a substantial amount of information
is obtained from them. Inability to see markedly deteriorates the quality of life. In particular, glau-
coma is an important disease that can result in loss of vision. In recent years, this disease has been
found to be associated with female hormones.

In recent years, sex hormone receptors have been reported to exist in the eyes, along with chang-
es in the cornea due to high and low concentrations of sex hormones. Research is ongoing regarding
the sex-based differences in some eye diseases, such as uveitis and glaucoma. The results of these
studies may eventually help develop treatment methods based on female hormones.

Here, we present a literature review of the sex-based differences in eye diseases, particularly the
effects of female hormones on the eyes, and discuss the incorporation of sex-based differences in the
treatment of eye diseases.
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Presence of sex hormone receptors in the eyes

For a long period, the eyes were considered “sexually neutral” structures. Therefore, no sex-based differences were believed to exist in the physiology or pathology of the eyes1).

Wickham et al.2) investigated whether various tissues in the anterior and posterior segments of the eye contained messenger RNAs (mRNAs) for androgen, estrogen, and progesterone receptors in adult male and female rats, rabbits, and humans. In rats, androgen, estrogen, and progesterone receptor mRNAs were identified in the lacrimal gland, lid, cornea, lens, and/or retina/ueva. However, the frequency of appearance of these receptor mRNAs showed apparent gender- and tissue-specific differences.

In rabbits, progesterone receptor mRNA was detected in all ocular tissues and androgen receptor mRNA was present 100% of male and female lacrimal glands, meibomian glands, palpebral and bulbar conjunctiva and retina/choroid samples. Similarly, estrogen receptor mRNA was identified in all lacrimal and meibomian glands of male and female rabbits. The presence of hormone receptors is of great significance. Further, data on hormones can be collected and used to induce the expression of hormones in the eyes.

Estrogen receptors (ER) are classified as α and β. In the retina, the mRNAs for ERα differed according to age and sex3). ERα protein of about 65 kDa was found in the retina and retinal pigment epithelium in young women but not in those of men or postmenopausal women. Sex and age affected the expression of the receptors. Estrogen levels are low in postmenopausal woman and in men of all

<table>
<thead>
<tr>
<th>Tissue</th>
<th>AR mRNA</th>
<th>PR mRNA</th>
<th>ER mRNA</th>
<th>65 kDa ERα protein</th>
<th>Reference (article number)</th>
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<tr>
<td>rat lacrimal gland</td>
<td>M(+) : F(+) M(±) : F(+) M(±) : F(+)</td>
<td></td>
<td></td>
<td></td>
<td>Wickham, et al. (2)</td>
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<td>M(+) : F(+) M(+) : F(+) M(±) : F(+)</td>
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<td>cornea</td>
<td>M(+) : F(+) M(+) : F(+) M(+) : F(+)</td>
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<tr>
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<tr>
<td>Retina/ueva</td>
<td>M(+) : F(±) M(+) : F(+) M(±) : F(+)</td>
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<td>rabbit lacrimal gland</td>
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<td>meibomian gland</td>
<td>M(+) : F(+) M(+) : F(+) M(+) : F(+)</td>
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<td>palpebral conjunctive</td>
<td>M(+) : F(+) M(+) : F(+) M(+) : F(+)</td>
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<tr>
<td>bulbar conjunctive</td>
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<tr>
<td>Iris/ciliary body</td>
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<td>lens</td>
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<tr>
<td>Retina/choroid</td>
<td>M(+) : F(+) M(+) : F(+) M(+) : F(+)</td>
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<tr>
<td>human lacrimal gland</td>
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<td>meibomian gland</td>
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<td>bulbar conjunctive</td>
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<tr>
<td>retina</td>
<td>M(±) : F(±) M(±) : F(±) M(±) : F(±)</td>
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<td>Ogueta, et al. (3)</td>
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ages. Therefore, the mRNA levels required for ERα translation decrease in the target ocular tissues. Thus, estrogen may play a role in the etiology of some eye diseases.

It is noteworthy that the presence of hormone receptors has been confirmed in various ocular tissues, which were considered to have few sex-based differences. Further studies are warranted to identify diseases involving sex-based differences and develop therapeutic strategies based on these variations.

**Changes in the eyes based on the hormone levels**

Female hormone levels are known to change because of menstruation, pregnancy, and menopause.

Sex hormone receptors have been found to exist in the cornea. Therefore, many reports have indicated that the cornea changes with fluctuations in the levels of sex hormones. These changes may cause problems of adaptation associated with contact lenses. Therefore, caution should be exercised.

Corneal sensitivity refers to the corneal touch thresholds measured by the electromagnetic aesthesiometer of Dräger. Corneal sensitivity increases on the day of or few days before ovulation. This suggests that increased estrogen levels before ovulation are associated with corneal sensitivity.

According to Kiely et al., corneal thickness slightly decreases toward the end of the menses; corneal thickness increases at ovulation compared to pre-ovulation, and also increases in early luteal phase of the menstrual cycle.

According to Ghahfarokhi et al., the thickness of the cornea was the highest on the day of ovulation and lowest at the end of the cycle.

Corneal thickness changes during the menstrual cycle, but remains almost unchanged during the early stages of ovulation. However, the cornea thickens for few days after ovulation and then becomes thin with the onset of menstruation. These findings strongly suggest that sex hormones act as controlling factors of the corneal thickness.

However, the association between the menstrual cycle and corneal thickness differs among individuals. Ghahfarokhi et al. reported different patterns of relationship between the corneal thick-

<table>
<thead>
<tr>
<th>Physiologic state</th>
<th>Author, reported year (article number)</th>
<th>Participants</th>
<th>Results</th>
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</thead>
<tbody>
<tr>
<td>Menstruation</td>
<td>Riss B, et al. 1982 (4)</td>
<td>5 healthy women</td>
<td>CTT rose in 4 women with proved ovulation in the days before or on the day of ovulation.</td>
</tr>
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<td></td>
<td>Kiely PM, et al. 1983 (5) (The second study)</td>
<td>2 women</td>
<td>Slight decrease in corneal thickness was evident toward the end of menses, and increased at ovulation compared to pre-ovulation. Also, increased during early luteal phase.</td>
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<td></td>
<td>Ghahfarokhi NA, et al. 2015 (6)</td>
<td>50 healthy women</td>
<td>The thickest cornea during the menstrual cycle at ovulation, and the thinnest occurred at the end of the cycle.</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Millodot M, et al. 1977 (7)</td>
<td>30 non-pregnant women 29 pregnant women</td>
<td>Most pregnant women tended to have a higher CTT with advancing pregnancy.</td>
</tr>
<tr>
<td></td>
<td>Riss B, et al. 1981 (8)</td>
<td>86 pregnant women</td>
<td>The thresholds were significantly higher among pregnant women compared to the non-pregnant group.</td>
</tr>
<tr>
<td></td>
<td>Tolunay HE, et al. 2016 (9)</td>
<td>235 pregnant women</td>
<td>The mean intraocular pressures were significantly higher in the first trimester and puerperal period than in the third trimester.</td>
</tr>
<tr>
<td></td>
<td>Efe YK, et al. 2012 (10)</td>
<td>25 pregnant women</td>
<td>The mean intraocular pressure in the second and third trimesters of pregnancy were found to be lower than those in the first trimester and at 3 months postpartum. The mean central corneal thickness in the second and third trimester of the pregnancy was measured to be higher than in the first trimester and at 3 months postpartum.</td>
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Keratometry test results became higher. So they con- 
morphological changes, including increased thick-
by pregnancy, i.e., corneal perception decreases, and 
corneal sensitivity was lower in women at 13-40 
first trimester and at 3 months after childbirth10). 
The activity of uveitis was reported to decrease 
during the first trimester and again increase after 
childbirth. In females, serum hormone levels were 
found to be high during pregnancy but considerably 
reduced post childbirth. Most cytokines, except 
transforming growth factor (TGF)-β, were undetect- 
able10).

Anterior uveitis due to Behcet’s disease and an-
ylosing spondylitis preferentially occurs in adult 
men. Therefore, acute anterior uveitis may be af-
fected by the levels of sex hormones16). A study 
that used rat models of endotoxin-induced uveitis 
revealed that cellular infiltration was more pro-
nounced in male rats than in female ones. Further, 
it increased in ovariec tomized female rats. Treat-
ment with estradiol(E2) suppressed cellular infiltr-
ation in male and ovariec tomized female rats. Im-
munoreactions for ER were observed in the nuclei 
of vascular endothelia and some stromal cells in the 
iris. This study suggests that the down-regulation 
of inflammatory genes by estrogen contributes to 
the inhibition of acute anterior uveitis14).

In another study, patients with Behcet’s disease 
showed marked increases in the nitric oxide (NO) 
and interleukin (IL)-12 levels compared to healthy 
controls. The blood cortisol levels were lower in 
patients with Behcet’s disease than in healthy con-
trols. However, in vitro, the NO levels were re-
duced by estradiol and cortisol but were increased 
by testosterone in both sexes. However, the pro-
duction profile of IL-12 was the same as that of NO 
in women, whereas the IL-12 levels were not re-
duced by estradiol or cortisol in men. These find-
ings indicate the presence of clinical sex-based dif-
fences in uveitis caused by Behcet’s disease, and 
males patients appeared to have compromised IL-12 
down-regulation mediated by estradiol and cortisol 
that increases the T helper (Th) 1 immune reaction15).

Another study16) aimed to compare experimen-
tal autoimmune uveoretinitis (EAU) in rats treated 
with estrogen, 5-dihydrotestosterone (5-DHT), pro-
gesterone, or estrogen + progestosterone combi-
ation. Among female rats, those treated with 
5-DHT showed a marked relief of EAU. Those 
treated with estrogen showed slight worsening in 
EAU. Neither progesterone alone nor estrogen +
progesterone affected EAU. However, in case of male rats, those treated with 5-DHT showed slight relief, whereas those treated with estrogen showed moderate relief. Progesterone was found to be ineffective. However, EAU slightly decreased with the combination of estrogen and progesterone. These facts are associated with the levels of cytokine messengers in the eyes, such as Th1 (interferon-γ) and Th2 (IL-10). Sex hormones aggravate autoimmune diseases by changing the cytokine balance. Thus, it can be hypothesized that sex hormones cause autoimmune diseases by inducing changes in the balance of cytokines16).

Estradiol (E2) generally promotes the secretion of anti-inflammatory cytokines and suppresses inflammatory cytokines. Thus, it induces local anti-inflammation. Several studies on non-infectious uveitis report similar findings. However, the associated candidate mediators show a wide variation, including TGF-β, IL-12, and IFN-γ. However, not all the mediators have been identified. The reason for the large number of individual differences in the effect of menstrual cycle on the state of uveitis also remains unknown.

**Glaucoma**

According to the Japanese Ophthalmological Society, glaucoma is the leading cause of blindness in Japan, with a prevalence of 5.0% among those aged ≥40 years. Glaucoma is characterized by enhanced apoptosis of the retinal ganglion cells and cupping of the optic nerve head17). The Rotterdam study18) that included 3078 women categorized by age at menopause into three groups (<45, 45-49, and ≥50 years) revealed that open-angle glaucoma was diagnosed in 78 women with natural menopause and 15 women with artificial menopause. Among women with natural menopause, those who reached menopause before 45 years of age were at a higher risk of developing open-angle glaucoma.

The Rotterdam study18) that included 3078 women categorized by age at menopause into three groups (<45, 45-49, and ≥50 years) revealed that open-angle glaucoma was diagnosed in 78 women with natural menopause and 15 women with artificial menopause. Among women with natural menopause, those who reached menopause before 45 years of age were at a higher risk of developing open-angle glaucoma.

In women who underwent bilateral oophorectomy, the risk of developing all types of glaucoma was elevated. However, estrogen therapy failed to reduce the risk19).

Conversely, the prevalence of retinal nerve fiber layer defect was higher in women not receiving estrogen replacement therapy than in those receiving the therapy20).

The blood flow in the inferior temporal retinal arteriole was significantly higher in women receiving hormone replacement therapy. An animal experiment also revealed that retinal blood flow significantly increased following the administration of E2 in ovariectomized rats21). These findings reflect that estrogen alone or in combination with progesterone is effective in increasing the retinal blood flow and protecting the retinal nerve fiber layer in postmenopausal women21).

In a study on 152,163 women aged ≥50 years receiving treatment with estrogen and other hormones, the risk of developing primary open-angle glaucoma decreased by 0.4% for every one-month increase in the treatment duration. This study suggested that the use of postmenopausal hormone might reduce the risk of primary open-angle glaucoma20). In another case, when hormone replacement therapy was administered to a woman with primary open-angle glaucoma who had been treated with eye drops containing no female hormones, her intraocular pressure decreased from 16-20 mmHg before the therapy to 12-15 mmHg at 4 weeks and 13-15 mmHg at 12 weeks after therapy initiation22). Estrogen activates the synthesis of collagen fibers and improves the compliance of ocular tissues17). Increased estrogen levels increase the amount of collagen fibers and the elasticity of the eyes. Thus, intraocular pressure may decrease. In particular, increased collagen fiber at the lamina cribrosa improves its compliance, and improved compliance leads to relief in the compression on the optic ganglia17). Estrogen may be a possible therapeutic option for glaucoma because it protects the eyes from damage caused by glaucoma and reduces the intraocular pressure. It is particularly promising in the treatment of postmenopausal women with glaucoma.

**Blood flow and diabetic retinopathy**

According to Marric-Bilkan24), micro-vascular complications of diabetes mellitus are more common in men than in women. However, subsequent macro-vascular complications are more frequent in women. Women without diabetes mellitus are at a lower risk of micro- and macro-vascular diseases throughout their lives as compared to men. However, the presence of diabetes mellitus introduces a great risk of vascular complications in women. Estrogen exerts a protective effect on the heart, whereas androgen adversely affects the blood vessels of the heart. Recent findings from studies based on these hypotheses indicate the diversity and complexity of the target organs for sex hormones, particularly in patients with diabetes mellitus.

Based on a retrospective study in patients with
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Type 2 diabetes mellitus treated at Japanese clinics, women with diabetic retinopathy are more likely to have the proliferative form of diabetes mellitus, and female sex is an independent risk factor for the progression of diabetic retinopathy.

One of the causes of new onset and aggravation of existing retinopathy during pregnancy is the change in the blood hormone levels during pregnancy.

Estrogen is considered to have a prophylactic effect against eye diseases. However, it does not always exert a prophylactic effect; adverse events, such as thrombosis, may also occur. Thus, caution should be exercised.

Macular hole

Macular hole is commonly observed in women. According to McCannel et al., idiopathic macular holes occur at an age and sex adjusted incidence 7.8 persons and 8.69 eyes per 100,000 population per year in an area of Minnesota, USA. Estrogen has a prophylactic effect against the progression of macular hole. However, this prophylactic effect is lost after menopause because of the sudden decrease in estrogen production. Consequently, women appear to be at a higher risk of developing retinopathies than men.

Inokuchi et al. suggested an association between E2 levels and the pathogenesis of idiopathic macular hole (IMH) because E2 levels in the vitreous body were significantly higher in patients with IMH than in the controls.

Conclusion

Sex-based differences in the field of ophthalmology, specifically in cases of uveitis, glaucoma, and diabetic retinopathy, were examined.

Female hormones exert an anti-inflammatory effect on each disease. Clinical pictures differ according to the concentration of female hormones. The hormones often exert a protective effect against the diseases. However, they can also cause thrombosis and other adverse reactions. The hormones do not always exert positive effects. In particular, when female hormone levels markedly fluctuate because of menopause, pregnancy, and delivery, the disease state may change. Thus, caution should be exercised.

Several studies that contribute to the development of therapeutic strategies have recently been performed. The importance of treatment based on detailed examinations has also been recognized in the treatment of eye diseases.

References