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Fukushima J. Med. Sci.,
Vol. 65, No. 2, 2019

[Review]

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(Received January 7, 2019, accepted April 18, 2019)

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 menopause. 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 damage caused by glaucoma and reduces intraocular pressure ; it is particularly promising in the treatment of postmenopausal women with glaucoma.

Estrogen is considered to have a prophylactic effect against eye diseases. However, there is a report 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 gender 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 ophthalmology 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 specific 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, glaucoma 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 changes 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 eyes[1].

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/uvea. 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 human eye's estrogen receptor, progesterone receptor and β-actin mRNAs were detected in almost all samples. Androgen receptor was identified in 100% of the male and female lacrimal glands and 100% of the male meibomian gland, bulbar conjunctiva, cornea and retinal pigment epithelial cell samples. However, androgen receptor mRNAs could not be detected in the female bulbar conjunctiva and cornea tissue pools, or in either of the two female meibomian glands. This study revealed that mRNAs for sex steroid receptors exist in various ocular tissues and these tissues might be the target organs for estrogen and/or progesterone.

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 sex[3]. 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 1. The mRNA or protein expression of receptors in the eye tissues

		AR mRNA	PR mRNA	ER mRNA	65 kDa ERα protein	Reference (article number)
rat	lacrimal grand	M(+) : F(+)	M(±) : F(+)	M(+) : F(+)		
	lid	M(+) : F(+)	M(+) : F(+)	M(±) : F(+)		
	cornea	M(+) : F(+)	M(+) : F(+)	M(+) : F(+)		
	lens	M(+) : F(+)	M(−) : F(−)	M(±) : F(±)		
	Retina/Uvea	M(+) : F(±)	M(+) : F(±)	M(+) : F(±)		
rabbit	lacrimal grand	M(+) : F(+)	M(+) : F(+)	M(+) : F(+)		
	meibomian gland	M(+) : F(+)	M(+) : F(+)	M(+) : F(+)		
	palpebral conjunctive	M(+) : F(+)	M(+) : F(+)	M(±) : F(±)		
	bulbar conjunctive	M(+) : F(±)	M(+) : F(+)	M(±) : F(+)		Wickham, *et al.* (2)
	cornea	M(±) : F(±)	M(+) : F(+)	M(−) : F(±)		
	Iris/ciliary body	M(+) : F(±)	M(+) : F(+)	M(+) : F(±)		
	lens	M(±) : F(±)	M(+) : F(+)	M(−) : F(±)		
	Retina/choroid	M(+) : F(±)	M(+) : F(+)	M(±) : F(±)		
human	lacrimal grand	M(+) : F(+)	M(+) : F(+)	M(+) : F(+)		
	meibomian gland	M(+) : F(±)	M(±) : F(+)	M(+) : F(+)		
	bulbar conjunctive	M(+) : F(−)	M(+) : F(+)	M(+) : F(+)		
	cornea	M(+) : F(−)	M(+) : F(+)	M(+) : F(+)		
	retina				M(−) : YF(+) : PF(−)	Ogueta, *et al.* (3)
	RPE/choroid					

AR : androgen receptor, PR : progesterone Receptor, ER : estrogen receptor, RPE : retinal pigment epithelium,
M : male, YF : young female, PF : postmenopausal female
(+) : detected, (±) : slightly detected, (−) : not detected

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[4].

Corneal sensitivity increases on the day of or few days before ovulation[4]. This suggests that increased estrogen levels before ovulation are associated with corneal sensitivity.

According to Kiely *et al.*[5], corneal thickness slightly decreases toward the end of the menses ; corneal thickness increases at ovulation compared with pre-ovulation, and also increases in early luteal phase of the menstrual cycle.

According to Ghahfarokhi *et al.*[6], 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.*[6] reported different patterns of relationship between the corneal thick-

Table 2. Review results. The changes of corneal sensibility, thickness, and intraocular pressure during the menstrual cycle and pregnancy

Physiologic state	Author, reported year (article number)	Participants	Results
Menstruation	Riss B, *et al.* 1982 (4)	5 healthy women	CTT rose in 4 women with proved ovulation in the days before or on the day of ovulation.
	Kiely PM, *et al.* 1983 (5)	(The second study) 2 women	Slight deacrease in corneal thickness was evident toward the end of menses, and increased at ovulation compared with pre-ovulation. Also, increased during early luteal phase.
	Ghahfarokhi NA, *et al.* 2015 (6)	50 healthy women	The thickest cornea during the menstrual cycle at ovulation, and the thinnest occurred at the end of the cycle.
Pregnancy	Millodot M, *et al.* 1977 (7)	30 non-pregnant women 29 pregnant women	Most pregnant women tended to have a higher CTT with advancing pregnancy.
	Riss B, *et al.* 1981 (8)	86 pregnant women	The thresholds were significantly higher among pregnant women compared to the non-pregnant group.
	Tolunay HE, *et al.* 2016 (9)	235 pregnant women	The mean intraocular pressures were significantly higher in the first trimester and puerperal period than in the third trimester.
	Efe YK, *et al.* 2012 (10)	25 pregnant women	The mean intraocular presssue 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 post partum.

ness and the menstrual cycle.

Corneal sensitivity starts to decrease at 31 weeks of gestation[7]. Riss *et al.*[8] reported that the corneal sensitivity was lower in women at 13–40 weeks of gestation than in non-pregnant women.

According to Tolunay *et al.*[9], intraocular pressure decreases during pregnancy. The mean intraocular pressures were significantly higher in first trimester and puerperal period than in the third trimester. Efe *et al.*[10] also reported this. Further, they reported that the central corneal thickness was greater during these trimesters than that during the first trimester and at 3 months after childbirth[10].

Corneal morphology and function are influenced by pregnancy, i.e., corneal perception decreases, and morphological changes, including increased thickness, are observed.

The changes in the cornea due to the menstrual cycle and pregnancy strongly suggest that sex hormones physiologically modulate the cornea via female hormone receptors that are localized in the cornea. However, detailed underlying mechanisms, including the biological mechanism of this modulation, remain unknown.

According to Coksure *et al.*[11], the ocular surface disease index and intraocular pressure of postmenopausal women became low after receiving oral daily treatment with drospirenone 2 mg plus estradiol 1 mg ; moreover, the tear film break-up time and Schirmer test results became higher. So they concluded that oral daily treatment with this combination reduced the risks of ocular diseases.

According to Verit *et al.*[12], although tibolone had no effects on visual acuity, intraocular pressure, tear functions, or visual evoked potentials, it might cause some early adverse effects on the electrophysiologic and structural characteristics of the retina among postmenopausal women.

Despite limited knowledge of the underlying mechanisms, the fact that the cornea changes due to fluctuations in the levels of sex hormones should be considered in daily clinical practice. These changes may affect the prescriptions of contact lenses, refractive surgery for astigmatism, etc. Thus, corneal refractive surgery is contraindicated for pregnant women. This concept has been accepted in Japan.

Uveitis

Eye diseases that may be associated with sex hormones include uveitis. Several reports have indicated that the fluctuations in the levels of sex hormones due to menstruation and pregnancy affect the state of uveitis.

Some patients with non-infectious uveitis observe symptomatic exacerbation immediately before menstruation. Further, their symptoms tend to stabilize during pregnancy and temporarily worsen after childbirth.

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 undetectable[13].

Anterior uveitis due to Behcet's disease and ankylosing spondylitis preferentially occurs in adult men. Therefore, acute anterior uveitis may be affected by the levels of sex hormones[14]. A study that used rat models of endotoxin-induced uveitis revealed that cellular infiltration was more pronounced in male rats than in female ones. Further, it increased in ovariectomized female rats. Treatment with estradiol(E_2) suppressed cellular infiltration in male and ovariectomized female rats. Immunoreactions 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 uveitis[14].

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 controls. However, *in vitro*, the NO levels were reduced by estradiol and cortisol but were increased by testosterone in both sexes. However, the production profile of IL-12 was the same as that of NO in women, whereas the IL-12 levels were not reduced by estradiol or cortisol in men. These findings indicate the presence of clinical sex-based differences in uveitis caused by Behcet's disease, and male patients appeared to have compromised IL-12 down-regulation mediated by estradiol and cortisol that increases the T helper (Th) 1 immune reaction[15].

Another study[16] aimed to compare experimental autoimmune uveoretinitis (EAU) in rats treated with estrogen, 5-dihydrotestosterone (5-DHT), progesterone, or estrogen + progesterone combination. 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 [IFN]-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 cytokines[16].

Estradiol (E_2) 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 head[17].

The Rotterdam study[18] 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 risk[19].

Conversely, the prevalence of retinal nerve fiber layer defect was higher in women not receiving estrogen replacement therapy than in those receiving the therapy[20].

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 E_2 in ovariectomized rats[21]. 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 women[21].

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 glaucoma[22]. 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 initiation[23]. Estrogen activates the synthesis of collagen fibers and improves the compliance of ocular tissues[17]. 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 ganglia[17]. 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-Bilkan[24], 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

type 2 diabetes mellitus treated at Japanese clinics[25], 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.*[26], 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[1].

Inokuchi *et al.*[27] suggested an association between E_2 levels and the pathogenesis of idiopathic macular hole (IMH) because E_2 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.

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