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Review Article

Sex hormones and dry eye disease: Current update

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ABSTRACT

Dry eye disease (DED) is a multifactorial disorder of the ocular surface that results in ocular discomfort, visual disturbance and damage to the ocular surface. It is one of the most common complaints in daily ophthalmic practice. The greater prevalence of dry eye in women compared to men suggests that sex hormones may have a role in this condition. Sex hormones; estrogen and androgens influence production of all components of the tear film including aqueous layer, lipid layer, and mucin layer. Various mechanisms such as decrease in hormonal levels, shift in feedback mechanisms, and changes in receptor receptivity interplay to alter the ocular surface homeostasis and subsequently result in DED. The purpose of this review is to briefly outline current scientific evidence on the influence of androgen and estrogen on the lacrimal and meibomian glands as well as on the ocular surface epithelia including conjunctival goblet cells during reproductive and menopausal periods. This article also outlines the updates regarding role of gonadal hormones in the treatment of dry eye.

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1. Introduction

According to international Dry Eye Workshop (DEWS) report in 2007, Dry eye disease (DED) is defined as a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface.¹ It is one of the most common complaints in ophthalmic practice. Common symptoms of DED include foreign body sensation, grittiness, itching, burning, stinging, tearing, photophobia, fluctuating or blurry vision, leading to ocular

discomfort and reduced visual acuity which significantly affects the quality of life of patients.^{2–5} Peri and post-menopausal women, elderly, contact lens wearers, those exposed to environmental and occupational factors, patients after refractive surgery, suffering from autoimmune diseases or under some topical or systemic therapies are more prone to dry eye disease.⁶ The prevalence of DED ranges from 7.8% to 33.7%, depending on population being studied and assessment methods used.⁷ A study in United States showed that the prevalence of DED in women over 50 years is 7% and in men over 50 years is 4%, nearly half of that in women.^{8,9} Other studies also showed that women has greater frequency and severity of DED than men, that's why women's well-being is much more affected by DED.¹⁰ The frequency of DED increases with increasing age in both men

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and women and postmenopausal women are at higher risk of developing DED than younger women and men.¹¹

2. Pathophysiology of Dry eye Disease

A precorneal tear film is important for maintaining a smooth refractive corneal surface for optimal vision.^{12,13} Dry eye occurs when the tear film is disturbed as a result of decreased tear production or increased tear evaporation.¹⁴ A normal tear film has three layers: inner hydrophilic mucin layer is mainly produced by conjunctival goblet cells and also by glycocalyx of the superficial layers of conjunctival and corneal epithelial cells, middle aqueous layer is produced by main and accessory lacrimal glands and outer lipid layer is secreted by meibomian glands (modified sebaceous glands). An integrated neural reflex loop (sensorimotor) balances aqueous production and tear evaporation thus maintaining normal tear film.¹⁵ Ocular surface system (OSS) or lacrimal functional unit comprises of corneal epithelium, conjunctival epithelium with goblet cells, limbal stem cells that maintains epithelial turnover, tear film that keeps ocular surface moist and lubricated, main and accessory lacrimal glands, meibomian glands, eyelids while blinking help in distribution of tear film over the cornea, nasolacrimal duct and sensorimotor nerves connecting all these structures. All the components of OSS work synergistically to maintain ocular surface homeostasis and function of OSS is regulated by nervous, endocrine, vascular and immune systems¹⁶ thus disturbance to any part of OSS compromises the normal neural feedback leading to impaired tear film and loss of ocular surface homeostasis.^{17,18} Hyperosmolarity of the tear film, either due to impaired production or increased evaporation of tears, activates inflammatory cascades in the ocular surface tissues which impairs the neural feedback mechanism to the lacrimal gland thus hampering tear production and clearance.^{19,20} Some evidence suggests that dry eye is an immune-based inflammatory disease affecting the ocular surface and lacrimal glands.^{21–23} Clinically, dry eye is confirmed by increased corneal and conjunctival staining, low tear film break up time (TBUT), low Schirmer's test score and tear hyperosmolarity.²⁴

2.1. DEWS classifies dry eye into two major categories

1. Evaporative tear deficiency - It is the major primary dry eye disease phenotype. Lipid layer, secreted by meibomian glands, prevents tear evaporation, decreases surface tension and delay TBUT, therefore it is important for stabilization of the tear film. Lipid layer abnormalities leads to more evaporation and increased osmolarity of the tear film. Hyperosmolarity of tear film initiates inflammatory cascades in the ocular surface tissues, nociceptors detect inflammation and send signals to lacrimal glands via autonomic

motor signals. The collection of symptoms along with hyperosmolarity of tears, signs of ocular inflammation in a setting of normal or higher than normal rate of aqueous fluid production is defined as evaporative dry eye. It is more commonly seen in women of 45 years or older.^{25–32}

2. Aqueous tear deficiency -It is characterized by decreased volume of tear production by the lacrimal glands. Reduced tear flow leads to hyperosmolarity of tears which initiates inflammatory cascades in the ocular surface tissues. Reduced lacrimal gland secretion can be primary due to any lacrimal gland disease pathology or secondary due to any ocular surface inflammation, which impairs sensory and autonomic secretomotor signals to the lacrimal gland leading to reduced secretion. Lacrimal gland atrophy, seen with CT scan, is age related in both men and women.^{29,33,34}

Mucin layer helps in maintaining moisture in the eye, aqueous layer maintains tear volume as it contains water, electrolytes and protein and lipid layer aids in stabilization of the tear film as it prevents tear evaporation.

Dry eye affects women two to four times more than men and post-menopausal women are more prone to it.⁹ Women with some systemic conditions like Sjogren's syndrome, complete androgen insensitivity syndrome, premature ovarian failure, polycystic ovary syndrome (PCOS) and post-menopausal women using HRT have high prevalence of dry eye disease.^{35–42} Use of androgen antagonists for some prostate conditions in men is a sex specific risk factor for dry eye.^{43–45} This shows that hormonal imbalance play an important role in the pathophysiology of dry eye disease, and gender and sex hormones may play a pivotal role in the etiology of dry eye.

3. Effects of gonadal hormones on Dry Eye -

3.1. Gonadal hormones and the Meibomian gland

Meibomian gland secretes lipid layer of the tear film, decreases surface tension and promotes stabilization of tear film by preventing evaporation of the underlying layer. Meibomian gland dysfunction leads to evaporative dry eye.⁴⁶ Sex hormones are known to regulate meibomian gland function.^{45,47–49} Androgens have positive impact on meibomian gland function and increases lipid secretion^{48,50} while estrogen and progesterone have a negative impact on meibomian gland function and thus decrease lipid secretion.^{51,52}

3.1.1. Effects of androgen on the meibomian gland

Meibomian gland is the target organ for androgen and is susceptible to effects of androgen.^{53,54} It also expresses mRNA for 5 α -reductase enzyme which converts testosterone to its more potent form dihydrotestosterone

(DHT).⁵⁵ Androgen stimulates expression of genes involved in lipid metabolic pathways and thus increases secretion of lipids from the meibomian gland, which forms the lipid layer of the tear film.^{48,54} Androgen also suppresses genes associated with keratinization of ductal epithelium, which is thought to be the probable cause of meibomian gland dysfunction, thus it enhances meibomian gland function.^{52,56} Its role in regulating the immune system in some studies shows that it imposes trophic effects on the lacrimal and meibomian gland function.⁵⁷ Thus androgen deficiency may lead to meibomian gland dysfunction, decreased quality and quantity of meibomian gland lipid layer leading to tear film instability, low tear film break-up time (TBUT) and subsequently evaporative dry eye. These changes are associated with gender and age, and are frequently seen in patients who are not responsive to androgen like women with complete androgen insensitivity syndrome and men with prostate cancer using androgen blockers. This shows the significance of androgen in the regulation of meibomian gland function.^{38,39,43,45,58–60}

Genetically lower levels of androgen in women than men and age related decrease in gonadal androgen synthesis in both the sexes may lead to greater risk of dry eye in these populations.^{59–63} In menopausal women, only 30% of the peak androgen level is found.^{61,64} The differences in meibomian gland lipid secretions between men and women may be due to differences in androgen levels between men and women.⁵⁹ With age, both sexes show structural and functional changes in the meibomian gland. Acinar cells atrophy and hyper keratinization of ductal epithelium causes more viscosity of the meibomian gland secretions leading to reduced gland function, increased tear film instability and dry eye.^{58,59,65–69}

A study in orchidectomized rabbits showed meibomian gland dysfunction due to androgen deficiency which got reversed on administering 19-nortestosterone.⁴⁸ Some studies showed that topical testosterone applied to the eyelids improve lipid layer thickness and TBUT and is used in men and women with meibomian gland dysfunction and evaporative dry eye.^{70,71} The use of androgen precursor DHEA (Dehydroepiandrosterone) in dry eye patients stimulate the production and release of lipids from the meibomian glands and thus improves signs and symptoms of DED.^{70,72} Surprisingly in Sjogren's syndrome, DHEA couldn't improve tear production and ocular surface pathology^{73,74} as according to many authors, intracrine conversion of DHEA to testosterone and DHT is suppressed in Sjogren's syndrome.⁷⁵

3.1.2. Effects of estrogen and progesterone on the meibomian gland

Estrogen and progesterone receptors are also present in meibomian gland and these hormones regulate the expression of several genes. The action of estrogen

on meibomian gland is opposite to that of androgen. Estrogen inhibits lipid synthesis in meibomian gland and promotes meibomian gland dysfunction and thus causes evaporative dry eye.⁵² This explains the increased prevalence of dry eye in postmenopausal women using hormone replacement therapy. As studies on mice show that estrogen effects on sebaceous glands doesn't occur directly through the interaction with their receptors but indirectly by antagonizing the effect of androgen on sebaceous glands, by blocking their uptake or conversion to more potent form DHT.^{76,77} Thus high prevalence of dry eye among women may not be due to increased action of estrogen but due to decreased action of the androgen in women. This also explains high prevalence of DED among post-menopausal women despite the cessation of estradiol synthesis in ovary. Testosterone upregulate the expression of genes involved in meibomian gland lipid synthesis while estrogen downregulate these genes and upregulate those genes which have the opposite effect.^{51,52} Progesterone downregulates the expression of genes involved in immune processes but its effect is much less than that of estrogen.⁵¹ A study in mice shows that the sex-related differences in gene expression in the meibomian glands are mainly due to androgen and partly due to estrogen and progesterone.^{78,79} Aromatase inhibition in mice leading to estrogen deficiency has no effect on histology of meibomian glands.⁷⁹ Thus, the sex-related differences in biological processes, molecular functions and cellular components in the meibomian gland could be due to the effects of androgen rather than estrogen and progesterone.^{78,80,81} More research is required to determine the definitive role of estrogen and progesterone on human meibomian gland and in evaporative dry eye.

3.2. Gonadal hormones and the lacrimal gland

Lacrimal gland's basic function is to synthesize and secrete water, proteins and electrolytes, which forms the aqueous layer of the tear film.^{82,83} Main and accessory lacrimal glands express genes for androgen and estrogen receptors and through regulation of the transcription of these genes, gonadal hormones control their structure and function.^{83–86} Androgens have a positive impact on lacrimal gland tissue and controls their morphology, cellular biology, biochemistry and secretory immune system, as shown in various animal studies, and is responsible for sex-related differences in the lacrimal gland.^{87,88} On the other hand, the role of estrogen and progesterone on lacrimal gland tissue is not very conclusive.^{89,90}

3.2.1. Effects of androgen on the Lacrimal gland

The lacrimal gland is also a target organ for androgens⁸⁴ and its structural, functional and pathological characteristics are regulated by androgens^{85,87,91,92} and these sex-related differences in androgen influence on lacrimal glands leads to sexual dimorphism in lacrimal gland characteristics, as

seen in many animal studies.^{91–95}

Lacrimal gland of male rabbit is larger in size than females.⁹⁶ Castration of male rats leads to decrease in size of lacrimal glands to that of female rats due to decrease in endogenous androgen. On treating castrated rats and female rats with DHT, there is a change in the characteristics of lacrimal gland to that of intact males.^{87,92} Androgen influences lacrimal gland function by increasing total DNA and protein in the gland and stimulating fluid secretion from the lacrimal gland.⁸⁸ Intact male rats synthesize and secrete more immunoglobulin A and glycoprotein from the acinar cells than female or castrated male rats. DHT treatment in castrated rats also stimulates the secretory immune system of the lacrimal gland.^{92,93,96,97}

Primary lacrimal gland deficiency exists in women who have decreased androgen levels such as menopausal women or ovariectomized women or women using oral contraceptives, in spite of their variable estrogen levels.^{98–100} In contrast, men on anti-androgen therapy don't show changes in their lacrimal gland secretion.¹⁰¹ This suggests that androgen may have sex-specific action. In autoimmune disease like Sjogren's syndrome, which is characterized by inflammatory changes in the lacrimal gland leading to aqueous deficient dry eye, reduced levels of androgen have been found.^{37,102}

The sex-related differences in the effect of androgen on the lacrimal gland is partly due to variations in gene expression.^{85,103–107} In orchietomized male and ovariectomized female rats, the number of binding sites and density of androgen receptor proteins are similar in the lacrimal gland⁹¹ but in intact male rats, binding sites and androgen receptor proteins exists in far more numbers than in intact female rats.^{84,102} Androgen use in castrated rats restore the number of androgen receptors and binding sites to that in intact male rats, suggesting that androgens may autoregulate their own binding sites.^{102,108} Use of androgen antagonists or mutations in receptor proteins lead to decreased androgen action and inhibition of transcription and translation of genes.^{92,109,110} These findings suggest that through alterations in gene activity, androgen action on the lacrimal gland can be regulated.⁸⁵

3.2.2. *Effect of estrogen and progesterone on the lacrimal gland*

Effect of estrogen and progesterone on the lacrimal gland has contradictory results. Some human and animal studies suggests that they have proinflammatory role and stimulates autoimmune disease in the lacrimal gland,^{111,112} whereas other studies suggest anti-inflammatory role of these hormones on the lacrimal gland^{88–90} and some studies didn't find any effect of estrogen on the morphology and function of lacrimal gland.^{93,95,97,106,113–117}

Recent studies show that in ovariectomized rats, there is decreased production and secretion, less TBUT

and increased staining of ocular surface^{117,118} and administration of estrogen worsen the findings.¹¹⁹ Estrogen and progesterone increases inflammation and autoimmune diseases in the lacrimal gland. One study in ovariectomized rabbits found that on estrogen treatment, there is an increase in the level of matrix metalloproteinases (MMPs) 2 and 9, a proteolytic enzyme involved in the regulation of inflammatory processes.¹²⁰

Some studies suggested that dry eye in postmenopausal women may be due to decreased levels of estrogen and progesterone which causes increased production of proinflammatory cytokines, fibrosis and atrophy of the lacrimal gland.^{121,122} Studies in rabbit and mouse models with Sjogren's syndrome shows that absence of estrogen causes inflammation and regressive changes in the lacrimal gland and estrogen administration causes reversal of these changes, inhibits lymphocyte infiltration and increases fluid production from the lacrimal gland.^{90,112,123} Estrogen and progesterone influences expression of many immune-related genes and also upregulates the genes that inhibits signaling of pro-inflammatory cytokines.^{86,124} This shows that estrogen may have anti-inflammatory role in the lacrimal gland. Aromatase knockout in C57BL/6J mice suggests that estrogen has neither proinflammatory nor anti-inflammatory role.¹²⁵

In lacrimal gland, estrogen and progesterone antagonize the expression of genes that are stimulated in response to androgen.⁵² In comparison to androgen, estrogen and progesterone have very little role in the sex-related differences in gene expression and sexual dimorphism of the lacrimal gland, so the aqueous deficient dry eye in women may not be due to them.^{85,86,96,103,114} More studies are required in humans to identify the role of estrogen and progesterone on the structure and function of the lacrimal gland and aqueous deficient dry eye.

3.3. *Gonadal hormones and the ocular surface*

Tissues of ocular surface, including cornea, conjunctiva and tear film are likely to be directly affected by gonadal hormones. Mucin layer is secreted mainly by conjunctival goblet cells and its main function is to stabilize the tear film and lubricate and protect the underlying ocular surface.^{126–128} Any disturbance in mucin distribution over the ocular surface, due to change in goblet cell density, can lead to tear film instability and dry eye.^{129–135}

Androgens have an effect on the conjunctival goblet cells and thus regulate mucin production.^{135,136} In women during menstruation, the cornea and conjunctiva are affected by physiological changes in the estrogen and progesterone concentrations.^{137–139} Estrogen has negative impact on cornea as high estrogen levels leads to decreased corneal sensitivity and thus leads to dry eye and inflammation of ocular surface. On the other hand, estrogen has positive impact on the conjunctival epithelium as it enhances

maturation of epithelial cells.¹⁴⁰

3.3.1. Effects of androgen on the ocular surface

MUC5A is the secretory mucin which is produced by conjunctival goblet cells and MUCs 1,4 and 16 are membrane-associated mucins which are secreted by corneal and conjunctival epithelium and form the inner hydrophilic glycocalyx part of the mucous layer of tear film.^{141–144} Women with complete androgen insensitivity syndrome have reduced levels of MUC5AC and MUC1 protein expression in the mucous layer of tear film, as a result of goblet cell dysfunction rather than decrease in goblet cell number.^{136,145}

Women with polycystic ovary syndrome (PCOS), despite having hyperandrogenism experience dry eye disease (DED).^{42,135} Hyperandrogenism in PCOS leads to goblet cell hyperplasia which leads to mucous hypersecretion but abnormal mucous filaments. These patients have increased MUC5A mRNA expression but reduced levels of MUC5A mucins in the conjunctival tissue and also have increased levels of MUC5AC in their tears, these findings can be attributed to abnormal mucous filaments on the ocular surface of PCOS patients.¹³⁵ Dry eye in PCOS has shorter TBUT and antiandrogen treatment has been demonstrated to increase TBUT and improves symptoms of dry eye but the side effects of prolonged systemic antiandrogen therapy should also be considered.

3.3.2. Effects of estrogen and progesterone on the ocular surface

Ocular surface tissues are susceptible to estrogen and progesterone levels. Hormonal changes during menstrual cycle, pregnancy, menopause, HRT and OCPs use in females have been linked to structural and functional changes in corneal and conjunctival epithelium, like decrease in corneal sensitivity and change in conjunctival maturation index and can also cause dry eye, affects visual function and leads to development of ocular symptoms.^{139,146–153} These effects in cornea and conjunctiva are due to estrogen and/or progesterone, as testosterone levels remain relatively constant during the menstrual cycle.^{137–139,152}

Cornea express receptor for both estrogen and progesterone and these hormones probably reaches cornea from the tear film and aqueous humor. High estrogen levels cause reduced corneal sensitivity and this leads to impaired neural feedback to lacrimal gland for tear production and thus leads to dry eye.^{149,152} So, gonadal hormones have an indirect effect on the regulation of structure and function of cornea but their direct effect on cornea in dry eye is not known.

Conjunctival epithelium is sensitive to estrogen as the change in maturation index of its cells correlates with the changes in hormone levels during the menstrual

cycle.¹³⁸ The relative levels of estrogen and progesterone in menstrual, follicular and luteal phase of the menstrual cycle correlate with relative proportions of immature parabasal, mature superficial and intermediate cells respectively.^{137,140,150,154} Post-menopause, these maturation changes in conjunctival epithelial cells are absent.^{140,154} and post-menopausal women have decreased number of goblet cells and are more susceptible to squamous metaplasia and inflammation.¹²⁹ On giving HRT in post-menopausal women, maturation of conjunctival cells occur and density of goblet cells increases, suggesting that estrogen have an influential effect on the maturation of conjunctival epithelial cells.^{155,156}

Some studies found that the other signs and symptoms of dry eye like tear turnover, volume, osmolarity and stability doesn't change despite changes in estrogen and progesterone levels.^{100,157} Studies in human corneal epithelial cells also shows that treatment with estrogen upregulates both proinflammatory cytokines and MMPs in the cells, thus an inflammatory component is also present in response to estrogen, which could exacerbate DED.¹⁵⁸

A study in ovariectomized mice shows that estrogen and progesterone exposure in ocular surface tissue didn't affect the distribution and expression of mucin¹⁴². In contrast, a study in rabbits shows that estrogen exposure increases mucin secretion from the conjunctival goblet cells but increased progesterone has no effect on mucin secretion.¹⁵⁹ This shows the complexity in hormonal regulation of mucin.

4. Hormonal treatment in Dry eye

Ophthalmic examination in dry eye shows decreased tear production with increased tear film break up time (TBUT), increased tear osmolarity, increased corneal and conjunctival staining, low Schirmer's test score in aqueous deficient dry eye and decreased levels of lactoferrin and lysozyme in tears.

First line of treatment in dry eye includes lubricating eye drops, second line includes anti-inflammatory drugs like steroid eye drops and immunomodulatory drugs like cyclosporine. In severe cases, punctual occlusion, eyelid corrective surgery, scleral contact lenses and autologous serum tears can be used, depending on the underlying cause.¹⁶⁰

Many studies suggest that there might be an important role of hormonal therapy in dry eye treatment, specifically in menopausal women.

4.1. Role of HRT in dry eye

Role of HRT in dry eye treatment is inconclusive as some studies show exacerbation of symptoms whereas other studies show improvement of symptoms with HRT and some studies also show no effect of HRT on dry eye. A large population based study on post-

menopausal women suggests that women receiving combined estrogen/progesterone HRT or only estrogen containing HRT developed more dry eye signs and symptoms as compared to women not receiving HRT with an odds ratio of 1.29 (prevalence of dry eye in estrogen alone HRT - 69% and estrogen plus progesterone HRT-29%).^{161,162} This also shows that adding progesterone to HRT may have a protective effect in reducing dry eye symptoms.¹⁶²

In some studies, it has been found that higher doses of HRT (estrogen alone or estrogen plus progesterone) results in higher incidence of dry eyes as compared to lower doses of HRT.¹⁶³

In contrast, some studies have shown beneficial effects of HRT on dry eye signs and symptoms in post-menopausal women. HRT, in the form of oral and transdermal estrogen and estrogen plus progesterone therapy, reduces dry eye symptoms and have a positive impact on tear production, tear osmolarity and tear film stability.^{147,155,164–172} Another study showed that topical application of estrogen eye drop and ointment has a beneficial role on tear function, thus improving dry eye symptoms. This shows that local estrogen therapy may be superior to systemic HT in improving dry eye symptoms as systemic HT can't penetrate the blood-eye barrier, thus hindering its effect on the conjunctivae.^{172,173} Duration of HRT also affects the outcome, as one study showed that women taking HRT for > 5 years had less ocular symptoms and increased tear production as compared to women taking HRT for <5 years.¹⁶⁷ A significant relationship between HRT and dry eye is yet to be established and larger prospective-controlled studies with long follow-up time are required in this field to reach a definite conclusion.

4.2. Role of Androgen treatment in dry eye

Androgens have a crucial role in tear production and have a positive impact on function of meibomian and lacrimal gland.¹⁷⁴ Testosterone reduces symptom of dry eye in postmenopausal women^{175,176} and in Klinefelter's syndrome patients¹⁷⁷ Patients with complete androgen insensitivity syndrome, men using androgen blockers and women having significantly low testosterone levels have higher chances of dry eye, this shows that androgen deficiency can lead to tear film instability and dysfunction.⁵⁰ These patients can be benefited by systemic androgen therapy but the undesirable side effects of systemic androgen therapy should also be considered when using in peri- and post-menopausal women. A study in postmenopausal women using Estratest therapy, a combination of methyltestosterone and estrogen, showed improvement in dry eye symptoms.¹⁷⁸ A synthetic steroid hormone, Tibolone, which has androgenic as well as estrogenic and progestogenic properties, was used in post-menopausal women with Sjogren's syndrome to

treat dry eye. After 3 and 12 months of treatment, it increased Schirmer's test scores and decreased dry eye symptoms.¹⁷⁹ Use of androgen precursors like DHEA in Sjogren's syndrome patients for 9 months showed no changes in dry eye symptoms.^{73,180} A study using depot testosterone in Sjogren's syndrome patients showed significant improvement in ocular surface inflammation and tear production.¹⁸¹ A recent study in women with low testosterone levels and evaporative dry eye treated with androgen patch showed improvement in Schirmer's test scores and TBUT after 3 weeks of treatment.¹⁸²

To prevent the side effects of systemic androgen therapy and to limit systemic absorption of androgen, local androgen treatment modalities like androgen eye drop and transdermal androgen cream has been developed. National Institute of Health found that significant number of dry eye patients become asymptomatic after using testosterone eye drop for 6 months.¹⁸³ Irritation is common with androgen eye drop due to poor solubility of androgen. To make it more soluble and less irritating, cyclodextrin, a solubilizing compound is used with androgen eye drop and this newer conjugated androgen eye drop yielded positive results in improving dry eye signs and symptoms.¹⁷⁴ Some studies also shows that application of testosterone cream to the eyelids significantly reduces dry eye symptoms and normalizes TBUT and lipid layer thickness of the tear film.^{70,184} These new local androgen treatment modalities are efficacious and more tolerable to the patient. Studies on dry eye and androgen therapy are limited but most study shows consistent positive relationship between androgen therapy and improvement in dry eye symptoms. Large population based clinical studies are required in this field to determine the benefit of using androgen therapy in dry eye disease.

4.3. Candidate selection and Prognosis for hormonal treatment of DED

Age and endogenous hormone levels are the most important factors which should be considered while selecting patients for hormonal treatment of DED.

HRT significantly improves tear production in patients < 50 years old than older patients >50 years and improvement in tear production and age of the patient are negatively correlated.¹⁸⁵ In early menopausal period, estrogen may be useful but in later life, systemic and ocular side effects are more common.¹⁸⁶ Androgen eye drops are more beneficial in peri- and post-menopausal women than pre-menopausal women.¹⁸⁴

Patients with abnormally low endogenous testosterone levels like women with complete androgen insensitivity syndrome, men on androgen blockers and women with abnormally low testosterone levels are most benefitted from systemic and local androgen treatment and shows complete resolution of symptoms after using androgen therapy.^{50,187}

5. Summary

Presence of gonadal hormone receptors, mRNAs and proteins in the meibomian gland, lacrimal gland, conjunctiva and cornea depicts that these tissues are influenced by gonadal hormones. Specific influence on gene expression by gonadal hormones may be the cause of sex-related differences in the structural and functional characteristics of these tissues. Dry eye disease (DED) is a multifactorial immune-mediated inflammatory disease affecting the ocular tissues and gonadal hormones are known to produce effects on the immune system. DED mostly affects women and elderly population and post-menopausal women are more commonly affected. It can be due to low androgen levels in these population as androgen has anti-inflammatory role on the ocular surface. Effects of estrogen and progesterone in dry eye is unclear as dry eye is seen in both high and low estrogen states. It is believed that estrogen and progesterone act indirectly via inhibiting androgen actions on the ocular surface. Recent evidence suggests that imbalances in the levels of testosterone, estrogen and progesterone affects the lacrimal functional unit/OSS, promotes inflammatory processes in them and influences the pathophysiology of dry eye.

HRT therapy, including systemic estrogen or estrogen plus progesterone therapy, have conflicting results on dry eye symptoms, mostly showing no benefit or increasing the symptoms of dry eye. On the other hand, systemic or local androgen therapy shows consistent beneficial effects in dry eye disease. However, more large scale human studies are still needed in this field to determine the effects of gonadal hormones on ocular surface tissues and dry eye disease. It may be possible to develop new therapeutic strategies targeting the pathophysiology of DED through palliation of hormonal imbalances.

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None.

7. Conflicts of interest

There are no conflicts of interest.

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