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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.

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 preocular 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 systems[16] 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 explicits mRNA for 5α-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] It's 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 orchiedctomized 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 eprocesses 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 androgens[84] 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 orchiectomized male and ovariectomized female rats, the number of binding sites and density of androgen receptor proteins are similar in the lacrimal gland[91] 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 hase 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 hase 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 haves 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 mucin[142]. 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 patients[177] 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, showsed improvement in dry eye symptoms.[178] A synthetic steroid hormone, Tibolone, which hase 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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7. Conflicts of interest

There are no conflicts of interest.

References

1. The definition and classification of dry eye disease: report of the Definition and Classification Subcommittee of the International Dry Eye Work Shop. *Ocul Surf*. 2007;5:75–92.
2. McGinnigle S, Naroo SA, Eperjesi F. Evaluation of Dry Eye. *Surv Ophthalmol* . 2012;57(4):293–316. doi:10.1016/j.survophthal.2011.11.003.
3. Miljanović B, Dana R, Sullivan DA, Schaumberg DA. Impact of Dry Eye Syndrome on Vision-Related Quality of Life. *Am J Ophthalmol*. 2007;143(3):409–15. doi:10.1016/j.ajo.2006.11.060.
4. Uchino M, Schaumberg DA. Dry Eye Disease: Impact on Quality of Life and Vision. *Curr Ophthalmol Rep*. 2013;1(2):51–7. doi:10.1007/s40135-013-0009-1.
5. Maurya RP. Dry eye disease: An overview. *Indian J Clin Exp Ophthalmol*. 2019;4(4):433–4.
6. Dorennavar L, Maurya RP, Singh VP, Singh MK, Sharma K, Sharma R, et al. The role of Rebamipide ophthalmic suspension in management of dry eye disease. *Indian J Clin Exp Ophthalmol*. 2015;1(4):191–6. doi:10.5958/2395-1451.2015.00025.6.
7. Smith JA. The epidemiology of dry eye disease: report of the Epidemiology Subcommittee of the International Dry Eye WorkShop. *Ocul Surf*. 2007;5:93–107.
8. Schaumberg DA, Dana R, Buring JE, Sullivan DA. Prevalence of dry eye disease among US men: estimates from the Physicians' Health Studies. *Arch Ophthalmol*. 2009;127:763–8.
9. Schaumberg DA, Sullivan DA, Buring JE, Dana MR. Prevalence of dry eye syndrome among US women. *Am J Ophthalmol*. 2003;136(2):318–26. doi:10.1016/s0002-9394(03)00218-6.
10. Schaumberg DA, Uchino M, Christen WG, Semba RD, Buring JE, Li JZ, et al. Patient Reported Differences in Dry Eye Disease between Men and Women: Impact, Management, and Patient Satisfaction. *PLoS ONE*. 2013;8(9):e76121. doi:10.1371/journal.pone.0076121.
11. Sullivan DA, Hammitt KM, Schaumberg DA, Sullivan BD, Begley CG, Gjorstrup P, et al. Report of the TFOS/ARVO Symposium on Global Treatments for Dry Eye Disease: An Unmet Need. *Ocul Surf* . 2012;10(2):108–16. doi:10.1016/j.jtos.2012.02.001.
12. Dursun D, Monroy D, Knighton R, Tervo T, Vesaluoma M, Carraway K, et al. The effects of experimental tear film removal on corneal surface regularity and barrier function. *Ophthalmology*. 2000;107(9):1754–60. doi:10.1016/s0161-6420(00)00273-6.
13. Goto E, Yagi Y, Matsumoto Y, Tsubota K. Impaired functional visual acuity of dry eye patients. *Am J Ophthalmol*. 2002;133(2):181–6. doi:10.1016/s0002-9394(01)01365-4.
14. Lemp MA. Report of the National Eye Institute/ Industry workshop on clinical trials in dry eyes. *Eye Contact Lens*. 1995;21:221–32.
15. Rosenthal P, Borsook D. The Corneal Pain System. Part I: The Missing Piece of the Dry Eye Puzzle. *Ocular Surface*. 2012;10(1):2–14. doi:10.1016/j.jtos.2012.01.002.
16. Gipson IK. The Ocular Surface: The Challenge to Enable and Protect Vision. *Invest Ophthalmol Vis Sci* . 2007;48(10):4391–8. doi:10.1167/iovs.07-0770.
17. Stern ME, Beuerman RW, Fox RI, Gao J, Mircheff AK, Pflugfelder SC, et al. The pathology of dry eye: The interaction between the ocular surface and lacrimal glands. *Cornea*. 1998;17:584–9.
18. Stern ME, Beuerman RW, Fox RI, Gao J, Mircheff AK, Pflugfelder SC, et al. A unified theory of the role of the ocular surface in dry eye. *Adv Exp Med Biol*. 1998;438:643–51.
19. Li DQ, Luo L, Chen Z, Kim HS, Song XJ, Pflugfelder SC, et al. JNK and ERK MAP kinases mediate induction of IL-1beta, TNF-alpha and IL-8 following hyperosmolar stress in human limbal epithelial cells. *Exp Eye Res*. 2006;82:588–96.
20. Luo L, Li DQ, Doshi A, Farley W, Corrales RM, Pflugfelder SC, et al. Experimental Dry Eye Stimulates Production of Inflammatory Cytokines and MMP-9 and Activates MAPK Signaling Pathways on the Ocular Surface. *Invest Ophthalmol Vis Sci* . 2004;45(12):4293–4301. doi:10.1167/iovs.03-1145.
21. Barabino S, Dana M. Dry eye syndromes. *Chem Immunol Allergy*. 2007;92:176–84.
22. Pflugfelder SC. Antiinflammatory therapy for dry eye. *Am J Ophthalmol*. 2004;137(2):337–42. doi:10.1016/j.ajo.2003.10.036.
23. Anti-inflammatory therapy for dry eye. Am J Ophthalmol 2004; 137: 337–342. 23.Research in dry eye: report of the Research Subcommittee of the International Dry Eye Work Shop (2007). *Ocul Surf*. 2007;5:179–93.
24. Bron AJ. Methodologies to diagnose and monitor dry eye disease: report of the Diagnostic Methodology Subcommittee of the International Dry Eye Work Shop. *Ocul Surf*. 2007;5:108–52.
25. Mathers WD, Lane JA. Meibomian gland lipids, evaporation, and tear film stability. *Adv Exp Med Biol*. 1998;438:349–60.
26. Guillon M, Maissa C. Tear film evaporation-effect of age and gender. *Cont Lens Anterior Eye*. 2010;33:171–75.
27. Maissa C, Guillon M. Tear film dynamics and lipid layer characteristics- effect of age and gender. *Cont Lens Anterior Eye*.

2010;33:176–82.
28. Bron AJ, Tiffany JM, Gouveia SM, Yokoi N, Voon LW. Functional aspects of the tear film lipid layer. *Exp Eye Res* . 2004;78(3):347–60. doi:10.1016/j.exer.2003.09.019.
29. Bron AJ, Yokoi N, Gaffney E, Tiffany JM. Predicted Phenotypes of Dry Eye: Proposed Consequences of Its Natural History. *Ocular Surface*. 2009;7(2):78–92. doi:10.1016/s1542-0124(12)70299-9.
30. Knop E, Knop N, Millar T, Obata H, Sullivan DA. The International Workshop on Meibomian Gland Dysfunction: Report of the Subcommittee on Anatomy, Physiology, and Pathophysiology of the Meibomian Gland. *Invest Ophthalmol Vis Sci* . 2011;52(4):1938–78. doi:10.1167/iovs.10-6997c.
31. Lemp MA, Crews LA, Bron AJ, Foulks GN, Sullivan BD. Distribution of Aqueous-Deficient and Evaporative Dry Eye in a Clinic-Based Patient Cohort. *Cornea*. 2012;31(5):472–8. doi:10.1097/ico.0b013e318225415a.
32. Blackie CA, Korb DR, Knop E, Bedi R, Knop N, Holland EJ, et al. Nonobvious Obstructive Meibomian Gland Dysfunction. *Cornea*. 2010;29(12):1333–45. doi:10.1097/ico.0b013e3181d4f366.
33. Min SG, Ha MS. Calculated CT volumes of lacrimal glands in normal Korean orbits. *J Korean Opthalmol Soc*. 2015;56:1–5.
34. Mircheff AK, Wang Y, Ding C, Warren DW, Schechter JE. Potentially Pathogenic Immune Cells and Networks in Apparently Healthy Lacrimal Glands. *Ocular Surface*. 2015;13(1):47–81. doi:10.1016/j.jtos.2014.06.003.
35. Maurya RP, Singh V, Gupta A, Singh VP, Kumar A, Yadav A, et al. Dry eye disease associated with Primary Sjogren syndrome: An update. *Indian J Clin Exp Ophthalmol*. 2021;7(2):259–69. doi:10.18231/j.ijceo.2021.055.
36. Sullivan D, Wickham L, Rocha E, Krenzer K, Sullivan B, Steagall R, et al. Androgens and Dry Eye in Sjogren's Syndromea. *Ann N Y Acad Sci* . 1999;876:312–24. doi:10.1111/j.1749-6632.1999.tb07656.x.
37. Sullivan DA, Belanger A, Cermak JM, Berube R, Papas AS, Sullivan RM, et al. Are women with Sjögren's syndrome androgen deficient? *J Rheumatol*. 2003;30:2413–9.
38. Cermak JM, Krenzer KL, Sullivan RM, Dana MR, Sullivan DA. Is Complete Androgen Insensitivity Syndrome Associated with Alterations in the Meibomian Gland and Ocular Surface? *Cornea*. 2003;22(6):516–21. doi:10.1097/00003226-200308000-00006.
39. Sullivan BD, Evans JE, Cermak JM, Krenzer KL, Dana MR, Sullivan DA, et al. Complete androgen insensitivity syndrome: effect on human meibomian gland secretions. *Arch Ophthalmol*. 2002;120:1689–99.
40. Smith JA, Vitale S, Reed GF, Grieshaber SA, Goodman LA, Vanderhoof VH, et al. Dry eye signs and symptoms in women with premature ovarian failure. *Arch Ophthalmol*. 2004;122:151–6.
41. Pflugfelder SC. Hormonal Deficiencies and Dry Eye. *Arch Ophthalmol*. 2004;122(2):273–4. doi:10.1001/archopht.122.2.273.
42. Yavas GF, Ozturk F, Kusbeci T, Ermis SS, Yilmazer M, Cevrioglu S, et al. Meibomian gland alterations in polycystic ovary syndrome. *Curr Eye Res*. 2008;33:133–8.
43. Sullivan BD, Evans JE, Krenzer KL, Dana RM, Sullivan DA. Impact of antiandrogen treatment on the fatty acid profile of neutral lipids in human meibomian gland secretions. *J Clin Endocrinol Metab*. 2000;85:4866–73.
44. Maurya RP, Singh VP, Chaudhary S, Roy M, Srivastav T. Prevalence of severe dry eye disease in postmenopausal women in North India: A teaching hospital study. *Indian J Obstet Gynecol Res*. 2019;6(1):94–6. doi:10.18231/2394-2754.2019.0021.
45. Krenzer KL, Dana MR, Ullman MD, Cermak JM, Tolls DB, Evans JE, et al. Effect of Androgen Deficiency on the Human Meibomian Gland and Ocular Surface1. *J Clin Endocrinol Metab* . 2000;85(12):4874–82. doi:10.1210/jcem.85.12.7072.
46. McCulley JP, Shine WE. The lipid layer of tears: dependent on meibomian gland function. *Exp Eye Res*. 2004;78(3):361–5. doi:10.1016/s0014-4835(03)00203-3.
47. Sullivan DA, Rocha EM, Ullman MD, Krenzer KL, Gao J, Toda I, et al. Androgen regulation of the meibomian gland. *Adv Exp Med Biol*. 1998;438:327–31.
48. Sullivan DA, Sullivan BD, Ullman MD, Rocha EM, Krenzer KL, Cermak JM, et al. Androgen influence on the meibomian gland. *Invest Ophthalmol Vis Sci*. 2000;41:3732–42.
49. Sullivan DA, Yamagami H, Liu M, Suzuki T, Krenzer KL, Cermak JM, et al. Sex steroids, the meibomian gland and evaporative dry eye. *Cornea*. 2000;19(Supplement 2):S128. doi:10.1097/00003226-200011002-00187.
50. Sullivan D, Sullivan B, Evans J, Schirra F, Yamagami H, Liu M, et al. Androgen Deficiency, Meibomian Gland Dysfunction, and Evaporative Dry Eye. *Ann N Y Acad Sci* . 2002;966(1):211–22. doi:10.1111/j.1749-6632.2002.tb04217.x.
51. Suzuki T, Schirra F, Richards SM, Jensen RV, Sullivan DA. Estrogen and Progesterone Control of Gene Expression in the Mouse Meibomian Gland. *Invest Ophthalmol Vis Sci* . 2008;49(5):1797–808. doi:10.1167/iovs.07-1458.
52. Sullivan DA, Jensen RV, Suzuki T, Richards SM. Do sex steroids exert sex-specific and/or opposite effects on gene expression in lacrimal and meibomian glands? *Mol Vis*. 2009;15:1553–72.
53. Rocha EM, Wickham LA, Silveira LAD. Identification of androgen receptor protein and 5alpha-reductase mRNA in human ocular tissues. *Br J Ophthalmol*. 2000;84:76–84.
54. Yamagami H, Schirra F, Liu M, Richards SM, Sullivan BD, Sullivan DA, et al. Androgen influence on gene expression in the meibomian gland. *Adv Exp Med Biol*. 2002;506(pt A):477–81.
55. Schirra F, Suzuki T, Dickinson DP, Townsend DJ, Gipson IK, Sullivan DA, et al. Identification of Steroidogenic Enzyme mRNAs in the Human Lacrimal Gland, Meibomian Gland, Cornea, and Conjunctiva. *Cornea*. 2006;25(4):438–42. doi:10.1097/01.ico.0000183664.80004.44.
56. Obata H. Anatomy and histopathology of human meibomian gland. *Cornea*. 2002;21:70–4.
57. Mrugacz M, Zywalewska N, Bakunowicz-Lazarczyk A. Neuronal and hormonal regulatory mechanisms of tears production and secretion. *Klin Oczna*. 2005;107:548–50.
58. Driver PJ, Lemp MA. Meibomian gland dysfunction. *Surv Ophthalmol*. 1996;40(5):343–67. doi:10.1016/s0039-6257(96)80064-6.
59. Sullivan BD, Evans JE, Dana MR, Sullivan DA. Influence of aging on the polar and neutral lipid profiles in human meibomian gland secretions. *Arch Ophthalmol*. 2006;124:1286–92.
60. Sullivan BD, Evans JE, Dana MR, Sullivan DA. Impact of androgen deficiency on the lipid profiles in human meibomian gland secretions. *Adv Exp Med Biol*. 2002;506:449–58.
61. Labrie F, Belanger A, Simard J, Van L, Labrie C. DHEA and Peripheral Androgen and Estrogen Formation: Intracrinology. *Ann N Y Acad Sci* . 1995;774(1 Dehydroepiand):16–28. doi:10.1111/j.1749-6632.1995.tb17369.x.
62. Labrie F, Bélanger A, Cusan L, Gomez JL, Candas B. Marked Decline in Serum Concentrations of Adrenal C19 Sex Steroid Precursors and Conjugated Androgen Metabolites During Aging. *J Clin Endocrinol Metab* . 1997;82(8):2396–402. doi:10.1210/jcem.82.8.4160.
63. Guillon M, Maïssa C. Tear film evaporation—Effect of age and gender. *Cont Lens Anterior Eye* . 2010;33(4):171–5. doi:10.1016/j.clae.2010.03.002.
64. Labrie F. DHEA, important source of sex steroids in men and even more in women. *Prog Brain Res*. 2010;182:97–148.
65. Hykin PG, Bron AJ. Age-Related Morphological Changes in Lid Margin and Meibomian Gland Anatomy. *Cornea*. 1992;11(4):334–42. doi:10.1097/00003226-199207000-00012.
66. Pochi PE, Strauss JS, Downing DT. Age-related Changes in Sebaceous Gland Activity. *J Invest Dermatol*. 1979;73(1):108–11. doi:10.1111/1523-1747.ep12532792.
67. Mathers WD, Lane JA, Zimmerman MB. Tear Film Changes Associated with Normal Aging. *Cornea*. 1996;15(3):229–34. doi:10.1097/00003226-199605000-00001.
68. Shimazaki J, Sakata M, Tsubota K. Ocular surface changes and discomfort in patients with meibomian gland dysfunction. *Arch Ophthalmol*. 1995;113:1266–70.

69. Norn M. Expressibility of meibomian secretion. Relation to age, lipid precorneal film, scales, foam, hair and pigmentation. *Acta Ophthalmol*. 1987;65:137–42.
70. Worda C, Nepp J, Huber JC, Sator MO. Treatment of keratoconjunctivitis sicca with topical androgen. *Maturitas*. 2001;37(3):209–12. doi:10.1016/s0378-5122(00)00181-x.
71. Schiffman RM, Bradford R, Bunnell B, Lai F, Bernstein P, Whitcup SW, et al. A multi-center, double-masked, randomized, vehicle-controlled, parallel group study to evaluate the safety and efficacy of testosterone ophthalmic solution in patients with meibomian gland dysfunction. *Invest Ophthalmol Vis Sci*. 2006;47:5608–8.
72. Zeligs MA, Gordon K. Dehydroepiandrosterone therapy for the treatment of eye disorders. (International Patent) International Publication Number: WO 94/04155; 1994.
73. Pillemer SR, Brennan MT, Sankar V, Leakan RA, Smith JA, Grisius M, et al. Pilot clinical trial of dehydroepiandrosterone (DHEA) versus placebo for Sjögren's syndrome. *Arthritis Care Res*. 2004;51(4):601–4. doi:10.1002/art.20540.
74. Hartkamp A, Geenen R, Godaert GLR, Bootsma H, Kruize AA, Bijlsma JWJ, et al. Effect of dehydroepiandrosterone administration on fatigue, well-being, and functioning in women with primary Sjogren syndrome: a randomised controlled trial. *Ann Rheum Dis* . 2008;67(1):91–7. doi:10.1136/ard.2007.071563.
75. Konttinen YT, Stegajev V, Al-Samadi A, Porola P, Hietanen J, Ainola M, et al. Sjogren's syndome and extragonadal sex steroid formation: a clue to a better disease control? *J Steroid Biochem Mol Biol*. 2015;145:237–44.
76. Azzi L, El-Alfy M, Labrie F. Gender differences and effects of sex steroids and dehydroepiandrosterone on androgen and oestrogen α receptors in mouse sebaceous glands. *Br J Dermatol*. 2006;154(1):21–7. doi:10.1111/j.1365-2133.2005.06847.x.
77. Sansone-Bazzano G, Reisner RM, Bazzano G. A Possible Mechanism of Action of Estrogen at the Cellular Level in a Model Sebaceous Gland. *J Invest Dermatol* . 1972;59(4):299–304. doi:10.1111/1523-1747.ep12627361.
78. Richards SM, Yamagami H, Schirra F, Suzuki T, Sullivan DA, Jensen RV, et al. Sex-Related Effect on Gene Expression in the Mouse Meibomian Gland. *Curr Eye Res*. 2006;31(2):119–28. doi:10.1080/02713680500514644.
79. Darabad RR, Suzuki T, Richards SM, Jensen RV, Jakobiec FA, Zakka FR, et al. Influence of Aromatase Absence on the Gene Expression and Histology of the Mouse Meibomian Gland. *Invest Ophthalmol Vis Sci* . 2013;54(2):987–98. doi:10.1167/iovs.12-10992.
80. Yamagami H, Richards SM, Sullivan BD, Liu M, Steagall RJ, Sullivan DA, et al. Gender-associated differences in gene expression of the meibomian gland. *Adv Exp Med Biol*. 2002;506:459–63.
81. Yamagami H, Schirra F, Liu M, Richards SM, Sullivan BD, Sullivan DA, et al. Androgen influence on gene expression in the meibomian gland. *Adv Exp Med Biol*. 2002;506:477–81.
82. Dartt DA. Signal transduction and control of lacrimal gland protein secretion: A review. *Curr Eye Res*. 1989;8(6):619–36. doi:10.3109/02713688908995762.
83. Ubels JL, Gipson IK, Spurr-Michaud SJ, Tisdale AS, Dyken RV, Hatton MP, et al. Gene Expression in Human Accessory Lacrimal Glands of Wolfring. *Invest Ophthalmol Vis Sci* . 2012;53(11):6738–47. doi:10.1167/iovs.12-10750.
84. Sullivan DA, Edwards JA, Wickham LA, Pena JDO, Gao J, Ono M, et al. Identification and endocrine control of sex steroid binding sites in the lacrimal gland. *Curr Eye Res*. 1996;15(3):279–91. doi:10.3109/02713689609007622.
85. Richards SM, Liu M, Jensen RV, Schirra F, Yamagami H, Lombardi MJ, et al. Androgen regulation of gene expression in the mouse lacrimal gland. *J Steroid Biochem Mol Biol* . 2005;96(5):401–13. doi:10.1016/j.jsbmb.2005.04.037.
86. Suzuki T, Schirra F, Richards SM, Treister NS, Lombardi MJ, Rowley P, et al. Estrogen's and Progesterone's Impact on Gene Expression in the Mouse Lacrimal Gland. *Invest Ophthalmol Vis Sci* . 2006;47(1):158–68. doi:10.1167/iovs.05-1003.
87. Sullivan DA, Block L, Pena JDO. Influence of androgens and pituitary hormones on the structural profile and secretory activity of the lacrimal gland. *Acta Ophthalmol Scand*. 1996;74:421–35.
88. Azzarolo AM, Mircheff AK, Kaswan RL, Stanczyk FZ, Gentschein E, Becker L, et al. Androgen support of lacrimal gland function. *Endocrine*. 1997;6(1):39–45. doi:10.1007/bf02738800.
89. Pfeilschifter J, Köditz R, Pfohl M, Schatz H. Changes in Proinflammatory Cytokine Activity after Menopause. *Endocrine Rev*. 2002;23(1):90–119. doi:10.1210/edrv.23.1.0456.
90. Ishimaru N, Saegusa K, Yanagi K, Haneji N, Saito I, Hayashi Y, et al. Estrogen Deficiency Accelerates Autoimmune Exocrinopathy in Murine Sjögren's Syndrome through Fas-Mediated Apoptosis. *Am J Pathol* . 1999;155(1):173–81. doi:10.1016/s0002-9440(10)65111-5.
91. Sullivan DA, Wickham LA, Rocha EM, Kelleher RS, Silveira LD, Toda I, et al. Influence of gender, sex steroid hormones, and the hypothalamic-pituitary axis on the structure and function of the lacrimal gland. *Adv Exp Med Biol*. 1998;438:11–42.
92. Sullivan DA, Bloch KJ, Allansmith MR. Hormonal influence on the secretory immune system of the eye: androgen control of secretory component production by the rat exorbital gland. *Immunology*. 1984;52:239–46.
93. Sullivan DA, Allansmith MR. Hormonal influence on the secretory immune system of the eye: androgen modulation of IgA levels in tears of rats. *J Immunol*. 1985;134:2978–82.
94. Sullivan DA. Influence of the hypothalamic-pituitary axis on the androgen regulation of the ocular secretory immune system. *J Steroid Biochem*. 1988;30:429–33.
95. Sullivan DA, Bloch KJ, Allansmith MR. Hormonal influence on the secretory immune system of the eye: androgen regulation of secretory component levels in rat tears. *J Immunol*. 1984;132:1130–35.
96. Azzarolo AM, Mazaheri AH, Mircheff AK, Warren DW. Sex-dependent parameters related to electrolyte, water and glycoprotein secretion in rabbit lacrimal glands. *Curr Eye Res*. 1993;12(9):795–802. doi:10.3109/02713689309020384.
97. Sullivan DA, Allansmith MR. Hormonal modulation of tear volume in the rat. *Exp Eye Res*. 1986;42(2):131–9. doi:10.1016/0014-4835(86)90037-0.
98. Mathers WD, Stovall D, Lane JA, Zimmerman MB, Johnson S. Menopause and tear function: the influence of prolactin and sex hormones on human tear production. *Cornea*. 1998;17:353–8.
99. Versura P, Campos EC. Menopause and dry eye. A possible relationship. *Gynecological Endocrinol*. 2005;20(5):289–98. doi:10.1080/09513590400027257.
100. Chen SP, Massaro-Giordano G, Pistilli M, Schreiber CA, Bunya VY. Tear Osmolarity and Dry Eye Symptoms in Women Using Oral Contraception and Contact Lenses. *Cornea*. 2013;32(4):423–8. doi:10.1097/ico.0b013e3182662390.
101. Sullivan DA, Krenzer KL, Sullivan BD, Tolls DB, Toda I, Dana MR, et al. Does androgen insufficiency cause lacrimal gland inflammation and aqueous tear deficiency? *Invest Ophthalmol Vis Sci*. 1999;40:1261–5.
102. Rocha FJ, Wickham LA, Pena JDO, Gao J, Ono M, Lambert RW, et al. Influence of gender and the endocrine environment on the distribution of androgen receptors in the lacrimal gland. *J Steroid Biochem Mol Biol*. 1993;46(6):737–49. doi:10.1016/0960-0760(93)90314-m.
103. Richards SM, Jensen RV, Liu M, Sullivan BD, Lombardi MJ, Rowley P, et al. Influence of sex on gene expression in the mouse lacrimal gland. *Exp Eye Res* . 2006;82(1):13–23. doi:10.1016/j.exer.2005.04.014.
104. Toda I, Wickham LA, Sullivan DA. Gender and Androgen Treatment Influence the Expression of Proto-oncogenes and Apoptotic Factors in Lacrimal and Salivary Tissues of MRL/lprMice. *Clin Immunol Immunopathol*. 1998;86(1):59–71. doi:10.1006/clin.1997.4466.
105. Gao J, Lambert RW, Wickham LA, Banting G, Sullivan DA. Androgen control of secretory component mRNA levels in the rat lacrimal gland. *J Steroid Biochem Mol Biol* . 1995;52(3):239–49. doi:10.1016/0960-0760(94)00172-i.

106. Winderickx J, Vercaeren I, Verhoeven G, Heyns W. Androgen-dependent expression of cystatin-related protein (CRP) in the exorbital lacrimal gland of the rat. *J Steroid Biochem Mol Biol* . 1994;48(2-3):165–70. doi:10.1016/0960-0760(94)90141-4.
107. Toda I, Sullivan BD, Wickham LA, Sullivan DA. Gender- and androgen-related influence on the expression of proto-oncogene and apoptotic factor mRNAS in lacrimal glands of autoimmune and non-autoimmune mice. *J Steroid Biochem Mol Biol* . 1999;71(1-2):49–61. doi:10.1016/s0960-0760(99)00119-3.
108. Ono M, Rocha FJ, Sullivan DA. Immunocytochemical location and hormonal control of androgen receptors in lacrimal tissues of the female MRL/Mp-Ipr/Ipr mouse model of sjögren's syndrome. *Exp Eye Res*. 1995;61(6):659–66. doi:10.1016/s0014-4835(05)80016-8.
109. Lambert RW, Kelleher RS, Wickham LA, Vaerman JP, Sullivan DA. Neuroendocrinimmune modulation of secretory component production by rat lacrimal, salivary, and intestinal epithelial cells. *Invest Ophthalmol Vis Sci* . 1994;35:1192–201.
110. Ubels JL, Wertz JT, Ingersoll KE, II RJ, Aupperlee MD. Down-regulation of Androgen Receptor Expression and Inhibition of Lacrimal Gland Cell Proliferation by Retinoic Acid. *Exp Eye Res* . 2002;75(5):561–71. doi:10.1006/exer.2002.2054.
111. Sato EH, Sullivan DA. Comparative influence of steroid hormones and immunosuppressive agents on autoimmune expression in lacrimal glands of a female mouse model of Sjögren's syndrome. *Invest Ophthalmol Vis Sci*. 1994;35:2632–42.
112. Mostafa S, Seamon V, Azzarolo AM. Influence of sex hormones and genetic predisposition in Sjögren's syndrome: A new clue to the immunopathogenesis of dry eye disease. *Exp Eye Res* . 2012;96(1):88–97. doi:10.1016/j.exer.2011.12.016.
113. Sullivan DA, Allansmith MR. Hormonal influence on the secretory immune system of the eye: endocrine interactions in the control of IgA and secretory component levels in tears of rats. *Immunology*. 1987;60:337–43.
114. Cornell-Bell AH, Sullivan DA, Allansmith MR. Gender-related differences in the morphology of the lacrimal gland. *Invest Ophthalmol Vis Sci*. 1985;26:1170–5.
115. Sullivan D, Kelleher R, Vaerman J, Hann L. Androgen regulation of secretory component synthesis by lacrimal gland acinar cells in vitro. *J Immunol*. 1990;145:4238–44.
116. Vanaken H, Claessens F, Vercaeren I, Heyns W, Peeters B, Rombauts W, et al. Androgenic induction of cystatin-related protein and the C3 component of prostatic binding protein in primary cultures from the rat lacrimal gland. *Mol Cell Endocrinol* . 1996;121(2):197–205. doi:10.1016/0303-7207(96)03866-x.
117. Singh S, Moksha L, Sharma N, Titiyal JS, Biswas NR, Velpandian T, et al. Development and evaluation of animal models for sex steroid deficient dry eye. *J Pharmacol Toxicol Methods* . 2014;70(1):29–34. doi:10.1016/j.vascn.2014.03.004.
118. Song X, Zhao P, Wang G, Zhao X. The effects of estrogen and androgen on tear secretion and matrix metalloproteinase-2 expression in lacrimal glands of ovariectomized rats. *Invest Ophthalmol Vis Sci*. 2014;55:745–51.
119. Vavilis D, Maloutas S, Nasioutziki M, Boni E, Bontis J. Conjunctiva is an estrogen-sensitive epithelium. *Acta Obstet Gynecol Scand* . 1995;74(10):799–802. doi:10.3109/00016349509021200.
120. Zylberberg C, Seamon V, Ponomareva O, Vellala K, Deighan M, Azzarolo AM, et al. Estrogen up-regulation of metalloproteinase-2 and -9 expression in rabbit lacrimal glands. *Exp Eye Res* . 2007;84(5):960–72. doi:10.1016/j.exer.2007.02.002.
121. Srinivasan S, Joyce E, Senchyna M, Simpson T, Jones L. Clinical signs and symptoms in post-menopausal females with symptoms of dry eye. *Ophthalmic Physiol Opt* . 2008;28(4):365–72. doi:10.1111/j.1475-1313.2008.00580.x.
122. Obata H, Yamamoto S, Horiuchi H, Machinami R. Histopathologic study of human lacrimal gland. Statistical analysis with special reference to aging. *Ophthalmology*. 1995;102:678–86.
123. Azzarolo AM, Eihausen H, Schechter J. Estrogen prevention of lacrimal gland cell death and lymphocytic infiltration. *Exp Eye Res*. 2003;77(3):347–54. doi:10.1016/s0014-4835(03)00120-9.
124. Alexander WS, Hilton DJ. The role of suppressors of cytokine signaling (SOCS) proteins in regulation of the immune response. *Annu Rev Immunol*. 2004;22:503–29.
125. Darabad RR, Suzuki T, Richards SM, Jakobiec FA, Zakka FR, Barabino S, et al. Does estrogen deficiency cause lacrimal gland inflammation and aqueous-deficient dry eye in mice? *Exp Eye Res* . 2014;127:153–60. doi:10.1016/j.exer.2014.07.017.
126. Gipson IK. Distribution of mucins at the ocular surface. *Exp Eye Res*. 2004;78(3):379–88. doi:10.1016/s0014-4835(03)00204-5.
127. Gipson IK, Argüeso P. Role of mucins in the function of the corneal and conjunctival epithelia. *Int Rev Cytol Salt Lake City*. 2003;p. 1–49.
128. Millar TJ, Tragoulias ST, Anderton PJ, Ball MS, Miano F, Dennis GR, et al. The Surface Activity of Purified Ocular Mucin at the Air-Liquid Interface and Interactions With Meibomian Lipids. *Cornea*. 2006;25(1):91–100. doi:10.1097/01.ico.0000164779.87795.3c.
129. Rivas L, Oroza MA, Perez-Esteban A, del Castillo JM. Morphological changes in ocular surface in dry eyes and other disorders by impression cytology. *Graefes Arch Clin Exp Ophthalmol* . 1992;230(4):329–34. doi:10.1007/bf00165940.
130. Ralph RA. Conjunctival goblet cell density in normal subjects and in dry eye syndromes. *Invest Ophthalmol Vis Sci*. 1975;14:299–302.
131. Nelson JD, Wright JC. Conjunctival Goblet Cell Densities in Ocular Surface Disease. *Arch Ophthalmol*. 1984;102(7):1049–51. doi:10.1001/archopht.1984.01040030851031.
132. Argueso P, Balaram M, Spurr-Michaud S, Keutmann HT, Dana MR, Gipson IK, et al. Decreased levels of the goblet cell mucinMUC5ACin tears of patients with Sjögren syndrome. *Invest Ophthalmol Vis Sci* . 2002;43:1004–11.
133. Danjo Y, Watanabe H, Tisdale AS, George M, Tsumura T, Abelson MB, et al. Alteration of mucin in human conjunctival epithelia in dry eye. *Invest Ophthalmol Vis Sci*. 1998;39:2602–9.
134. Nelson JD, Havener VR, Cameron JD. Cellulose acetate impressions of the ocular surface. Dry eye states. *Arch Ophthalmol*. 1983;101:1869–72.
135. Bonini S, Mantelli F, Moretti C, Lambiase A, Bonini S, Micera A, et al. Itchy-Dry Eye Associated with Polycystic Ovary Syndrome. *Am J Ophthalmol*. 2007;143(5):763–71. doi:10.1016/j.ajo.2007.01.030.
136. Mantelli F, Moretti C, Micera A, Bonini S. Conjunctival mucin deficiency in complete androgen insensitivity syndrome (CAIS). *Graefes Arch Clin Exp Ophthalmol* . 2007;245(6):899–902. doi:10.1007/s00417-006-0452-x.
137. Versura P, Fresina M, Campos EC. Ocular surface changes over the menstrual cycle in women with and without dry eye. *Gynecol Endocrinol* . 2007;23(7):385–90. doi:10.1080/09513590701350390.
138. Serrander AM, Peek KE. Changes in contact lens comfort related to the menstrual cycle and menopause. A review of articles. *J Am Optom Assoc*. 1993;64:162–66.
139. Feldman F, Bain J, Matuk AR. Daily Assessment of Ocular and Hormonal Variables Throughout the Menstrual Cycle. *Arch Ophthalmol*. 1978;96(10):1835–38. doi:10.1001/archopht.1978.03910060347010.
140. Kramer P, Lubkin V, Potter W, Jacobs M, Labay G, Silverman P, et al. Cyclic Changes in Conjunctival Smears from Menstruating Females. *Ophthalmology*. 1990;97(3):303–7. doi:10.1016/s0161-6420(90)32588-5.
141. Inatomi T, Spurr-Michaud S, Tisdale AS, Zhan Q, Feldman ST, Gipson IK, et al. Expression of secretory mucin genes by human conjunctival epithelia. *Invest Ophthalmol Vis Sci*. 1996;37:1684–92.
142. Lange C, Fernandez J, Shim D, Spurr-Michaud S, Tisdale A, Gipson IK, et al. Mucin gene expression is not regulated by estrogen and/or progesterone in the ocular surface epithelia of mice. *Exp Eye Res* . 2003;77(1):59–68. doi:10.1016/s0014-4835(03)00064-2.
143. Inatomi T, Spurr-Michaud S, Tisdale AS, Gipson IK. Human corneal and conjunctival epithelia express MUC1 mucin. *Invest Ophthalmol Vis Sci*. 1995;36:1818–27.
144. Gipson IK, Hori Y, Argüeso P. Character of Ocular Surface Mucins and Their Alteration in Dry Eye Disease. *Ocular Surface*.

2004;2(2):131–148. doi:10.1016/s1542-0124(12)70149-0.
145. Mitchell S, Abel P, Madaan S, Jeffs J, Chaudhary K, Stamp G, et al. Androgen-Dependent Regulation of Human MUC1 Mucin Expression. *Neoplasia*. 2002;4(1):9–18. doi:10.1038/sj.neo.7900194.
146. Millodot M. The influence of pregnancy on the sensitivity of the cornea. *Br J Ophthalmol* . 1977;61(10):646–9. doi:10.1136/bjo.61.10.646.
147. Affinito P, Sardo AS, Carlo CD, Sammartino A, Tommaselli GA, Bifulco G, et al. Effects of hormone replacement therapy on ocular function in postmenopause. *Menopause*. 2003;10(5):482–7. doi:10.1097/01.gme.0000063568.84134.35.
148. Kiely P, Carney L, Smith G. Menstrual Cycle Variations of Corneal Topography and Thickness. *Am J Optom Physiol Opt* . 1983;60(10):822–9. doi:10.1097/00006324-198310000-00003.
149. Riss B, Binder S, Riss P, Kemeter P. Corneal sensitivity during the menstrual cycle. *Br J Ophthalmol*. 1982;66(2):123–6. doi:10.1136/bjo.66.2.123.
150. Guttridge NM. Changes in ocular and visual variables during the menstrual cycle. *Ophthalmic Physiol Opt*. 1994;14(1):38–48. doi:10.1111/j.1475-1313.1994.tb00555.x.
151. Soni P. Effects of Oral Contraceptive Steroids on the Thickness of Human Cornea. *Am J Optom Physiol Opt*. 1980;57(11):825–34. doi:10.1097/00006324-198011000-00008.
152. Millodot M, Lamont A. Influence of menstruation on corneal sensitivity. *Br J Ophthalmol* . 1974;58(8):752–56. doi:10.1136/bjo.58.8.752.
153. Ward MM, Stone SC, Sandman CA. Visual perception in women during the menstrual cycle. *Physiol Behav* . 1978;20(3):239–43. doi:10.1016/0031-9384(78)90215-9.
154. Vavilis D, Maloutas S, Nasioutziki M, Boni E, Bontis J. Conjunctiva is an estrogen-sensitive epithelium. *Acta Obstet Gynecol Scand* . 1995;74(10):799–802. doi:10.3109/00016349509021200.
155. Pelit A, Bağiş T, Kayaselçuk F, Dursun D, Akova Y, Aydin P, et al. Tear Function Tests and Conjunctival Impression Cytology before and after Hormone Replacement Therapy in Postmenopausal Women. *Eur J Ophthalmol* . 2003;13(4):337–42. doi:10.1177/112067210301300402.
156. Vavilis D, Agorastos T, Vakiani M, Jafetas J, Panidis D, Konstantinidis T, et al. The effect of transdermal estradiol on the conjunctiva in postmenopausal women. *Eur J Obstet Gynecol Reprod Biol* . 1997;72(1):93–6. doi:10.1016/s0301-2115(97)85911-8.
157. Tomlinson A. Effect of oral contraceptives on tear physiology. *Ophthalmic Physiol Opt* . 2001;21(1):9–16. doi:10.1016/s0275-5408(00)00005-3.
158. Suzuki T, Sullivan DA. Estrogen Stimulation of Proinflammatory Cytokine and Matrix Metalloproteinase Gene Expression in Human Corneal Epithelial Cells. *Cornea*. 2005;24(8):1004–9. doi:10.1097/01.ico.0000160973.04072.a5.
159. Aragona P, Puzzolo D, Micali A, Ferreri G, Britti D. Morphological and Morphometric Analysis on the Rabbit Conjunctival Goblet Cells in Different Hormonal Conditions. *Exp Eye Res* . 1998;66(1):81–8. doi:10.1006/exer.1997.0406.
160. Milner MS, Beckman KA, Luchs JI, Allen QB, Awdeh RM, Berdahl J, et al. Dysfunctional tear syndrome: Dry eye disease and associated tear film disorders - New strategies for diagnosis and treatment. *Curr Opin Ophthalmol*. 2017;27(1):47.
161. Schaumberg DA, Buring JE, Sullivan DA, Dana MR. Hormone replacement therapy and dry eye syndrome. *JAMA*. 2001;286:2114–9.
162. Shaharuddin B, Ismail-Mokhtar S, E H. Dry eye in post-menopausal Asian women on hormone replacement therapy. *Int J Ophthalmol*. 2008;1:158–60.
163. AlAwlaqi A, Hammadeh M. Examining the relationship between hormone therapy and dry-eye syndrome in postmenopausal women. *Menopause*. 2016;23(5):550–5. doi:10.1097/gme.0000000000000570.
164. Coksuer H, Ozcura F, Oghan F, Haliloglu B, Coksuer C. Effects of estradiol–drospirenone on ocular and nasal functions in postmenopausal women. *Climacteric*. 2011;14(4):482–7. doi:10.3109/13697137.2010.539724.
165. Evans V, Miller TJ, Eden JA, Willcox MDP. Menopause, hormone replacement therapy and tear function. *Adv Exp Med Biol*. 2002;507:1029–33.
166. Moon JH, Jung JW, Shin KH, Paik HJ. Effect of hormone replacement therapy on dry eye syndrome in postmenopausal women: a prospective study. *J Korean Ophthalmol Soc*. 2010;51:175–9.
167. Jensen AA, Higginbotham EJ, Guzinski GM, Davis IL, Ellish NJ. A survey of ocular complaints in postmenopausal women. *J Assoc Acad Minor Phys*. 2000;11:43–9.
168. Altintaş Ö, Caglar Y, Yüksel N, Demirci A, Karabaş L. The Effects of Menopause and Hormone Replacement Therapy on Quality and Quantity of Tear, Intraocular Pressure and Ocular Blood Flow. *Ophthalmologica*. 2004;218(2):120–9. doi:10.1159/000076148.
169. Guaschino S, Grimaldi E, Sartore A, Mugittu R, Mangino F, Bortoli P, et al. Visual function in menopause: the role of hormone replacement therapy. *Menopause*. 2003;10:53–7.
170. Okon´A, Jurowski P, Gos´R. The influence of the hormonal replacement therapy on the amount and stability of the tear film among peri- and postmenopausal women. *Klin Oczna*. 2001;103:177–81.
171. Metka M, Enzelsberger H, Knogler W, Schurz B, Aichmair H. Eye manifestations as climacteric symptom. *Geburtshilfe Frauenheilkd*. 1991;51:143–5.
172. Sator MO, Joura EA, Golaszewski T, Gruber D, Frigo P, Metka M, et al. Treatment of menopausal keratoconjunctivitis sicca with topical oestradiol. *BJOG: An International Journal of Obstetrics and Gynaecology*. 1998;105(1):100–102. Available from: https://dx.doi.org/10.1111/j.1471-0528.1998.tb09358.x. doi:10.1111/j.1471-0528.1998.tb09358.x.
173. Akramian J, Wedrich A, Nepp J, Sator M. Estrogen therapy in keratoconjunctivitis sicca. *Adv Exp Med Biol*. 1998;438:1005–1009.
174. Dawson T. Testosterone eye drops: A novel treatment for dry eye disease. *Ophthalmology Times*. 2015;.
175. Appelmans M. La ke´rato-conjonctivite se'che de Gougerot-Sjo¨gren. *Arch Ophtalmol (Paris)*. 1948;8:577–588.
176. Bruckner R. Uber einem erfolgreich mit perandren behandelten fall von Sjogren'schem symptomen complex. *Ophthalmologica*. 1945;110:37–42.
177. Bizzarro A, Valentini G, Martino GD, DaPonte A, Bellis AD, Iacono G, et al. Influence of Testosterone Therapy on Clinical and Immunological Features of Autoimmune Diseases Associated with Klinefelter's Syndrome. *J Clin Endocrinol Metab* . 1987;64(1):32–6. doi:10.1210/jcem-64-1-32.
178. Scott G, Yiu SC, Wasilewski D, Song J, Smith RE. Combined Esterified Estrogen and Methyltestosterone Treatment for Dry Eye Syndrome in Postmenopausal Women. *Am J Ophthalmol* . 2005;139(6):1109–10. doi:10.1016/j.ajo.2004.11.042.
179. Sartore A, Grimaldi E, Guaschino S. The treatment of Sjögren's syndrome with tibolone: a case report. *Am J Obstet Gynecol* . 2003;189(3):894. doi:10.1067/s0002-9378(03)00366-1.
180. Forsblad-d'Elia H, Carlsten H, Labrie F, Konttinen YT, Ohlsson C. Low Serum Levels of Sex Steroids Are Associated with Disease Characteristics in Primary Sjogren's Syndrome; Supplementation with Dehydroepiandrosterone Restores the Concentrations. *J Clin Endocrinol Metab* . 2009;94(6):2044–51. doi:10.1210/jc.2009-0106.
181. Akudugu JM, Slabbert JP, Serafin A, Bohm L. Frequency of Radiation-Induced Micronuclei in Neuronal Cells Does Not Correlate with Clonogenic Survival. *Radiat Res* . 2000;153(1):62–7. doi:10.1667/0033-7587(2000)153[0062:forimi]2.0.co;2.
182. Nanavaty MA, Long M, Malhotra R. Transdermal androgen patches in evaporative dry eye syndrome with androgen deficiency: a pilot study. *Br J Ophthalmol*. 2014;98(4):567–9. doi:10.1136/bjophthalmol-2013-304637.
183. Plc A. Safety and efficacy study of a testosterone eye drop for the treatment of meibomian gland dysfunction. Clinical trials, National Institute of Health; 2012. Available from: https://clinicaltrials.gov/ct

2/show/NCT00755183. Last accessed on 2017 Jun 13].;.
184. Conner CG. Symptomatic relief of dry eye assessed with the OSDI in patients using 5% testosterone cream. *Invest Ophthalmol Vis Sci*. 2005;46:2032.
185. Feng Y, Feng G, Peng S, Li H. The effects of hormone replacement therapy on dry eye syndromes evaluated by Schirmer test depend on patient age. *Cont Lens Anterior Eye*. 2016;39:124–7.
186. Sherwin BB. Estrogen and cognitive aging in women. *Neurosci*. 2006;138:1021–6.
187. Dach J. Bioidentical Hormones and Natural Thyroid [Last accessed on 2017 Jun 13].; 2014. Available from: http://www.bioidenticalhormones101.com/Dry_Eye_Syndrome15.html.

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