ejpmr, 2018,5(5), 192-198

SJIF Impact Factor 4.897

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

SEX HORMONE AND THEIR OPHTHALMIC IMPLICATIONS

Anjum A.[1], Ahmed S.[2], Waris A.[3]*, Akhtar N.[1] and Ahmed A.[1]

[1]Ms Ophthalmology, Institute of Ophthalmology, Jnmch, Amu, Aligarh.
[2]Faculty of Medicine, Al Imam Mohammad Ibn Saud Islamic University, Riyadh, Kingdom of Saudi Arabia.
[3]Ms, Fico (Uk), Fics (Usa), Frcs (Glasg), Frcs (Edin), Vr Faculty, Institute Of Ophthalmology, Jnmch, Amu, Aligarh.

***Corresponding Author: Dr. Waris A.**

Ms, Fico (Uk), Fics (Usa), Frcs (Glasg), Frcs (Edin), Vr Faculty, Institute Of Ophthalmology, Jnmch, Amu, Aligarh.

Article Received on 06/03/2018 **Article Revised on 26/03/2018** **Article Accepted on 16/04/2018**

ABSTRACT

Sex steroid hormones have an influence, not only on the structure but also the functionality of ocular tissues, mainly the meibomian gland, lacrimal gland, conjunctiva, cornea, lens, and retina. Also, there exists a sexual dimorphism as far as ocular tissues are concerned and changes in the sex steroid hormonal milieu affect the vision [1, 2, 3, 4]. Sex steroid hormones have also been proposed as a treatment of conditions like dry eye syndrome and high intraocular pressure. Still today, less of information exists per se the exact mechanism of action and the specific ocular processes affected by the sex hormone in ocular health and disease. Current understanding of sex hormone and their ophthalmic implications can reveal the underlying potential of sex steroids.

KEYWORDS: *Eye, sex hormone, hormone action, lacrimal gland, conjunctiva, cornea, intraocular pressure.*

INTRODUCTION

In eye disease, hormones play an important role, since it is known that their balance is an individual signature, and their production depends on the environment, age and disease. Hormones are the main orchestrators of the body's physiology and affect organ and tissue behavior in two ways: directly, acting through cell receptors and modulating cell function, and/or indirectly, through regulation of metabolism and the organ and tissue milieu in which cell functions are carried out.

The physiology of the eye, its health or disease state, also depends on the equilibrium of the several hormones that may affect its condition. As very often happens in biomedical research, recognition and understanding of a specific pathology is the key to the understanding of the mechanisms that regulate the normal functioning of organs and tissues. Only few researches in this field have progressed to explore the links between certain eye diseases and specific hormonal changes. A better understanding of this aspect of endocrine ophthalmology can make therapeutic interventions more precise and effective.

As today, the role of sex steroid hormones and the exact mechanisms in maintaining the ocular health are still largely unknown. Gender-based differences may influence the occurrence of several ocular conditions suggesting the possibility that fluctuations in sex steroid homeostasis may have direct effects on the eye physiology.[1,2] There is still a gap in our knowledge regarding the sex hormone and its role in not only determining sexual dimorphism but also in affecting the physiology of a non-reproductive system, such as that of eye. The developmental, anatomical and physiological ocular parameters differ significantly in males and females.[3,4] Sex steroid hormones (SSH), such as estrogen, progesterone, and androgen, may be related to various ocular pathologies, as they can act through sex steroid hormone receptors present in the ocular tissue. Any pathology which is going to affect the levels of the sex hormone can affect the ocular tissues as well.[5,36]

Sex Hormone: Synthesis and Target Tissues

Primarily the gonads (ovaries or testes) and the adrenal glands synthesized and secrete sex steroid hormones, namely androgens, estrogens and progestogens, into the blood circulation.[08] Cholesterol is the common precursor involved in the biochemical pathways for synthesis of sex hormones in the endocrine glands.

The ovaries produce estrogen in females and smaller amount is produced by the testes in males and by adrenal glands in both the sexes. The testes mainly produce the androgens and to a lesser extent, androgens are also produced by the ovaries and adrenal glands. The steroid precursors are converted into sex steroids in the peripheral intracrine tissues such as the skin and adipose tissue.[12] The adrenal glands produce the androgens namely dehydroepiandrosterone (DHEA), DHEA-sulphate (DHEA-S) and androstenedione. These steroid precursors release into the circulation and allow for the production of half the active androgens in males and approximately three-quarters of estrogens in

premenopausal females by the gonads and peripheral tissues.[12]

In the presence of the 17 β-hydroxysteroid dehydrogenase (17 β-HSD) enzyme, the gonads and peripheral intracrine tissues are capable of converting circulating gonadal and adrenal androstenedione into functionally active testosterone.[13,14] The aromatase enzyme complex converts the testosterone and androstenedione that are synthesized by the ovaries and, to a lesser extent, the testes and peripheral tissues, into estradiol and oestrone respectively.[13] The enzyme 5 α-reductase converts the testosterone further into a more potent androgen, dihydrotestosterone (DHT) in peripheral tissues. Adjustments to amount of active sex hormone available in the tissue can be made according to local requirements and is done by regulating the level of expression and activity of steroidogenic enzymes in peripheral intracrine tissues.[12,15,16]

Many peripheral target tissues including the human ocular surface and adnexa contain the enzymatic machinery necessary for intracrine synthesis and metabolism of androgens and estrogens.[15,17,18] Although epithelial cells of the human lacrimal gland, meibomian gland, conjunctiva and cornea have been shown to contain messenger RNAs (mRNAs) for steroidogenic enzymes, such as 17 β-HSD, aromatase and 5 α-reductase further studies are required to determine whether these mRNAs are subsequently translated into proteins that produce enzymes for the synthesis of sex steroid hormone.[15,17,19] The peripheral tissues produce sex hormones and exert their effect to initiate transcriptional regulation of target genes, also known as 'classical' genomic actions, by local binding to hormone-specific receptors inside the nucleus or cytoplasm of the target cell.[16] The mRNAs for sex hormone receptor in the lacrimal gland, meibomian gland, conjunctiva and cornea of humans and various animal species are translated into hormone receptor proteins.[20,21] After the hormonal binding to the receptor, the hormone-receptor complex interacts with a specific DNA sequence within the target cell nucleus and modulates gene transcription and expression.[22,23,24] The number of genes influenced by exposure to sex hormone appears extensive in the ocular tissues and also includes genes responsible for lipid secretion and wound repair.[25]

Sex Hormone: Ocular Tissue Response

3.1 Sex Hormone and the Meibomian Glands

To increase the surface tension and promote stability of the tear film to prevent evaporation of the underlying tear layers, the meibomian glands produce and secrete lipids.[26] Sex hormones have a role in regulating the function of meibomian glands.[07,27,28,29] The meibomian gland function and the meibomian gland lipids, both quality and quantity has been found to be enhanced by the androgens.[28,30] Whereas the estrogens and progesterone have a role in suppression of sebaceous gland functions and thus reduces lipid production.

The meibomian gland is the target organ for androgens and its function to some extent is regulated by androgens.[17,20,22,28] Meibomian gland dysfunction and compromised meibomian gland secretions may result from low androgenic activity and lead to evaporative dry eye.[06,07,31,32] Such changes are associated with age and gender and are reported in individuals non-responsive to androgen, due to use of androgen antagonists or dysfunctional androgen receptors.[06,07,31,32] The levels of circulating androgens in women is found to be inherently lower as compared to men and there is also an age-related reduction in gonadal androgen production in both male and female.[22,33] This might contribute to increased risk of dry eye in these populations.[31,32,34] In females under 30 years of age, the total androgen production is approximately two-thirds of that found in the males.[33,35] Thereafter in both the sexes, the adrenal secretion of precursor steroids is found to be markedly decrease with only 30 percent of peak levels remaining in the females of menopausal age.[33,35] A structural and functional meibomian gland change has been observed in both men and women with advancing age. Reduction in quality and quantity of meibomian gland lipids leads to signs and symptoms of dry eye that may be exacerbated further by the concurrent increase in age-related eyelid and eyelid margin abnormalities seen with chronic blepharitis.[31,46,47,92] The fact that women with dysfunctional androgen receptors due to complete androgen insensitivity syndrome and men using anti-androgen therapy for prostate cancer show signs of ocular surface abnormalities and significant meibomian gland dysfunction, emphasizes upon the fact that the androgens are important in the regulation of meibomian gland function.[06,07,32]

Predisposition of the meibomian glands to the influence of female sex hormone is suggested by the presence of estrogen and progesterone receptors in the meibomian glands of human and various animal species.[20,54,55] The action of androgens is antagonized by the influence of estrogen on the meibomian gland, with resultant effects of dysfunction of meibomian glands and suppression of lipid synthesis leading to evaporative dry eye. The exacerbation of signs and symptoms of dry eye in post-menopausal women using estrogen replacement therapy is explained by antagonistic effects of estrogen. However, the direct influence of estrogen and progesterone on the human meibomian gland is yet to be understood. The estrogens have shown to have negative effects on the function and structure of sebaceous glands in other tissues of various species and meibomian gland is a large sebaceous gland.[36,38,56,88,91] Although both in males and females the number of estrogen receptors expressed in the human meibomian gland is similar.[54,55] Thus the number of estrogen receptors may be weakly related to stability of the tear film lipid layer or to subjective symptoms of dry eye.[55] The effects of estrogen in sebaceous gland are not a result of direct interaction with their receptors but rather indirectly, through antagonizing the action of androgen.[88] In the

sebaceous glands it appears that estrogen and androgens antagonize the regulation of binding sites that correspond to the opposing hormone. Thus, a higher prevalence of dry eye in women is due to reduction in androgenic activity, rather than an increase in estrogen action. This provides a plausible explanation for the increased frequency of dry eye in post-menopausal women despite the cessation of ovarian estradiol production. So it's the effects of androgen, rather than of estrogen or progesterone, that are responsible for the mechanisms that underlie the sex-related differences in biological processes, molecular functions and cellular components in the meibomian gland.[11,23]

3.2 Sex Hormone and the Lacrimal Gland

The lacrimal glands have the primary function of synthesis and secretion of water and electrolytes and proteins that contribute to aqueous layer of the tear film.[62,63] Sex hormone regulates the gene of transcription and to some extent mediates the structure and functionality of the main lacrimal glands.[64] Recently it has been found that the genes for estrogen and androgen receptors are also expressed on the accessory lacrimal glands.[63] There is a sex-related variation in function of the lacrimal gland and it has a role in modulating the morphology, molecular biology, biochemistry and secretory immune system of the tissue in various animal species and androgens are found to be partly accountable for this influence.[67,68] Whereas the roles of estrogens and progesterone in the lacrimal gland is unclear.[69]

For the androgens, like the meibomian gland, the lacrimal gland is also a target organ.[64] There is significant influence of the androgens on the sex-related functional, structural and pathological characteristics of lacrimal gland.[67] In autoimmune disease such as Sjögren's syndrome, there is a reduced influence of androgen that results in changes of inflammation in the lacrimal gland and leads to aqueous-deficient dry eye.[72] In female with altered endocrine states, the dry eye is related to reduce in serum androgen levels. Despite the variable estrogen levels observed in women after ovariectomy or menopause and during use of oral contraceptive, a primary lacrimal gland deficiency has been noted.[73] These observations contrast with those in men taking anti-androgen therapy, who do not show a change in their tear secretion[74], suggesting that androgen action may be sex-specific.

Although the molecular functions, biological processes and cellular components of the lacrimal gland are influenced by the estrogen and progesterone, the nature and extent of the influence is yet to be fully understood. Some studies in relation to progression of inflammation and autoimmune disease in the lacrimal gland have shown that the estrogen and/or progesterone may have a role.[65] Whereas few studies also suggest significant anti-inflammatory influences on the anatomy and physiology of the tissue by these hormones.[69] Some studies have shown that a diminishing levels of circulating estrogen and progesterone leads to increase in inflammatory cytokines, diffuse fibrosis and atrophy of the lacrimal gland and making the post-menopausal women susceptible to dry eye syndrome.[70]

3.3 Sex Hormone and the Conjunctiva

The sex hormone can have a direct influence on the tissues of the ocular surface, including the conjunctiva, cornea and tear film. The mucin layer helps to stabilize the tear film and thus lubricate, hydrate and protect the ocular surface. It is derived from the conjunctival goblet cells that have a central role.[75,76,77] Patients with dry eye exhibit alteration of goblet cell density and changes in mucin distribution on the ocular surface that have implications for tear film stability.[78,79] Of all the 19 types of mucin identified, at least four types are present on the ocular surface of humans.[80,81] The conjunctival goblet cells produce secretory mucin MUC5A, which is a large gel-forming glycoprotein.[81] A study showed a reduced MUC1 and MUC5AC protein expression in the mucous layer of tear film conducted in women with complete androgen insensitivity syndrome and dry eye.[84] The reduction in MUC5AC expression with androgen deficiency has been attributed to compromised goblet cell function rather than a decline in goblet cell number.[84,85]

During menstruation and menopause, a cyclical variation in the conjunctival epithelium has been observed. Even the maturity of the conjunctival tissue strongly correlates with the levels of estrogen. Another surprising fact is the bleeding through ocular tissue which accounts for 1% of all extragonadal sites of vicarious menstruation.[36]

The conjunctival epithelium is estrogen sensitive and the cells show changes in the mucin production and maturation that follows the variation of hormone during the menstrual cycle.[66] The conjunctival epithelium consists mainly of immature parabasal cells during the menstrual phase of the cycle as both estrogen and progesterone levels are at their lowest.[61,90] The relative proportions of parabasal, intermediate and mature superficial conjunctival cells correspond to the relative levels of estrogens and/or progesterone in the menstrual, luteal and follicular phase, respectively.[88,89] These maturational changes in the conjunctival epithelium are absent post-menopause.[88,61]

3.4 Sex Hormone and the Cornea

Alteration in the circulating hormone levels has influence on corneal and conjunctival tissues as these tissue are sensitive to the changes. Ocular symptoms can develop as a result of corneal alterations, including changes in the corneal sensitivity and visual function which in turn is influenced by the hormonal changes that occur with the menstrual cycle, contraceptive use, pregnancy, menopause and hormone replacement therapy.[81,82,83,84,85] The functional and structural changes that occur in the cornea and conjunctiva during menstruation have been

attributed to the effects of estrogen and/or progesterone, as the testosterone levels remain relatively consistent throughout the cycle.[71,89] Receptors for estrogen and progesterone are expressed on cornea and these hormones are available to the cornea from aqueous humour or the tear film. Phases of elevated estrogen reduce the corneal sensitivity and disrupt the feedback mechanism to the lacrimal gland for normal tear production.[86,87] Studies have shown the influence of sex steroid hormones and altered corneal functions and topography under different physiological conditions. The presence of estrogen receptors, progesterone receptors, and androgen receptors in the nuclei of corneal epithelium has been also shown. During pregnancy, premenstrual phase, and lactation there are changes in the corneal curvature and thickness that can result in visual changes and vision disturbances.[4,91] These studies imply that sex hormones have a role in the regulation of corneal anatomy and physiology.

3.5 Sex Hormone and the Lens

A sexual dichotomy has been observed in age-related cataracts; with the females having a higher incidence of cataracts, as compared with age-matched men. However, only the postmenopausal females have this increased risk.[38,40] In females the sex steroid hormone have a protective effect in context of cataractogenesis and has been supported by the Beaver Dam Eye Study that suggests estrogen to have a protective effect on lens in perspective of age-related opacities.[37] The result also showed that there is a decreased risk to develop severe nuclear sclerosis with current use of post-menopausal estrogen. Also from menarche to menopause the women is a protected and there is decreased risk of nuclear sclerosis and cortical opacities. Proper ionic milieu and hydration of lens cells are essential to maintaining the transparency of the crystalline lens. The retention of hydration and increase in water imbibition in the target tissues are influenced by estrogen. Estrogen by its non-genomic action maintains proper ionic composition in the target tissues.[39] Thus the maintenance of the ionic composition and hydration status in the lens, confer protective role of estrogen.[3,38]

3.6 Sex Hormone and the Retina

Studies suggest a relationship between estrogen and retinal disorders. Various known and unknown mechanisms are responsible for the protective role of estrogen on retina. Various genomic and non-genomic effects prevent retinal changes and this effect confers the protective influence of estrogen on the target tissue.[93] Epidemiological studies have indicated eye disorders such as cataract, idiopathic full-thickness macular hole and age-related macular degeneration (AMD) are associated with age and sex, and showed an increased incidence of eye diseases in the aging population, in particular the postmenopausal females.[51,53] The increase in morbidity due to ocular problem observed in the post-menopausal women can be related to decrease in the levels of the hormone. Prevalent incidence of AMD in post-menopausal women has been linked to steep decline in the circulating estrogen levels. Eye Disease Case–Control Study Group showed an increase in the incidence of macular degeneration in post-menopausal females who are estrogen deficient.[50] Several cellular processes including inflammation are found to be regulated by estrogen.[57]

In the elderly male population, there is a gradual decrease in circulating sex steroids and androgens along with slow and long-lasting decline in the hormonal activity.[58] The decline in the sex steroids acts as inducers of milieu changes in the retina that in turn influence the pathological events in the aging eye.[59]

3.7 Sex Hormone and the Intraocular pressure (IOP)

There are studies showing the role of estrogen treatment in lowering of intraocular pressure in post-menopausal females whereas no significant effect of estrogen treatment in males and pre-menopausal females. Studies also revealed the therapeutic role of estrogen as an adjunct in the treatment of glaucoma. Role of sex hormone in controlling the intra-ocular pressure has been shown and supported by studies showing a rise in intraocular pressure during the menstrual phase and lowering of intraocular pressure in cases of glaucoma with estrogen and progesterone.[3,4,11]

3.8 Sex Hormone and Ocular Apoptosis

There is evidence that different ocular tissues undergo a programmed cell death. Gender-related differences can influence variable gene expression which in turn can mediate a programmed cell death in ocular tissues.[9] The secretion of sex steroid hormones is controlled by hypothalamic neuroendocrine axis, which in turn can be affected by melatonin secreted from the retinal tissue and mainly secreted by the pineal gland.[10]

CONCLUSION

Diabetic retinopathy is the most common complication of diabetes mellitus that impairs the individual functioning and diminishes the quality of life. It ultimately imposes sever health burden on society and can cause significant morbidity if not addressed appropriately. The modifiable and non-modifiable risk factors are found to be the reason for the development of the diabetic retinopathy. The treatment modalities for management of diabetic retinopathy are available and found to be efficacious in different controlled studies, but the best treatment is prevention and strict control of the risk factors. In conclusion, overall health of the patients affects the development of diabetes and diabetic retinopathy. Health education about the maintenance of good systemic health and motivation of patients to strive for better management of issues related to health is a shared responsibility of ophthalmologists and other eye care providers.

REFERENCES

1. Zetterberg, M., 2016. Age-related eye disease and gender. Maturitas, 83: pp.19– 26.
2. Ogueta, S.B. et al., 1999. Estrogen receptor in the human eye: influence of gender and age on gene expression. Invest Ophthalmol Vis Sci, 40(9): 1906–1911.
3. Gupta PD, Johar K, Sr, Nagpal K, Vasavada AR. Sex hormone receptors in the human eye. Surv Ophthalmol., 2005; 50: 274–84. [PubMed]
4. Wagner H, Fink BA, Zadnik K. Sex- and gender-based differences in healthy and diseased eyes. Optometry., 2008; 79: 636–52. [PubMed]
5. Sullivan DA. Tearful relationships? Sex, hormones, the lacrimal gland, and aqueous-deficient dry eye. Ocul Surf., 2004; 2: 92–123. [PubMed]
6. 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: 4866–4873.
7. Krenzer KL, Dana MR, Ullman MD, Cermak JM, Tolls DB, Evans JE, Sullivan DA. Effect of androgen deficiency on the human meibomian gland and ocular surface. J Clin Endocrinol Metab, 2000; 85: 4874–4882.
8. Nussey SS, Whitehead SA. Endocrinology: An Integrated Approach. Abingdon, Oxford: Taylor & Francis, 2001.
9. Wilson SE. Stimulus-specific and cell type-specific cascades: Emerging principles relating to control of apoptosis in the eye. Exp Eye Res., 1999; 69: 255–66. [PubMed]
10. Rufiange M, Dumont M, Lachapelle P. Correlating retinal function with melatonin secretion in subjects with an early or late circadian phase. Invest Ophthalmol Vis Sci., 2002; 43: 2491–9. [PubMed]
11. Mitchell P, Smith W, Attebo K, Healey PR. Prevalence of open angle glaucoma in Australia. The Blue Mountains Eye Study. Ophthalmology., 1996; 103: 1661–9. [PubMed]
12. Labrie F, Belanger A, Simard J, Van L-T, Labrie C. DHEA and peripheral androgen and estrogen formation: Intracinology. Ann N Y Acad Sci., 1995; 774: 16–28.
13. Wierman ME. Sex steroid effects at target tissues: mechanisms of action. Adv Physiol Educ, 2007; 31: 26–33.
14. Labrie F, Luu-The V, Lin SX, Labrie C, Simard J, Breton R, Belanger A. The key role of 17 beta-hydroxysteroid dehydrogenases in sex steroid biology. Steroids, 1997; 62: 148–158.
15. Schirra F, Suzuki T, Dickinson DP, Townsend DJ, Gipson IK, Sullivan DA. Identification of steroidogenic enzyme mRNAs in the human lacrimal gland, meibomian gland, cornea and conjunctiva. Cornea, 2006; 25: 438–442.
16. Labrie F, Luu-The V, Labrie C, Belanger A, Simard J, Lin S-X, Pelletier G. Endocrine and intracrine sources of androgens in women: inhibition of breast cancer and other roles of androgens and their precursor dehydroepiandrosterone. Endocr Rev., 2003; 24: 152–182.
17. Rocha EM, Wickham LA, da Silveira LA, Krenzer KL, Yu FS, Toda I, Sullivan BD et al. Identification of androgen receptor protein and 5alpha-reductase mRNA in human ocular tissues. Br J Ophthalmol, 2000; 84: 76–84.
18. Perra MT, Lantini MS, Serra A, Cossu M, De Martini G, Sirigu P. Human meibomian glands: a histochemical study for androgen metabolic enzymes. Invest Ophthalmol Vis Sci., 1990; 31: 771–775.
19. Wickham LA, Rocha EM, Gao J, Krenzer KL, da Silveira LA, Toda I, Sullivan DA. Identification and hormonal control of sex steroid receptors in the eye. Adv Exp Med Biol., 1998; 438: 95–100.
20. Wickham LA, Gao J, Toda I, Rocha EM, Ono M, Sullivan DA. Identification of androgen, estrogen and progesterone receptor mRNAs in the eye. Acta Ophthalmol.
21. Suzuki T, Kinoshita Y, Tachibana M, Matsushima Y, Kobayashi Y, Adachi W, Sotozono C et al. Expression of sex steroid hormone receptors in human cornea. Curr Eye Res., 2001; 22: 28–33.
22. Schirra F, Suzuki T, Richards SM, Jensen RV, Liu M, Lombardi MJ, Rowley P et al. Androgen control of gene expression in the mouse meibomian gland. Invest Ophthalmol Vis Sci., 2005; 46: 3666–3675.
23. Yamagami H, Schirra F, Liu M, Richards SM, Sullivan BD, Sullivan DA. Androgen influence on gene expression in the meibomian gland. Adv Exp Med Biol., 2002; 506: 477–481.
24. Steagall RJ, Yamagami H, Wickham LA, Sullivan DA. Androgen control of gene expression in the rabbit meibomian gland. Adv Exp Med Biol., 2002; 506: 465–476.
25. Marin-Castaño ME, Elliot SJ, Potier M, Karl M, Striker LJ, Striker GE, Csaky KG, Cousins SW. Regulation of Estrogen Receptors and MMP-2 Expression by Estrogens in Human Retinal Pigment Epithelium. Invest Ophthalmol Vis Sci., 2003; 44: 50–59.
26. McCulley JP, Shine WE. The lipid layer of tears: dependent on meibomian gland function. Exp Eye Res., 2004; 78: 361–365.
27. Sullivan DA, Rocha EM, Ullman MD, Krenzer KL, Gao J, Toda I, Dana MR et al. Androgen regulation of the meibomian gland. Adv Exp Med Biol., 1998; 438: 327–331.
28. Sullivan DA, Sullivan BD, Ullman MD, Rocha EM, Krenzer KL, Cermak JM, Toda I et al. Androgen influence on the meibomian gland. Invest Ophthalmol Vis Sci., 2000; 41: 3732–3742.
29. Sullivan DA, Yamagami H, Liu M, Suzuki T, Krenzer KL, Cermak JM, Sullivan RM et al. Sex steroids, the meibomian gland and evaporative dry eye. Cornea, 2000; 19: S128.
30. Sullivan DA, Sullivan BD, Evans JE, Schirra F, Yamagami H, Liu M, Richards SM et al. Androgen deficiency, meibomian gland dysfunction, and evaporative dry eye. Ann N Y Acad Sci., 2002; 966: 211–222.
31. 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: 1286–1292.

32. 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: 449–458.
33. Labrie F, Belanger 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: 2396–2402.
34. Guillon M, Maïssa C. Tear film evaporation—effect of age and gender. Cont Lens Anterior Eye., 2010; 33: 171–175.
35. Labrie F. DHEA, important source of sex steroids in men and even more in women. Prog Brain Resh., 2010; 182: 97–148.
36. Sikorski R, Toczołowski J, Liber B, Jedrzejewski A. [Supplementary bleeding into the vitreous body] Pol Tyg Lek., 1978; 33: 1217–8. [PubMed]
37. B.E. Klein, R. Klein, L.L. Ritter Is there evidence of an estrogen effect on age-related lens opacities? The Beaver Dam Eye Study Arch Ophthalmol, 1994; 112: 85-91.
38. Leske MC, Wu SY, Nemesure B, Yang L, Hennis A Barbados Eye Studies Group. Nine year incidence of lens opacities in the Barbados Eye Studies. Ophthalmology., 2004; 111: 483–90. [PubMed]
39. S. Singh, P.D. Gupta Mechanism of action of estradiol; Non-genomic events J. Sengupta, D. Ghosh (Eds.), Cellular and molecular signalling in reproduction, New-age Interanational (P) Ltd, New Delhi, 1997; 69-83.
40. P.M. Livingston, C.S. Guest, Y. Stanislavsky, et al. A population-based estimate of cataract prevalence: the Melbourne Visual Impairment Project experience Dev Ophthalmol, 1994; 26: 1-6.
41. Pochi PE, Strauss JS, Downing DT. Age-related changes in sebaceous gland activity. J Invest Dermatol, 1979; 73: 108–111.
42. Driver PJ, Lemp MA. Meibomian gland dysfunction. Surv Ophthalmol, 1996; 40: 343–367.
43. Mathers WD, Lane JA, Zimmerman MB. Tear film changes associated with normal aging. Cornea, 1996; 15: 229–234.
44. Shimazaki J, Sakata M, Tsubota K. Ocular surface changes and discomfort in patients with meibomian gland dysfunction. Arch Ophthalmol, 1995; 113: 1266–1270.
45. Norn M. Expressibility of meibomian secretion. Relation to age, lipid precorneal film, scales, foam, hair and pigmentation. Acta Ophthalmol, 1987; 65: 137–142.
46. Mathers WD, Shields WJ, Sachdev MS, Petroll WM, Jester JV. Meibomian gland dysfunction in chronic blepharitis. Cornea, 1991; 10: 277–285.
47. Den S, Shimizu K, Ikeda T, Tsubota K, Shimmura S, Shimazaki J. Association between meibomian gland changes and aging, sex, or tear function. Cornea, 2006; 25: 651–655.
48. Zeligs M, Gordon K. Dehydroepiandrosterone therapy for the treatment of dry eye disorders. Int Patent Application WO, 1994; 94/04155.
49. Worda C, Nepp J, Huber JC, Sator MO. Treatment of keratoconjunctivitis sicca with topical androgen. Maturitas, 2001; 37: 209–212.
50. The Eye Disease Case-Control Study Group. Risk factors for central retinal vein occlusion. Arch Ophthalmol., 1996; 114: 545–54. [PubMed]
51. Klein, R., Klein, B.E. & Linton, K.L., 1992. Prevalence of age-related maculopathy. The Beaver Dam Eye Study. Ophthalmology, 99(6): 933– 43.
52. Obata H. Anatomy and histopathology of human meibomian gland. Cornea, 2002; 21: S70-S74.
53. Zetterberg, M., 2016. Age-related eye disease and gender. Maturitas, 83: 19– 26.
54. Esmaeli B, Harvey JT, Hewlett B. Immunohistochemical evidence for estrogen receptors in meibomian glands. Ophthalmology, 2000; 107: 180–184.
55. Auw-Haedrich C, Feltgen N. Estrogen receptor expression in meibomian glands and its correlation with age and dry-eye parameters. Graefes Arch Clin Exp Ophthalmol, 2003; 241: 705–709.
56. 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: 1938–1978.
57. Paimela, T. et al., 2007. The effect of 17beta-estradiol on IL-6 secretion and NF-kappaB DNA-binding activity in human retinal pigment epithelial cells. Immunol Lett, 110(2): 139–144.
58. Schulster, M., Bernie, A. & Ramasamy, R., 2016. The Role of Estradiol in Male Reproductive Function. Asian Journal of Andrology, 18(August 2015); 1– 6.
59. Carlo A., Pia A., Silvia B., Ilaria M., Antonio G., Marcella M., Effect of sex steroid hormone fluctuations in the pathophysiology of male retinal pigment epithelial cells. Journal of Cellular Physiology, 12 January 2018.
60. Suzuki T, Schaumberg DA, Sullivan BD, Liu M, Richards SM, Sullivan RM, Dana MR et al. Do estrogen and progesterone play a role in the dry eye of Sjögren's syndrome? Ann N Y Acad Sci., 2002; 966: 223–225.
61. Vavilis D, Maloutas S, Nasioutziki M, Boni E, Bontis J. Conjunctiva is an estrogen-sensitive epithelium. Acta Obstet Gynecol Scand, 1995; 74: 799–802.
62. Dartt DA. Signal transduction and control of lacrimal gland protein secretion: a review. Curr Eye Res., 1989; 8: 619–636.
63. Ubels JL, Gipson IK, Spurr-Michaud SJ, Tisdale AS, Van Dyken RE, Hatton MP. Gene expression in human accessory lacrimal glands of Wolfring. Invest Ophthalmol Vis Sci., 2012; 53: 6738–6747.
64. Sullivan DA, Edwards JA, Wickham LA, Pena JD, Gao J, Ono M, Kelleher RS. Identification and endocrine control of sex steroid binding sites in the lacrimal gland. Curr Eye Res., 1996; 15: 279–291.
65. 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: 88–97.

66. 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: 162–166.
67. 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: 421–435.
68. Azzarolo AM, Mircheff AK, Kaswan RL, Stanczyk FZ, Gentschein E, Becker L, Nassir B, Warren DW. Androgen support of lacrimal gland function. Endocrine, 1997; 6: 39–45.
69. Azzarolo AM, Eihausen H, Schechter J. Estrogen prevention of lacrimal gland cell death and lymphocytic infiltration. Exp Eye Res., 2003; 77: 347–354.
70. Obata H, Yamamoto S, Horiuchi H, Machinami R. Histopathologic study of human lacrimal gland. Statistical analysis with special reference to aging. Ophthalmology, 1995; 102: 678–686.
71. Feldman F, Bain J, Matuk AR. Daily assessment of ocular and hormonal variables throughout the menstrual cycle. Arch Ophthalmol, 1978; 96: 1835–1838.
72. 112Rocha FJ, Wickham LA, Pena JDO, Gao J, Ono M, Lambert RW, Kelleher RS 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: 737–749.
73. Chen SP, Massaro-Giordano GMD, Pistilli MMM, Schreiber CA, Bunya VY. Tear osmolarity and dry eye symptoms in women using oral contraception and contact lenses. Cornea, 2013; 32: 423–428.
74. Sullivan DA, Krenzer KL, Sullivan BD, Tolls DB, Toda I, Dana MR. Does androgen insufficiency cause lacrimal gland inflammation and aqueous tear deficiency? Invest Ophthalmol Vis Sci 1999; 40: 1261–1265.
75. Gipson IK. Distribution of mucins at the ocular surface. Exp Eye Res., 2004; 78: 379–388.
76. Gipson IK, Argüeso P. Role of mucins in the function of the corneal and conjunctival epithelia. In: Kwang WJ ed. International Review of Cytology. Salt Lake City: Academic Press, 2003; 1–49.
77. Millar TJ, Tragoulias ST, Anderton PJ, Ball MS, Miano F, Dennis GR, Mudgil P. The surface activity of purified ocular mucin at the air-liquid interface and interactions with meibomian lipids. Cornea, 2006; 25: 91–100.
78. Ralph RA. Conjunctival goblet cell density in normal subjects and in dry eye syndromes. Invest Ophthalmol Vis Sci., 1975; 14: 299–302.
79. Nelson JD, Wright JC. Conjunctival goblet cell densities in ocular surface disease. Arch Ophthalmol, 1984; 102: 1049–1051.
80. Gipson IK, Inatomi T. Mucin genes expressed by the ocular surface epithelium. Prog Retin Eye Res., 1997; 16: 81–98.
81. Inatomi T, Spurr-Michaud S, Tisdale AS, Zhan Q, Feldman ST, Gipson IK. Expression of secretory mucin genes by human conjunctival epithelia. Invest Ophthalmol Vis Sci., 1996; 37: 1684–1692.
82. Inatomi T, Spurr-Michaud S, Tisdale AS, Gipson IK. Human corneal and conjunctival epithelia express MUC1 mucin. Invest Ophthalmol Vis Sci., 1995; 36: 1818–1827.
83. Gipson IK, Hori Y, Argüeso P. Character of ocular surface mucins and their alteration in dry eye disease. Ocul Surf, 2004; 2: 131–148.
84. Mantelli F, Moretti C, Micera A, Bonini S. Conjunctival mucin deficiency in complete androgen insensitivity syndrome (CAIS). Graefes Arch Clin Exp Ophthalmol, 2007; 245: 899–902.
85. Mitchell S, Abel P, Madaan S, Jeffs J, Chaudhary K, Stamp G, Lalani E-N. Androgen-dependent regulation of human MUC1 mucin expression. Neoplasia, 2002; 4: 9–18.
86. Millodot M, Lamont A. Influence of menstruation on corneal sensitivity. Br J Ophthalmol, 1974; 58: 752–756.
87. Riss B, Binder S, Riss P, Kemeter P. Corneal sensitivity during the menstrual cycle. Br J Ophthalmol, 1982; 66: 123–126.
88. Kramer P, Lubkin V, Potter W, Jacobs M, Labay G, Silverman P. Cyclic changes in conjunctival smears from menstruating females. Ophthalmology, 1990; 97: 303–307.
89. Versura P, Fresina M, Campos EC. Ocular surface changes over the menstrual cycle in women with and without dry eye. Gynecol Endocrinol, 2007; 23: 385–390.
90. Guttridge NM. Changes in ocular and visual variables during the menstrual cycle. Ophthalmic Physiol Opt., 1994; 14: 38–48.
91. Kiely PM, Carney LG, Smith G. Menstrual cycle variations of corneal topography and thickness. Am J Optom Physiol Opt., 1983; 60: 822–9. [PubMed]
92. Hykin PG, Bron AJ. Age-related morphological changes in lid margin and meibomian gland anatomy. Cornea, 1992; 11: 334–342.
93. Evans JR, Schwartz SD, McHugh JD, Thamby-Rajah Y, Hodgson SA, Wormald RP, et al. Systemic risk factors for idiopathic macular holes: A case-control study. Eye (Lond), 1998; 12: 256–9. [PubMed]