Review Article

Dry Eye Syndrome in Menopause and Perimenopausal Age Group

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Abstract

Dry eye disease (DED) is a multifactorial ocular surface disease that causes symptoms of ocular pain, discomfort, and decreased visual acuity. It significantly affects quality of life of patients. It is more prevalent in the females and is being specifically in the menopausal and postmenopausal age group. This is believed to be due to the changes in balance of sex hormones. Sex hormones – estrogens and androgens – influence production of all components of the tear film including aqueous layer, lipid, and mucin. 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. Several studies have suggested potential role of hormone replacement therapy in menopause-associated dry eye symptoms. The purpose of this review is to help the non ophthalmic physicians about DED encountered commonly in menopausal age group. It is important for primary care physicians to understand DED due to its high prevalence, often debilitating symptoms and the potentially preventable and treatable nature of the condition.

Keywords: *Dry eye syndrome, hormones, menopause*

Introduction

Dry eye disease (DED) is defined by the International Dry Eye Workshop 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] This can cause debilitating symptoms including burning, foreign body sensation, and decreased vision and affect activities of daily living. This disease is a common cause for visits to ophthalmologists and primary care physicians alike. Different studies have found a relatively wide range of prevalence estimates, ranging from 7% to 33%.[2,3] This discrepancy depends on the population being studied and the criteria used to define dry eye.

Postmenopausal women have higher incidence of DED. Large-scale epidemiological studies done in the United States have shown that the rate of DED in women over 50 years old is nearly double that in men over 50, at 7% and 4%, respectively.[4] Numerous studies have demonstrated that there is a hormonal etiology behind this group's susceptibility to DED.[5-7] Androgens have been proven to have an effect on tear production and function.[5] However, the correlation between systemic estrogen and testosterone and DED is less clear. Further, systemic hormone replacement therapy has been both harmful and beneficial depending on the hormones and the patients.[8] Novel androgen formulations that can be given topically to the eyelids, or as eye drops, have shown promising results with decreased systemic side effects.[9,10]

Given high prevalence of DED, it is important for gynecologists and for primary care physicians to understand DED to recognize symptoms and start initial lubricating therapy and identify patients who would benefit from ophthalmology referral for further interventions.

Hormone Effects on Dry Eye

The tear film has three major components – the aqueous layer secreted by the lacrimal gland, the lipid layer

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secreted by the meibomian glands, and mucin secreted by the conjunctival goblet cells. Tear production, evaporation, drainage, health of corneal epithelial cells, corneal subbasal nerve plexus and corneal inflammatory and immune status interplay to maintain ocular surface homeostasis. By influencing the above-mentioned mechanisms, sex hormones play a role in pathogenesis of DED.

Both androgens and estrogen have known effects on the synthesis and components of the tear film. Sex steroid receptors are present on the meibomian glands, which are the sebaceous glands on the eyelids responsible for producing the oil component of tears that prevents evaporation.[11] Androgen binding results in synthesis and secretion of lipids from these glands, while estrogens actually cause a decrease in lipid production.[12] For this reason, increased levels of estradiol are believed to be a risk factor for dry eye.

However, the exact relationship between serum sex hormone levels and clinical symptoms of dry eye remains unclear and controversial. Ablamowicz *et al*. found that estrogen and testosterone were both increased in a group of women with dry eye compared to a matched group without dry eye, but this difference was not significant.[5] In contrast, Gagliano *et al*. found that postmenopausal women with severe evaporative dry eye had lower levels of estradiol and testosterone than the control group.

One possible explanation is that testosterone is increased as a result of dry eye and meibomian gland dysfunction by a feedback mechanism. It has been observed that testosterone levels increase as more meibomian glands are lost in postmenopausal women. In addition, testosterone has been shown to be protective against meibomian gland damage and dropout in mouse models.[5] This may be why testosterone, which is believed to be beneficial in dry eye patients, is often paradoxically increased in women with dry eye.

Clinical Considerations in Dry Eye Disease

Clinically, patients present with symptoms of dryness, burning, blurred vision, tearing, and light sensitivity. Medical history, surgical history, concurrent medications, environmental exposures to allergens, smoking, etc., need to be evaluated to identify potential contributing factors. On ophthalmic examination, decreased tear lake with increased tear breakup time is seen. Corneal surface staining is seen on slit-lamp bimicroscopy. Schirmer's test shows decreased tear production in aqueous deficiency. Increased tear osmolarity and decreased levels of lactoferrin and lysozyme are seen. First line of treatment is lubricating eye drops. If ineffective, second line of treatment includes anti-inflammatory medications such as steroid eye drops and immunomodulatory eye drops such as cyclosporine. In severe cases, depending on underlying cause, punctal occlusion, eyelid corrective surgery, and interventions such as scleral contact lenses and autologous serum tears may be indicated.[13]

In menopause-related dry eye, role of hormonal therapy has been investigated and may play a potential role in treatment.

Effects of Hormonal Replacement Therapy

Hormonal replacement therapy (HRT) has proven both beneficial and harmful to postmenopausal women depending on the specific hormones used and the organ system being studied. This is the case in dry eye as well. It is debated whether HRT increases, decreases, or does not affect risk of dry eye. Schaumberg *et al*. found that estrogen plus progesterone HRT significantly increased the risk over no HRT with an odds ratio of 1.29.[14] It has also been reported that greater doses of both estrogen only and estrogen plus progesterone HRT result in increased dry eye symptom severity compared with lower doses of the same treatments.[8] Other studies have found that HRT actually decreases ocular complaints and increases the quantitative tear production.[15,16] Further, Jensen *et al*. reported women taking >5 years of HRT had significantly fewer ocular complaints and greater tear production than women taking <5 years of HRT.[16]

Although the exact relationship between HRT and dry eye remains debatable, switching from an estrogen containing therapy, or stopping HRT altogether, if patients experience dry eye symptoms could allow for significant symptom improvement. The effects of estrogen plus progesterone therapy are less clear, but the most recent and largest controlled study showed a dose-dependent increased risk of dry eye symptoms in women taking estrogen and estrogen plus progesterone HRT.[8] The authors of this study suggest that the reason for the discrepancy in results is that the studies finding beneficial effects of HRT were more prone to selection bias and subjectivity as they relied on patient's reports of symptoms and numerous caregivers were used.[8]

Topical Androgen Treatments

It has been demonstrated that androgens play a critical role in tear production and consistency through their effects on meibomian and lacrimal gland function.[10] Sullivan *et al*. provided evidence that a lack of androgens leads to tear film dysfunction when he found men taking androgen blockers and patients with complete androgen insensitivity syndrome had higher rates of dry eye.[17] For

these reasons, numerous studies have been conducted assessing the efficacy of androgen therapy for dry eye.

Androgens are widely considered to be beneficial in dry eye and can provide some symptomatic improvement if included in systemic treatment. This appears especially true in women with abnormally low testosterone levels, men on androgen blockers, and patients with complete androgen insensitivity syndrome.[17]

Hormonal, and specifically androgen, replacement therapy can have significant side effects when administered systemically, which are especially undesirable for peri- and post-menopausal women. For this reason, androgen eye drops are an appealing route of delivery to limit systemic absorption. A study by the National Institute of Health found that 30% of dry eye patients receiving a testosterone eye drop became asymptomatic compared to 8% in the control group after 6 months of treatment.[18] However, due to the poor solubility of androgens, patients experienced significant irritation with the eye drops. This inspired Connor *et al*. to use a transdermal preparation to be applied to the eyelids, which resulted in a 51% decrease in dry eye symptoms.[9] A novel method for making androgen eye drops less irritating, using a solubilizing compound named cyclodextrin, yielded positive results. Ten of 12 patients receiving testosterone eye drops with cyclodextrin had significant improvement in signs and symptoms after 2 weeks.[10] These transdermal preparations and newer conjugated androgen eye drops produce symptom relief and are tolerable to most patients.[10]

However, benefits of androgen therapy remain controversial as well. A recent prospective-controlled study, studying testosterone treatment in dry eye syndrome, did not find any additional benefit in signs or symptoms from placebo for topical testosterone or systemic testosterone and estrogen.[19] However, the limitation of this study was a very small sample size (n = 40) and very short follow-up period of only 8 weeks.

Candidates for Treatment and Prognosis

Identifying which patients will most benefit most from hormonal treatment of DED is critical to optimal management of the disease. Several factors influence patient selection – age and endogenous hormonal levels – seem to be the most important considerations.

Feng *et al*. found that HRT improved tear production in patients with dry eye, but that the effect was only significant in participants <50 years old. The improvement in tear production was also negatively correlated with age.[20] Additional studies have shown that estrogen can be helpful in early menopausal period but both systemic and ocular adverse may be more with estrogen in later life.[21] However, the notion that younger patients benefit more from androgen eye drop therapy is limited to peri- and post-menopausal women, as Connor *et al*. demonstrated that this therapy in premenopausal women did not lead to the same degree of symptom relief.[9]

In addition to age, the patient's endogenous androgen level has also been stated to be a determinant of treatment response. Case reports exist where women with abnormally low testosterone levels experienced complete symptomatic relief from androgen eye drops and systemic testosterone therapy.[22] Men on androgen blockers and patients with complete androgen insensitivity syndrome are also good candidates for androgen therapy.[17] In contrast, patients with Sjogren's syndrome, a disease in which both dry eye and androgen deficiency are hallmarks, did not see improved symptoms with androgen supplementation in two separate studies.[23,24] Although the exact relationship between baseline testosterone levels and response to therapy remains somewhat unclear, it does appear that patients with abnormally low endogenous levels are more likely to show a positive response.

Future Direction and Summary of Dry Eye in Menopause

There is a paucity of large prospective-controlled studies with long follow-up times to evaluate the role of HRT in DED in menopausal age group. The numerous positive results seen in case series should be impetus for larger prospective studies with longer follow-up time. In addition, studies focusing specifically on perimenopausal women and women within 10 years of menopause should be conducted, as these patients are likely to show the greatest benefit.[20] It is also essential to investigate the most optimal route of therapy. Side effects and the risk benefit ratio of the hormonal treatment also need to be considered carefully before initiating therapy.

Conclusion

Alteration of sex hormones plays an important role in the pathophysiology of DED in perimenopausal and menopausal age group. DED remains very underrecognized in this group. Often, simple measures such as lubrication may provide relief. In more severe cases, anti-inflammatory, immunomodulatory, and rarely surgical interventions are required. Novel hormonal replacement treatments, both systemic and topical, are also evolving. It is important for all healthcare providers to understand DED to recognize, treat, and seek ophthalmologic intervention where applicable.

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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 WorkShop (2007).Ocul Surf 2007;5:75-92.
2. Lin PY, Tsai SY, Cheng CY, Liu JH, Chou P, Hsu WM. Prevalence of dry eye among an elderly Chinese population in Taiwan: The Shihpai Eye Study. Ophthalmology 2003;110:1096-101.
3. McCarty CA, Bansal AK, Livingston PM, Stanislavsky YL, Taylor HR. The epidemiology of dry eye in Melbourne, Australia. Ophthalmology 1998;105:1114-9.
4. Schaumberg DA, Sullivan DA, Buring JE, Dana MR. Prevalence of dry eye syndrome among US women. Am J Ophthalmol 2003;136:318-26.
5. Ablamowicz AF, Nichols JJ, Nichols KK. Association between serum levels of testosterone and estradiol with meibomian gland assessments in postmenopausal women. Invest Ophthalmol Vis Sci 2016;57:295-300.
6. Golebiowski B, Badarudin N, Eden J, You J, Hampel U, Stapleton F. Does endogenous serum oestrogen play a role in meibomian gland dysfunction in postmenopausal women with dry eye? Br J Ophthalmol 2017;101:218-22.
7. Versura P, Giannaccare G, Campos EC. Sex-steroid imbalance in females and dry eye. Curr Eye Res 2015;40:162-75.
8. AlAwlaqi A, Hammadeh M. Examining the relationship between hormone therapy and dry-eye syndrome in postmenopausal women: A cross-sectional comparison study. Menopause 2016;23:550-5.
9. Conner CG. Symptomatic relief of dry eye assessed with the OSDI in patients using 5% testosterone cream. Invest Ophthalmol Vis Sci 2005;46:2032.
10. Dawson T. Testosterone eye drops: A novel treatment for dry eye disease. Ophthalmology Times; 2015. Available from: http://ophthalmologytimes.modernmedicine.com/ophthalmologytimes/news/testosterone-eye-drops-novel-treatment-dry-eye-disease. [Last accessed on 2017 Jun 13].
11. Esmaeli B, Harvey JT, Hewlett B. Immunohistochemical evidence for estrogen receptors in meibomian glands. Ophthalmology 2000;107:180-4.
12. 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;49:1797-808.
13. 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 Suppl 1:3-47.
14. Schaumberg DA, Buring JE, Sullivan DA, Dana MR. Hormone replacement therapy and dry eye syndrome. JAMA 2001;286:2114-9.
15. Metka M, Enzelsberger H, Knogler W, Schurz B, Aichmair H. Eye manifestations as climacteric symptom. Geburtshilfe Frauenheilkd 1991;51:143-5.
16. Jensen AA, Higginbotham EJ, Guzinski GM, Davis IL, Ellish NJ. A survey of ocular complaints in postmenopausal women. J Assoc Acad Minor Phys 2000;11:44-9.
17. Sullivan DA, Sullivan BD, Evans JE, Schirra F, Yamagami H, Liu M, *et al.* Androgen deficiency, Meibomian gland dysfunction, and evaporative dry eye. Ann N Y Acad Sci 2002;966:211-22.
18. 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/ct2/show/NCT00755183. Last accessed on 2017 Jun 13].
19. Golebiowski B, Badarudin N, Eden J, Gerrand L, Robinson J, Liu J, *et al.* The effects of transdermal testosterone and oestrogen therapy on dry eye in postmenopausal women: A randomised, placebo-controlled, pilot study. Br J Ophthalmol 2016. pii: Bjophthalmol-2016-309498.
20. 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.
21. Sherwin BB. Estrogen and cognitive aging in women. Neuroscience 2006;138:1021-6.
22. Dach J. Bioidentical Hormones and Natural Thyroid; 2014. Available from: http://www.bioidenticalhormones101.com/Dry_Eye_Syndrome15.html. [Last accessed on 2017 Jun 13].
23. 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;94:2044-51.
24. 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 Rheum 2004;51:601-4.