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.

Postmenopause 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...
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.\textsuperscript{11} Androgen binding results in synthesis and secretion of lipids from these glands, while estrogens actually cause a decrease in lipid production.\textsuperscript{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.\textsuperscript{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.\textsuperscript{9} 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, punctual occlusion, eyelid corrective surgery, and interventions such as scleral contact lenses and autologous serum tears may be indicated.\textsuperscript{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.\textsuperscript{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.\textsuperscript{8} Other studies have found that HRT actually decreases ocular complaints and increases the quantitative tear production.\textsuperscript{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.\textsuperscript{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.\textsuperscript{18} 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.
Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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