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THE ROLE OF ESTROGEN AND ANDROGEN DEFICIENCY IN THE DEVELOPMENT AND PROGRESSION OF DRY EYE DISEASE

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ABSTRACT

Background: Dry eye disease (DED) is a multifactorial disorder involving loss of tear-film and ocular-surface homeostasis. Sex hormones influence several ocular-surface tissues, including the lacrimal and meibomian glands, corneal epithelium and conjunctiva. Hormonal changes may therefore modify susceptibility to both aqueous-deficient and evaporative forms of DED.

Objective: To review current evidence on the biological and clinical relationships between estrogen and androgen signaling and the development and progression of DED, with particular attention to meibomian gland function, tear-film stability and ocular-surface inflammation.

Methods: This narrative review synthesizes the source manuscript and selected peer-reviewed literature, including the TFOS DEWS III reports published in 2025, earlier TFOS consensus reports and clinical epidemiological evidence. The available evidence was critically compared and organized by hormonal pathway and clinical relevance. No original patient data or experimental measurements were generated.

Results: Androgens contribute to the regulation of meibomian and lacrimal gland physiology and ocular-surface immune activity. Reduced androgen signaling has been associated with impaired glandular function and may contribute to both evaporative and aqueous-deficient DED. Estrogen effects are more complex and depend on tissue, concentration, receptor context and hormonal environment. Observational evidence has linked postmenopausal hormone therapy, particularly estrogen-only therapy, with a higher prevalence of dry-eye symptoms or diagnosis; these findings do not establish causality. Hormonal influences interact with aging, autoimmune disease, medication exposure, environmental conditions and inflammatory pathways.

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Conclusion: Sex-hormone signaling is an important component of ocular-surface biology but should not be considered an isolated cause of DED. Clinical assessment should identify the dominant disease subtype and relevant systemic factors. Hormone therapy should not be initiated solely to treat DED without an independent medical indication and specialist assessment. Further prospective and mechanistic studies are required.

Keywords: dry eye disease; estrogen; androgen; sex hormones; meibomian gland dysfunction; tear film; ocular surface; inflammation; menopause; Sjögren disease.

INTRODUCTION

Dry eye disease is a common, multifactorial ocular-surface disorder that can impair visual function, comfort, reading, digital-device use and quality of life. The TFOS DEWS III consensus defines dry eye as a multifactorial, symptomatic disease characterized by loss of homeostasis of the tear film and/or ocular surface, in which tear-film instability and hyperosmolarity, ocular-surface inflammation and damage, and neurosensory abnormalities are etiological factors [1]. This updated definition emphasizes that symptoms and clinical signs must be considered together and that DED should be evaluated according to its underlying drivers.

The tear film is a dynamic interface rather than a simple three-layer fluid. Its lipid component, largely supplied by the meibomian glands, limits evaporation; the aqueous component contributes water, electrolytes and proteins; and the mucin/glycocalyx system supports surface wetting and epithelial protection. Dysfunction in any of these components, eyelid abnormalities, inflammation or altered sensory processing may destabilize the ocular surface.

Sex-related differences in DED have been repeatedly reported. Biological sex, age, hormonal status, sex chromosomes, immune regulation, environmental exposures and healthcare-seeking behavior may all contribute. The TFOS DEWS III Digest identifies sex, gender and hormones as an important domain in contemporary DED research and summarizes evidence published after the TFOS DEWS II reports [2]. Estrogens and androgens are of particular interest because their receptors and downstream signaling pathways are present in ocular-surface and adnexal tissues.

The relationship is not simply that one hormone is protective and the other harmful. Androgen signaling generally supports aspects of lacrimal and meibomian gland function, whereas estrogen effects vary by tissue, dose, receptor subtype and physiological context. This complexity is clinically relevant in menopause, aging, endocrine disorders and autoimmune conditions.

AIM AND REVIEW QUESTIONS

The aim of this article is to critically review the role of estrogen and androgen deficiency or imbalance in the pathophysiology and clinical expression of dry eye disease.

The review addresses the following questions: (i) how sex-hormone signaling influences the lacrimal and meibomian glands and ocular-surface epithelium; (ii) how

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reduced androgen activity may contribute to tear-film instability and inflammation; (iii) why estrogen-related findings are heterogeneous; and (iv) how hormonal status should be considered in contemporary DED assessment and management.

MATERIALS AND METHODS

This article is structured as a narrative literature review. The original Uzbek-language manuscript supplied by the authors was used as the thematic basis. Its principal topics—estrogen and androgen signaling, meibomian gland function, tear-film stability, menopause, inflammatory mediators and Sjögren disease—were retained and reorganized. The evidence base was updated with relevant peer-reviewed publications and international consensus documents, particularly the TFOS DEWS III Diagnostic Methodology, Management and Therapy, and Digest reports published in 2025 [1–3], together with foundational epidemiological evidence on hormone replacement therapy [4].

The literature was appraised descriptively according to relevance to the review questions, publication type and clinical or mechanistic contribution. Consensus reports, clinical observational studies and mechanistic research were considered separately because they provide different levels and types of evidence. This was not a registered systematic review: a complete database-specific search strategy, duplicate screening process and formal risk-of-bias assessment were not available in the source material. Accordingly, no claim of exhaustive systematic retrieval or meta-analysis is made.

No human participants were recruited, no clinical records were analyzed and no new laboratory experiments were performed. Therefore, the article reports no original clinical or experimental dataset.

HORMONAL REGULATION OF THE OCULAR SURFACE

4.1. Androgen signaling and glandular function

Androgens are involved in the development and maintenance of several ocular adnexal tissues. Their actions are relevant to the meibomian glands, which synthesize and secrete meibum, the lipid material that contributes to the outermost tear-film compartment. By supporting lipid production and glandular differentiation, androgen signaling may help maintain the quality and spread of the tear-film lipid layer.

Reduced androgen activity may be associated with altered meibum composition, impaired secretion and meibomian gland dysfunction. When the lipid layer becomes insufficient or unstable, evaporation can increase and tear-film breakup may occur earlier. This can contribute to evaporative DED. Androgen effects are not limited to the eyelids: experimental and clinical literature also implicates androgen signaling in lacrimal gland function and immune regulation of the ocular surface [2,5].

The biological response depends on local tissue metabolism as well as circulating hormone concentrations. Consequently, a serum androgen measurement alone may not fully represent intracrine signaling within ocular tissues. This is one reason why the relationship between systemic endocrine status and ocular symptoms may vary among individuals.

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4.2. Estrogen signaling: context-dependent effects

Estrogen receptors have been described in ocular-surface tissues, including the cornea, conjunctiva and ocular adnexa. Estrogen signaling may influence epithelial differentiation, cell proliferation, wound repair, vascular responses and inflammatory pathways. However, experimental findings are not uniform, and the direction of the response may differ according to receptor subtype, concentration, exposure duration, age and the hormonal environment.

Epidemiological findings illustrate this complexity. In the Women's Health Study, a cohort of postmenopausal women, hormone replacement therapy was associated with a higher likelihood of reported dry-eye diagnosis or severe symptoms. The adjusted odds ratio was 1.69 for estrogen-only therapy and 1.29 for estrogen combined with progesterone/progestin, compared with no hormone therapy [4]. These are observational associations and should not be interpreted as proof that estrogen directly causes DED. Residual confounding, treatment selection and differences in symptom reporting may influence the results.

Thus, estrogen should not be characterized as uniformly protective or uniformly detrimental to the ocular surface. Its effects need to be interpreted within the wider endocrine and clinical context.

4.3. Menopause, aging and hormonal imbalance

The menopausal transition involves substantial changes in ovarian hormone production and may coincide with changes in ocular-surface symptoms. Aging itself also affects tear production, eyelid structure, meibomian gland morphology, corneal sensitivity, medication use and systemic disease burden. It is therefore difficult to attribute DED in an older individual to estrogen decline alone.

In men, age-related changes in androgen status may also influence ocular adnexal physiology. However, the relationship between circulating testosterone and DED is not sufficiently straightforward to support hormone testing or supplementation in every patient with dry-eye symptoms. A targeted endocrine assessment may be appropriate when the history or systemic findings indicate a possible hormonal disorder.

INFLAMMATION, HYPEROSMOLARITY AND OCULAR-SURFACE DAMAGE

Tear-film instability and increased evaporation can raise tear osmolarity and expose epithelial cells to hyperosmotic stress. This stress may activate inflammatory signaling, epithelial damage pathways and changes in sensory nerve function. Inflammatory mediators discussed in DED research include interleukin-1β, interleukin-6, tumor necrosis factor-α, interferon-γ and matrix metalloproteinase-9. Their expression and clinical significance vary by disease subtype and stage; they should not be treated as universal diagnostic markers in every patient.

Androgen signaling may modulate immune activity in lacrimal and other ocular tissues. Experimental evidence summarized in TFOS DEWS III indicates that androgen effects on immune-associated gene expression can be substantial, although responses may

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depend on the biological model and tissue microenvironment [2]. The possible contribution of reduced androgen activity to chronic ocular-surface inflammation is therefore biologically plausible, but the magnitude of this effect in individual patients remains incompletely defined.

In Sjögren disease, lymphocytic infiltration and dysfunction of the lacrimal glands can cause marked aqueous tear deficiency. This autoimmune process is distinct from isolated age-related hormonal change, although endocrine and immune mechanisms may interact. Patients with persistent dryness, dry mouth, systemic autoimmune symptoms or severe aqueous deficiency may require evaluation for an underlying systemic disorder.

CLINICAL ASSESSMENT AND IMPLICATIONS

A hormonal history can complement, but cannot replace, a standard ophthalmic assessment. Relevant questions may include menopausal status, endocrine disease, hormone therapy, antiandrogen or other medication exposure, autoimmune history and the timing of symptom onset. The examination should establish whether symptoms are accompanied by objective evidence of tear-film or ocular-surface homeostatic loss.

The TFOS DEWS III Diagnostic Methodology report recommends a structured approach that combines symptom screening with objective assessment. It describes the OSDI-6 screening questionnaire and objective measures such as non-invasive tear breakup time, tear osmolarity and ocular-surface staining [1]. The precise test selection should follow the clinical setting and the current consensus criteria.

Table 1. Clinical Parameters for the Assessment of Dry Eye Disease and Their Relevance to Sex Hormonal Status

Clinical domain	Potential assessment	Relevance to hormonal context
Symptoms	Validated symptom questionnaire; onset, duration and fluctuation	Establishes symptom burden; ask about temporal association with menopause or medication changes.
Tear-film stability	Non-invasive tear breakup time or an appropriate clinical alternative	May reveal instability compatible with evaporative or mixed DED.
Tear osmolarity	Tear-film osmolarity where available	Provides evidence of disturbed tear-film homeostasis; not a hormone-specific test.
Ocular-surface integrity	Corneal and conjunctival staining	Assesses epithelial damage and supports DED diagnosis when interpreted with symptoms.

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Eyelid and meibomian glands	Lid-margin examination, gland expressibility and meibum quality; imaging where available	Identifies meibomian gland dysfunction, a possible contributor to evaporative DED.
Systemic context	Medication review and targeted assessment for endocrine or autoimmune disease	Identifies coexisting factors; investigations should be clinically indicated.

A key practical implication is that the presence of menopause or suspected androgen deficiency should not automatically determine the DED subtype. The clinician should identify whether aqueous deficiency, lipid deficiency/meibomian gland dysfunction, eyelid abnormalities, ocular-surface inflammation or neurosensory dysfunction predominates. Mixed mechanisms are common.

MANAGEMENT: EVIDENCE-BASED AND CAUTIOUS APPROACH

Current DED management is directed toward the identified disease drivers rather than toward a presumed hormonal cause alone. The TFOS DEWS III Management and Therapy report describes an individualized approach that may include tear-film supplementation, eyelid hygiene, warm compresses and therapies targeting inflammation or meibomian gland dysfunction, selected according to clinical findings [3]. Environmental modification, regular blinking during prolonged screen use and attention to medication-related dryness may also be useful.

Hormone replacement therapy should not be initiated, discontinued or modified solely on the basis of dry-eye symptoms. The observational association reported in the Women's Health Study is important for clinical awareness but does not establish an individual treatment effect [4]. Decisions about systemic hormone therapy require assessment of the patient's overall indications, benefits, contraindications and risks by the relevant treating specialist.

Likewise, androgen-based ocular treatments remain an area requiring further high-quality evidence. Potential biological rationale does not establish routine clinical efficacy, optimal dosing, long-term safety or an appropriate patient-selection strategy. At present, hormonal manipulation should not replace established ophthalmic evaluation and evidence-based DED management.

DISCUSSION

The available literature supports a meaningful relationship between sex-hormone signaling and ocular-surface physiology. Androgens appear to have important roles in the lacrimal and meibomian glands and in immune regulation. Estrogen effects are more heterogeneous and may vary across tissues and clinical settings. These differences help explain why epidemiological associations, experimental observations and individual clinical experiences do not always point in the same direction.

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The updated TFOS DEWS III framework is particularly relevant because it places hormonal influences within a broader, multifactorial model of DED. The disease may involve lipid, aqueous or mucin/glycocalyx deficiencies, eyelid anomalies, ocular-surface cell damage, inflammation, oxidative stress and neurosensory abnormalities [1–3]. Hormonal status is therefore best considered one component of a comprehensive assessment.

Several limitations should be acknowledged. First, much of the evidence linking hormones to DED is observational or mechanistic, and causal inference is limited. Second, hormone concentrations, receptor expression and local steroid metabolism may differ by age, sex, systemic disease and tissue. Third, DED definitions and diagnostic methods have changed over time, making comparisons between older and newer studies difficult. Finally, the present article is a narrative review and does not provide a registered protocol, exhaustive database search or quantitative synthesis.

Future research should include prospective longitudinal cohorts across menopausal and age groups, standardized DED phenotyping, careful recording of hormone exposure and medication use, and studies that distinguish circulating hormone levels from local tissue signaling. Clinical trials of hormone-related interventions should use validated symptom and sign outcomes, prespecified safety monitoring and clearly defined DED subtypes.

CONCLUSION

Estrogen and androgen signaling contribute to the biological regulation of the ocular surface and its adnexal glands. Reduced androgen activity may impair meibomian and lacrimal gland function and contribute to evaporative or aqueous-deficient DED. Estrogen effects are context-dependent, and observational evidence associating postmenopausal hormone therapy with dry-eye outcomes does not establish causality. Hormonal status should therefore be considered as one element of a multifactorial clinical assessment, not as a stand-alone explanation or treatment target. Diagnosis and management should follow current evidence-based ophthalmic guidance, with endocrine or rheumatological evaluation when clinically indicated.

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