TFOS DEWS III: **Digest Summary**

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Stapleton F, Argüeso P, Asbell P, et al. TFOS DEWS III Digest Report. *American Journal of Ophthalmology.* 2025;doi:10.1016/j.ajo.2025.05.040

The TFOS DEWS III Digest[1] summarizes the interdisciplinary research findings on dry eye disease (DED) since the 2017 TFOS DEWS II reports.[2] It covers seven topics that were published as individual reports in the 2017 issue (Sex, Gender, and Hormones; Epidemiology; Pathophysiology; Tear Film; Pain and Sensation; Iatrogenic Dry Eye; Clinical Trial Design) and reviews their impact on diagnosis, subtypes, and management of DED.

Sex, Gender, and Hormones

Since the 2017 Sex, Gender, and Hormones report,[3] multiple studies have continued to show a significant sexual dimorphism in the structure and/or function of the lacrimal gland, meibomian gland, cornea and eyelid. These differences may contribute to the higher prevalence of DED in women. Examples include a higher magnitude of acinar atrophy, periacinar fibrosis, periductal fibrosis, ductal proliferation, fatty infiltration, and lymphocyte infiltration in female lacrimal glands during aging, and differences in structure and sensitivity of the cornea, with thinner corneal epithelia, and higher corneal sensitivity and nerve regeneration in women. Women also report greater DED symptom severity. Sex differences are known to impact immune function, with women more prone to autoimmune disease. Hormones are a major factor in the prevalence and severity of DED; androgens are extremely important in the regulation of the ocular surface and adnexa, and androgen deficiency is associated with, and a risk factor for, DED. Very little research has addressed how gender-affirming hormone therapies may impact the ocular surface and adnexa in transgender and gender-diverse individuals. The authors concluded that despite major advances in the last eight years, further research is required to fully understand the role of sex, gender, and hormones in DED.

Epidemiology

Prevalence data ***(Figure 1)*** were determined using a meta-analysis for different diagnostic criteria and stratified by age and sex including evidence published since the 2017 report.[4] While DED prevalence increased with age based on the Women's Health Studies (WHS) criteria or when any sign of MGD was used as a criterion, prevalence did not change with age when a diagnosis was made based on the presence of signs and symptoms of DED. Similarly, DED was more prevalent in women when diagnosed based on the WHS criteria or when a clinical diagnosis was made, while signs of meibomian gland dysfunction (MGD) were more likely in males. The report also provided an overview of non-modifiable (e.g. age, sex, race or auto-immune conditions) and modifiable risk factors (such as medication use or environmental/lifestyle factors) to assist in the diagnosis of DED.

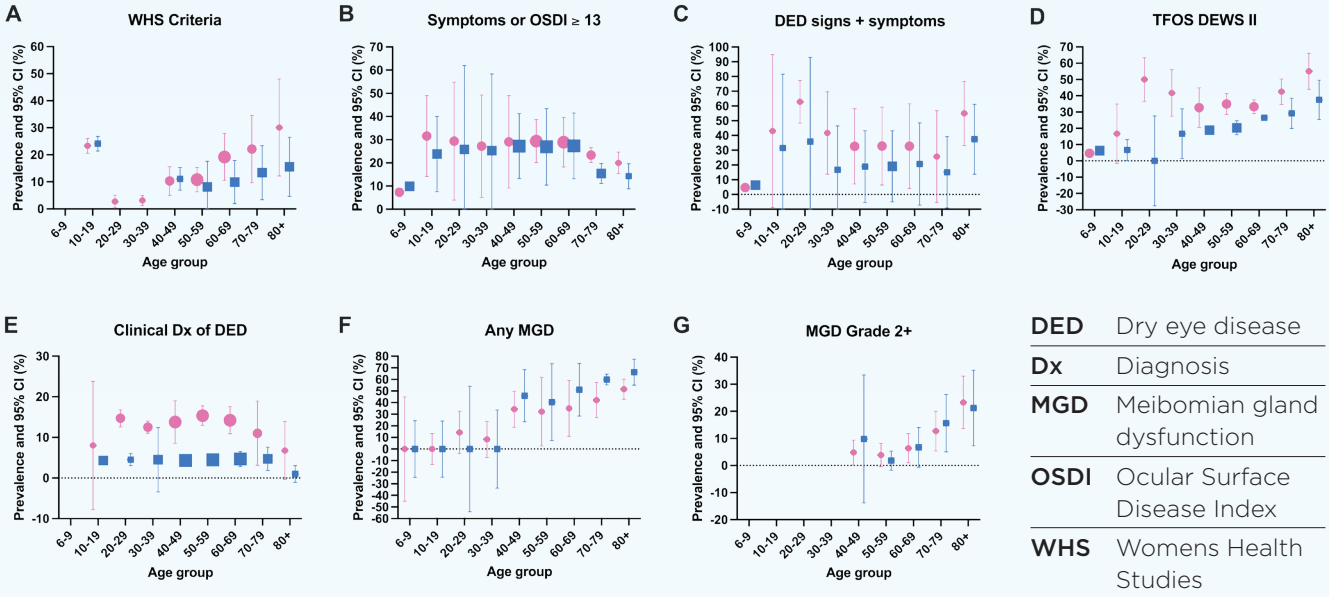

Figure 1: *Prevalence of DED based on age and sex for different diagnostic criteria. Blue squares denote data from males and pink circles denote data from females.*

Pathophysiology

Research since the previous TFOS DEWS II Pathophysiology report[5] has contributed to a more refined distinction between aqueous deficient dry eye and more evaporative types. Recent findings suggest that inflammation is more closely associated with aqueous deficient dry eye compared to a muted increase in inflammatory mediators for more evaporative types, suggesting that inflammation may not be active for every DED patient. The digest authors report that evaporative processes are triggered by phenotypic alterations in corneal epithelial cells that lead to a compromised glycocalyx, keratinization of the meibomian glands or desiccating stress due to blink irregularities or reduced blinking. Triggers for aqueous deficient dry eye are reported to include androgen deficiency or autoimmunity, causing a cascade of protease release, cytokine expression, inflammatory cell recruitment, dendritic cell maturation, and an adaptive T-cell mediated response. Hyperosmolarity plays a central role in DED, directly damaging epithelial cells, promoting oxidative stress, and triggering inflammatory processes. Recent studies have also reported on the importance of the glycocalyx for DED pathogenesis, with mounting evidence that a compromised glycocalyx is a trigger for DED.

Tear Film

The reproducibility of some clinical tear film measurements remains a challenge, with variations in non-invasive tear break-up time (NITBUT) across instruments and poor interchangeability with fluorescein-based measures. Correlations between tear film and ocular surface measures or comparisons to subjective symptoms were inconsistent. Research on tear lipids reveal that meibum quality and lipid composition strongly influence evaporation resistance in in vitro studies, as well as tear film stability. The tear proteome may have the potential to discriminate between DED sub-types and to monitor Sjögren's disease. In their conclusion, the authors propose a need for different biomarkers that better align the in vitro study findings with tear film components.

Pain and Sensation

The report reiterates the importance of corneal sensory nerves for ocular surface health, and how DED may be both a cause and consequence of nerve abnormalities. Disruptions to the corneal nerve structure through surgery, trauma, systemic disease or aging may lead to a reduced nerve fibre density and increased nerve tortuosity. These changes contribute to discomfort, pain, and impaired reflexes such as tearing and blinking, which may impact DED

progression. Corneal nerve alterations have been found to coincide with the onset of DED, and multiple studies have found a reduced corneal nerve fibre density and increased tortuosity in patients with DED or with neurological corneal pain compared to healthy controls. Certain morphological alterations such as microneuromas appear to be more common in corneal neuropathic pain. Tear hyperosmolarity, inflammation and disruptions of the tear film have also been reported as a potential reason for nerve fibre damage. The report identified in vivo confocal microscopy as a valuable clinical tool to image the corneal nerve fibre structure for changes in the density and branching of the fibers or to monitor changes associated with systemic diseases such as diabetic neuropathy. Additionally, corneal sensitivity testing (to assess underlying somatosensory abnormalities) is a useful tool for clinical practice.

Iatrogenic Dry Eye

Iatrogenic DED is a form of dry eye that has been induced by medication or procedures, with topical medications, surgical and non-surgical procedures, contact lens wear and systemic drug use being considered the main causes. Glaucoma medications cause ocular surface deterioration and DED, with studies showing greater prevalence in patients with glaucoma compared to healthy controls. Other medications that have been reported to cause DED are topical drugs (e.g. for allergy treatment, miotics, mydriatics or topical and local anesthetics) and their preservatives, especially medications containing benzalkonium chloride. Where available, preservative-free eye drops are the preferred option for topical ophthalmic treatment. Among others, systemic drugs associated with causing or contributing to DED include nonsteroidal anti- inflammatory drugs (NSAIDs), diuretics, vasodilators, antibiotics, antidepressants and antihistamines. Contact lens-associated DED is typically caused by an interaction between the contact lens, the lens material and the ocular surface, with increased tear film evaporation and mechanical interactions between the lids and the lenses often being reported. Surgical procedures such as laser-assisted in situ keratomileusis, photorefractive keratectomy, corneal crosslinking or treatment with botulinum toxin can all contribute to DED. Clinicians will need to find the right balance between successful treatment of the underlying disease while also managing the concurrent DED, which may require interprofessional collaboration if any modifications to current medications are required.

Clinical Trial Design

The 2025 clinical trial design section focused on how recommendations from the corresponding TFOS DEWS II report[6] translated into innovation in clinical trial design and into improving DED trial success by matching therapies to responsive patient groups (e.g. for aqueous and evaporative type DED, MGD or contact lens discomfort). In addition to better matching the treatments to the specific patient population, further improvements to clinical trial designs included more stringent control on concomitant treatments, identifying and controlling potential sources of error (based on failure rates in previous, discontinued clinical trials), as well as the inclusion of mechanistic biomarkers. This has been possible due, in part, to more recent flexibility in application of the FDA draft guidance. As a result of these changes, six new DED medications have been approved in the USA since the recommendations of the 2017 report[6], compared to only two between 2003 and 2016.

Summary

Table 1 links the various sections of the Digest report to the subclassification sections referred to in the TFOS DEWS III Diagnostic Methodology and Management and Therapy reports[7, 8], and describes how these sections inform readers of the drivers of DED.

Figure 2 provides an overview of the key findings from the various sections of the Digest report.

Table 1: *Digest sections & drivers of DED*

	Drivers of dry eye disease								
	Tear film deficiencies			Eyelid anomalies		Ocular surface abnormalities			
	Lipid	Aqueous	Mucin/glycocalyx	Blink/lid closure	Lid margin	Anatomical misalignment	Neural dysfunction	Ocular surface cell damage/disruption	Primary inflammation/ oxidative stress
Sex, gender & hormones	✓	✓				✓	✓	✓	✓
Epidemiology	✓	✓	✓		✓		✓	✓	✓
Pathophysiology	✓	✓	✓	✓	✓	✓	✓	✓	✓
Tear film	✓	✓	✓	✓	✓	✓			
Pain and sensation							✓	✓	✓
Iatrogeny	✓	✓	✓	✓	✓	✓	✓	✓	✓
Clinical trials design	✓	✓	✓		✓		✓	✓	✓

Figure 2: *Key findings from the various reports*

Key References

1. Stapleton F, Argueso P, Asbell P, et al. TFOS DEWS III Digest Report. *Am J Ophthalmol.* Jun 3 2025;Nov 2025;279:451-553.
2. Nelson JD, Craig JP, Akpek EK, et al. TFOS DEWS II Introduction. *Ocul Surf.* Jul 2017;15(3):269–275.
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5. Bron AJ, de Paiva CS, Chauhan SK, et al. TFOS DEWS II Pathophysiology Report. *Ocul Surf.* Jul 2017;15(3):438–510.
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7. Wolffsohn JS, Benitez-Del-Castillo J, Loya-Garcia D, et al. TFOS DEWS III Diagnostic Methodology. *Am J Ophthalmol.* May 30 2025;Nov 2025;279:387-450.
8. Jones L, Craig JP, Markoulli M, et al. TFOS DEWS III Management and Therapy Report. *Am J Ophthalmol.* Jun 2 2025;Nov 2025;279:289-386.

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