Synopsis of TFOS (tear film and ocular surface society) DEWS (dry eye work shop) II Report, 2017

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The TFOS DEWS II report was published on 21 July 2017, revising the definition of dry eye disease (DED) and giving new insight into the way the disease is diagnosed and treated. The initial focus on DED began with the publication of the report of the National Eye Institute/Industry Workshop on Clinical Trials in Dry Eye in 1995. It was the first formal attempt to define and classify DED, in addition to reviewing its management, treatment, and the design of clinical trials. Now, 10 years later, progress continues with the publication of this 2017 Report of the TFOS (tear film and ocular surface society) International Dry Eye Workshop II (TFOS DEWS II). This workshop, a 2-year effort for 12 subcommittees made up of 150 experts from 23 countries, has led to the creation and publication of this substantial report (almost 400 pages).

The report has been divided into the following subheadings:
1. Definition and classification.
2. Sex, gender and hormones.
3. Epidemiology.
4. Tear film.
5. Pain and sensation.
6. Pathophysiology.
7. Iatrogenic dry eye.
8. Diagnostic methodology.
10. Clinical trial design.
11. Public awareness and education.
12. Industry liaison.

Definition and Classification
The revised definition of DED acknowledged the significant role of inflammation and hyperosmolarity within the DED pathway. ‘Dry eye is 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’.

The loss of tear film homeostasis can arise from a multitude of factors that encompass eyelid and blink abnormalities, in addition to ocular surface or tear component deficiencies. These changes can induce focal or global tear film instability and tear hyperosmolarity in response to excessive evaporation from the ocular surface, and are regarded as significant entry points that contribute to the pathogenesis and perpetuation of a cycle of events, or ‘Vicious Circle’, in DED. Mounting evidence of the potential role of neurosensory abnormalities in the understanding and management of DED. Neuropathic pain occurs due to overt damage within the somatosensory nervous system, distinguishing it from DED. Nociceptive pain occurs in response to local tissue damage.

Classification

Sex, gender and hormones
Female sex is an established risk factor for DED-related autoimmune diseases such as Sjogren syndrome. Female sex is also among the most widely studied and consistently identified risk factors for DED throughout the world. Sex, gender and hormones exert significant influence on the ocular surface and adnexa, and play a significant role in the pathogenesis of aqueous-deficient and evaporative DED. However, further studies are required to clarify the precise nature, extent, and mechanisms of these sex, endocrine and gender effects on the eye in health and disease. A better understanding how these factors influence the pathophysiology of DED may result in improved, more tailored and appropriate options for the treatment of DED.
Epidemiology
The epidemiology of DED continues to be a challenge due to the lack of a standardized worldwide definition. This has resulted in epidemiologic studies using different diagnostic criteria based on symptoms and signs and self-reported diagnoses. A meta-analysis of published prevalence data estimated the impact of age and sex. Global mapping of prevalence was undertaken. The prevalence of DED ranged from 5 to 50%. The prevalence of signs was higher and more variable than symptoms. The meta-analysis confirmed that prevalence increases with age; however, signs showed a greater increase per decade than symptoms. Women have a higher prevalence of DED than men, although differences become significant only with age. Risk factors were categorized as modifiable/non-modifiable, and as consistent, probable or inconclusive. Asian ethnicity was a mostly consistent risk factor. While disease definitions vary between studies, the prevalence of disease increases with age and females are more frequently affected, with the exception of MGD where sex effects are more equivocal. Limited studies have been carried out in youth and there remains a need for studies in populations below 40 years of age. Prevalence appears to be higher in Asian than in Caucasian populations, although studies have not been conducted in major geographic regions. There are limited studies of both disease incidence and the natural history of treated and untreated disease, both of which remain future needs for this field.

Tear film
Clinically, DED is characterized by loss of tear volume, more rapid breakup of the tear film and increased evaporation of tears from the ocular surface. The tear film is composed of many substances including lipids, proteins, mucins and electrolytes. All of these contribute to the integrity of the tear film, but exactly how they interact is still an area of active research. Tear film osmolarity increases in DED. Changes to other components such as proteins and mucins can be used as biomarkers for DED.

DED implies major changes to the tear film structure and function, which are associated with this disease. Historically, the tear film has been viewed as a 3-layer ‘sandwich’ composed of distinct lipid, aqueous and mucin layers. Evidence continues to support the more contemporary two-phase model of the tear film, with a lipid layer overlying a mucus aqueous phase. While it may be that the whole tear film (lipids, mucins, proteins and salts) prevents tear film evaporation and collapse, additional studies are needed to confirm or deny this concept. While tear proteins are reported to change in DED, no definitive set of proteins or changes in protein levels have been validated to aid in diagnosis. There is a need to further characterize the biochemistry of the tear film to identify new markers that can be used to diagnose, and perhaps predict and treat, DED. There is also a need for ways to dynamically measure tear film osmolarity and markers of inflammation over the whole ocular surface.

Pathophysiology
Its central mechanism is evaporative water loss leading to hyperosmolar tissue damage which, either directly or by inducing inflammation, causes a loss of both epithelial and goblet cells. The consequent decrease in surface wettability leads to early tear film breakup and amplifies hyperosmolarity via a Vicious Circle. Pain in dry eye is caused by tear hyperosmolarity, loss of lubrication, inflammatory mediators and neurosensory factors, while visual symptoms arise from tear and ocular surface irregularity. Increased friction targets damage to the lids and ocular surface, resulting in characteristic punctate epithelial keratitis, superior limbal keratoconjunctivitis, filamentary keratitis, lid parallel conjunctival folds, and lid wiper epitheliopathy. Hybrid DED, with features of both aqueous deficiency and increased evaporation, is common and efforts should be made to determine the relative contribution of each form to the total picture.

Inflammation of the ocular surface can cause inhibition of lacrimal secretion and loss of
epithelial barrier function at the ocular surface. Tear film breakup, leading to localized hyperosmolarity, can result in ocular surface damage either directly or through the cascade of inflammation that it initiates. Improved understanding of the role of subclinical inflammation in the early stages of DED also warrants further study.

Iatrogenic dry eye

Dry eye can be caused by a variety of iatrogenic interventions. The increasing number of patients looking for eye care or cosmetic procedures involving the eyes, together with a better understanding of the pathophysiological mechanisms of DED, have led to the need for a specific report about iatrogenic dry eye within the TFOS DEWS II. Topical medications can cause DED due to their allergic, toxic and immuno-inflammatory effects on the ocular surface. Preservatives, such as benzalkonium chloride, may further aggravate DED. A variety of systemic drugs can also induce DED secondary to multiple mechanisms. Moreover, the use of contact lens induces or is associated with DED. However, one of the most emblematic situations is DED caused by surgical procedures such as corneal refractive surgery as in laser-assisted in situ keratomileusis (LASIK) and keratoplasty due to the mechanisms intrinsic to the procedure (i.e. corneal nerve cutting) or even by the use of post-operative topical drugs. Cataract surgery, lid surgeries, botulinum toxin application and cosmetic procedures are also considered risk factors to iatrogenic DED, which can cause patient dissatisfaction, visual disturbance and poor surgical outcomes. Future recommendations for research include conducting further epidemiologic studies to better define risk factors, creating less toxic medications and preservatives, devising less invasive ophthalmic procedures, and developing strategies for the detection of early DED prior to surgical interventions.

Diagnostic methodology

The sensitivity and specificity of tests for the diagnosis of DED are dependent on the inclusion criteria for DED. If DED is suspected, screening with questionnaire such as the 5-item dry eye questionnaire (DEQ-5) or the ocular surface disease index (OSDI), will help to decide for further evaluation with tear break-up time (non-invasive methods preferred), tear film osmolarity determination, and ocular surface staining (that includes the cornea, conjunctiva and lid margin) with fluorescein and lissamine green. Identification of a disruption in tear film homeostasis with these tests allows a diagnosis of dry eye to be made. Other tests, such as meibography, lipid layer interferometry, evaporation and tear volume measurements can help clarify where the individual with DED falls on the evaporative and aqueous deficient DED subtype classification spectrum and promote the selection of appropriate therapeutic interventions.

Management and therapy

Restoration of tear film homeostasis is the ultimate goal in the management of DED, and this involves breaking the vicious circle of the disease. Management of DED is often difficult and challenging. In summary, the management of DED remains something of an art, not easily lending itself to a rigid, evidence-based algorithm that accommodates all patients with dry eye symptoms and signs. All eye care providers who treat DED must exercise their clinical expertise to judge the significance of each of the varied pathogenic processes (aqueous deficiency, MGD, inflammation, etc.) that may manifest similar subjective complaints and similar signs of disrupted ocular surface homeostasis.

Available options to treat DED have increased dramatically. The last decade has seen new developments in topical lubricants (particularly lipid-containing drops), autologous serum options, and punctual plug designs. There have been many new developments to help with lid hygiene, as well as the availability of new treatments for demodex infestation, devices to manage MGD, and rigid gas permeable scleral lenses. In addition to the various options to manage the inflammatory processes associated with DED that have come to market, the impact of dietary modifications (particularly the value of essential fatty acid supplements) is better understood and the potential value of various complementary medicines has come under discussion. While the prescribing of lubricants remains the mainstay of early treatment for DED, of particular value would be studies comparing the efficacy of products with and without lipids in evaporative and in aqueous-deficient DED. Studies to determine the impact of various formulations on tear film osmolarity and the duration of treatment required for changes to occur are also worthy of consideration, particularly for lubricants expected to influence tear film stability.

Clinical trials

In order to improve the quality of clinical trials going forward, to optimize resources, and increase the opportunity for novel therapeutics for patients with DED, the TFOS DEWS II Clinical Trials subcommittee has the following recommendations. First, that studies be conducted consistent with good clinical practice (GCP). This involves using GMP-quality clinical trial material. While this may be a daunting task, clinical trialists should consult colleagues and drug development experts who are familiar with this system of controls. This includes appropriate protections for the study subjects. GCP also requires compliance with
appropriate regulatory requirements in the jurisdiction of study conduct, and may require additional regulatory filings if the investigational shipment is prepared and shipped from another state or country. Design, treatments, and sample size need to align with the investigational treatment, the objectives of the study, and the phase of development.

References