Chapter

Introductory Chapter: Recent Advances in the Evaluation and Treatment of Dry Eye Disease

Danial Roshandel and Helia Ashourizadeh

1. Introduction

Dry eye disease (DED) is one of the most common ophthalmic disorders that is associated with significant vision-related, lifestyle, and economic burdens [1–3]. DED is defined as "a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles" [4]. The tear film is composed of a muco-aqueous layer protected by a lipid layer against evaporation and anchored to the corneal surface by a glycocalyx layer. Both the quantity and the quality of the tear film are important in maintaining ocular surface homeostasis [5]. Regardless of the underlying etiology, tear hyperosmolarity is the core component in the pathophysiology of the DED. It triggers a cascade of events that eventually leads to reduced expression of glycocalyx mucins, apoptotic death of surface epithelial cells, and loss of goblet cells, which in turn aggravates the hyperosmolarity state and produces a vicious circle [6]. An increase in tear osmolarity may result from decreased aqueous production, excessive evaporation, and, more commonly, a combination of both [4]. Both conditions manifest tear instability, defective tear film protection of the ocular surface, and surface damage.

The etiology, pathophysiology, diagnosis, evaluation, and treatment of DED have been studied and reviewed extensively. Due to the rapid growth of research data in this field, which has resulted in remarkable advances in understanding the risk factors, etiologies, and mechanisms of DED, along with the development of novel diagnostic and therapeutic strategies, regular updates on the recent findings and evidence are mandatory. For instance, a simple PubMed search using "dry eye disease" keyword returns more than 700 review articles (accessed on 1st May 2023), more than half of which have been published over the past 3 years.

2. Etiology and risk factors

DED is a multifactorial disorder with a complex interaction between intrinsic and extrinsic factors. Aging, hormonal changes, systemic diseases and medications, environmental conditions, contact lens wearing, eyelid abnormalities, and

meibomian gland dysfunction (MGD) have been implicated in the development of DED. In recent years, factors such as lifestyle, societal, and environmental changes have been highlighted in recent studies as potential risk factors for DED that can threaten ocular surface health. In addition, the emergence of the COVID-19 pandemic and issues related to lockdowns have brought factors such as prolonged use of electronic devices and face masks and limited access to medical care during the lockdown periods to researchers' attention as important risk factors for the development and/or worsening of DED [7–10]. The impact of lifestyle changes (e.g., increased screen time and reduced outdoor activity) and environmental challenges (e.g., global warming and food insecurity) on the development, course, and management of DED requires further studies. Computer vision syndrome is another example of emerging risk factor for DED [11]. Evidence regarding the genetic predisposition to DED are limited, though further investigation can improve our understanding of the etiology and mechanisms of DED [12].

3. Diagnosis, classification, and evaluation

Diagnosis, classification, and evaluation of DED have evolved significantly over the past decade. Ancillary tests have been used extensively for diagnosing DED, determining the severity, classifying the underlying pathophysiology, and monitoring the disease course and response to therapies. Although a range of standard methods for evaluation and classification of DED has been developed and validated, newer techniques and endpoints need further investigation before they can be used in clinical trials as outcome measures. The tear film and ocular surface dry eye workshop II Diagnostic Methodology Report recommends that several factors be considered when diagnosing and evaluating DED. These factors include evaluating the symptoms and assessing the impact on vision quality. In addition, tear stability, tear volume, tear film composition, ocular surface damage, inflammation, and eyelid co-morbidities [13]. Ocular surface disease index (OSDI) and dry eye questionnaire-5 (DEQ-5) are the most common questionnaires used in clinical settings including clinical trials and are recommended by the DEWS II for the initial evaluation of dry eye symptoms. A comprehensive review of available questionnaires used in clinical studies and practice can be found in TFOS DEWS II Epidemiology Report – 2017 and a thorough review article by Okumura and colleagues [1, 14].

Numerous methods have been described to assess tear film stability. The tear film breakup time (TBUT) measures the time between a complete blink and the appearance of the first break in the tear film. TBUT is typically measured by applying fluorescein and observing the appearance of dry spots (FTBUT). An abnormal result is indicated if dry spots appear in less than 10 seconds. TBUT tests can have drawbacks such as low sensitivity and specificity, the use of fluorescein, which can affect measurements, and an invasive nature that can be uncomfortable for patients [15, 16]. Noninvasive breakup time (NIBUT) measurements have become increasingly popular in clinical practice and research due to the limitations of standard TBUT tests. Specialized equipment such as corneal topography systems, keratometers, videokeratoscopy, and interferometry-aided devices are typically used to perform these measurements [17–20].

Thermography, aberrometry, osmolarity variability, and tear evaporation rate are other methods to assess tear stability [13]. Tear evaporation is usually assessed by studies on the tear film lipid layer (TFLL) and meibomian gland structure and

function. Several interferometry and thermography instruments have been introduced to measure the TFLL thickness and dynamics [21, 22]. Various methods are used to assess tear volume, including Schirmer's test without anesthesia and stimulation, which is the most popular method. Another technique to indirectly assess tear volume is strip meniscometry, which measures the lower tear meniscus volume. Tear meniscus height (TMH) can also be measured using slit-lamp bio-microscopy or digital imaging to estimate tear volume and determine aqueous deficient severity. Recently, optical coherence tomography (OCT) has emerged as a more precise method to measure tear film-related parameters. Staining of the cornea, conjunctiva, or lid margin by the fluorescein and/or Lissamine green is a reliable marker of ocular surface damage in the setting of DED. In vivo confocal microscopy [23], impression cytology [24], and ocular surface sensitivity [25] assessment are other methods to evaluate surface damage.

4. Treatment

Treatment strategies may vary depending on factors such as the type of DED (i.e., aqueous tear deficiency, evaporative tear deficiency, or combination of both), disease severity according to clinical signs (e.g., ocular surface damage) and subjective symptoms (e.g., blurred vision, pain, etc.), impact on the daily living activities and quality of life, and the underlying condition. While most mild cases can be managed by conservative measures, severe cases with a major impact on the quality of life may require a more aggressive treatment or surgical intervention.

Lubricating agents such as artificial tears are the mainstay of the treatment of DED. Numerous formulations and combinations of artificial tears are commercially available [26]. In addition, multiple new formulations and compounds are under investigation in clinical trials (e.g., NCT04701086, NCT05356728, and NCT04702776). Anti-inflammatory drops play an indispensable role in the management of moderate to severe dry eye, especially DED associated with Sjögren syndrome (SS). While corticosteroids and nonsteroidal anti-inflammatory drops such as cyclosporine and tacrolimus eye drops are being widely used for the treatment of DED in primary SS and chronic graft versus host disease [27, 28], novel agents are under investigation in various clinical trials (e.g., NCT04819269, NCT05201170 and NCT04792580).

MGD is a major cause of evaporative dry eye. Evaluation and management of MGD can be challenging. Noninvasive assessment of using in vivo confocal microscopy and anterior segment OCT can provide useful information regarding the structure and function of the meibomian glands [29]. Warm compress and lid hygiene are still the main treatments for MGD. Other methods such as intense pulsed light and vectored thermal pulsation therapy have shown promising results [30, 31].

Although conservative and medical treatments can effectively ameliorate the symptoms of DED in many patients, severe cases may require additional measures including scleral contact lenses such as prosthetic replacement of the ocular surface ecosystem [32], minimally invasive interventions such as temporary or permanent punctal occlusion [33], or more invasive surgeries such as tarsorrhaphy and salivary gland and oral mucosal grafting [34, 35]. A combination of these approaches may be used in extreme cases to prevent devastating complications such as corneal perforation.

5. Conclusion

The emergence of lifestyle, environmental, and societal risk factors and development of novel evaluation techniques and treatment strategies for DED warrants regular updates on the most recent advances and their impact on the practice pattern. The prolonged use of visual display terminals continues to be a growing concern regarding ocular surface health and can be a major risk factor for DED in the coming years. Global warming and air pollution are other potential major risk factors for DED in the future. Recent advances in the objective assessment of the tear film and meibomian glands were useful for the classification and evaluation of DED and are gaining popularity as accurate and reliable outcome measures in DED clinical trials. Similarly, artificial tear formulations have evolved notably, which may result in better ocular surface protection index and more efficient and prolonged symptom relief. In addition, novel topical anti-inflammatory drugs that selectively block immunologic responses in the ocular surface have shown promising results in clinical trials. Finally, cell and gene-based therapies may offer permanent solution for DED in certain circumstances, which requires further exploration in the future.

Author details

Danial Roshandel[1*] and Helia Ashourizadeh[2]

1 Centre for Ophthalmology and Visual Science (incorporating Lions Eye Institute), Perth, Western Australia, Australia

2 Department of Ophthalmology, Mayo Clinic, Rochester, USA

*Address all correspondence to: danial.roshandel@uwa.edu.au

References

[1] Stapleton F, Alves M, Bunya VY, Jalbert I, Lekhanont K, Malet F, et al. TFOS DEWS II epidemiology report. The Ocular Surface. 2017;**3**:334-365. DOI: 10.1016/j.jtos.2017.05.003

[2] McDonald M, Patel DA, Keith MS, Snedecor SJ. Economic and humanistic burden of dry eye disease in Europe, North America, and Asia: A systematic literature review. The Ocular Surface. 2016;**2**:144-167. DOI: 10.1016/j.jtos.2015.11.002

[3] Morthen MK, Magno MS, Utheim TP, Snieder H, Jansonius N, Hammond CJ, et al. The vision-related burden of dry eye. The Ocular Surface. 2022;**23**:207-215. DOI: 10.1016/j.jtos.2021.10.007

[4] Craig JP, Nichols KK, Akpek EK, Caffery B, Dua HS, Joo CK, et al. TFOS DEWS II definition and classification report. The Ocular Surface. 2017;**3**:276-283. DOI: 10.1016/j.jtos.2017.05.008

[5] Willcox MDP, Argueso P, Georgiev GA, Holopainen JM, Laurie GW, Millar TJ, et al. TFOS DEWS II tear film report. The Ocular Surface. 2017;**3**:366-403. DOI: 10.1016/j.jtos.2017.03.006

[6] Bron AJ, de Paiva CS, Chauhan SK, Bonini S, Gabison EE, Jain S, et al. TFOS DEWS II pathophysiology report. The Ocular Surface. 2017;**3**:438-510. DOI: 10.1016/j.jtos.2017.05.011

[7] Burgos-Blasco B, Arriola-Villalobos P, Fernandez-Vigo JI, Oribio-Quinto C, Ariño-Gutierrez M, Diaz-Valle D, et al. Face mask use and effects on the ocular surface health: A comprehensive review. The Ocular Surface. 2023;**27**:56-66. DOI: 10.1016/j.jtos.2022.12.006

[8] Galor A, Britten-Jones AC, Feng Y, Ferrari G, Goldblum D, Gupta PK, et al. TFOS lifestyle: Impact of lifestyle challenges on the ocular surface. The Ocular Surface. 2023;**28**:262-303. DOI: 10.1016/j.jtos.2023.04.008

[9] Alves M, Asbell P, Dogru M, Giannaccare G, Grau A, Gregory D, et al. TFOS lifestyle report: Impact of environmental conditions on the ocular surface. The Ocular Surface. 2023;**29**:1-52. DOI: 10.1016/j.jtos.2023.04.007

[10] Stapleton F, Abad JC, Barabino S, Burnett A, Iyer G, Lekhanont K, et al. TFOS lifestyle: Impact of societal challenges on the ocular surface. The Ocular Surface. 2023;**28**:165-199. DOI: 10.1016/j.jtos.2023.04.006

[11] Pavel IA, Bogdanici CM, Donica VC, Anton N, Savu B, Chiriac CP, et al. Computer vision syndrome: An ophthalmic pathology of the modern era. Medicina (Kaunas, Lithuania). 2023;**59**(2). DOI: 10.3390/medicina59020412

[12] Roshandel D, Semnani F, Rayati Damavandi A, Masoudi A, Baradaran-Rafii A, Watson SL, et al. Genetic predisposition to ocular surface disorders and opportunities for gene-based therapies. The Ocular Surface. 2023;**29**:150-165. DOI: 10.1016/j.jtos.2023.05.003

[13] Wolffsohn JS, Arita R, Chalmers R, Djalilian A, Dogru M, Dumbleton K, et al. TFOS DEWS II diagnostic methodology report. The Ocular Surface. 2017;**3**:539-574. DOI: 10.1016/j.jtos.2017.05.001

[14] Okumura Y, Inomata T, Iwata N, Sung J, Fujimoto K, Fujio K, et al. A review of dry eye questionnaires: Measuring patient-reported outcomes

and health-related quality of life. Diagnostics (Basel). 2020;**10**(8):559. DOI: 10.3390/diagnostics10080559

[15] Trees GR, Tomlinson A. Effect of artificial tear solutions and saline on tear film evaporation. Optometry and Vision Science. 1990;**12**:886-890. DOI: 10.1097/00006324-199012000-00002

[16] Vitali C, Moutsopoulos HM, Bombardieri S. The European Community study group on diagnostic criteria for Sjogren's syndrome. Sensitivity and specificity of tests for ocular and oral involvement in Sjogren's syndrome. Annals of the Rheumatic Diseases. 1994;**53**(10):637-647. DOI: 10.1136/ard.53.10.637

[17] Blackie CA, Solomon JD, Scaffidi RC, Greiner JV, Lemp MA, Korb DR. The relationship between dry eye symptoms and lipid layer thickness. Cornea. 2009;**7**:789-794. DOI: 10.1097/ICO.0b013e318191b870

[18] Alonso-Caneiro D, Iskander DR, Collins MJ. Tear film surface quality with soft contact lenses using dynamic-area high-speed videokeratoscopy. Eye & Contact Lens. 2009;**5**:227-231. DOI: 10.1097/ICL.0b013e3181b3350f

[19] Mengher LS, Bron AJ, Tonge SR, Gilbert DJ. A non-invasive instrument for clinical assessment of the pre-corneal tear film stability. Current Eye Research. 1985;**1**:1-7. DOI: 10.3109/02713688508999960

[20] Liu Z, Pflugfelder SC. Corneal surface regularity and the effect of artificial tears in aqueous tear deficiency. Ophthalmology. 1999;**5**:939-943. DOI: 10.1016/S0161-6420(99)00513-8

[21] Bai Y, Ngo W, Nichols JJ. Characterization of the thickness of the tear film lipid layer using high resolution microscopy. The Ocular Surface. 2019;**2**:356-359. DOI: 10.1016/j.jtos.2018.12.003

[22] Purslow C, Wolffsohn JS, Santodomingo-Rubido J. The effect of contact lens wear on dynamic ocular surface temperature. Contact Lens & Anterior Eye. 2005;**1**:29-36. DOI: 10.1016/j.clae.2004.10.001

[23] Alhatem A, Cavalcanti B, Hamrah P. In vivo confocal microscopy in dry eye disease and related conditions. Seminars in Ophthalmology. 2012;**5-6**:138-148. DOI: 10.3109/08820538.2012.711416

[24] Tole DM, McKelvie PA, Daniell M. Reliability of impression cytology for the diagnosis of ocular surface squamous neoplasia employing the biopore membrane. The British Journal of Ophthalmology. 2001;**2**:154-158. DOI: 10.1136/bjo.85.2.154

[25] Belmonte C, Nichols JJ, Cox SM, Brock JA, Begley CG, Bereiter DA, et al. TFOS DEWS II pain and sensation report. The Ocular Surface. 2017;**3**:404-437. DOI: 10.1016/j.jtos.2017.05.002

[26] Semp DA, Beeson D, Sheppard AL, Dutta D, Wolffsohn JS. Artificial tears: A systematic review. Clinical Optometry (Auckl). 2023;**15**:9-27. DOI: 10.2147/opto.S350185

[27] Shih KC, Lun CN, Jhanji V, Thong BY, Tong L. Systematic review of randomized controlled trials in the treatment of dry eye disease in Sjogren syndrome. Journal of Inflammation (London, England). 2017;**14**:26. DOI: 10.1186/s12950-017-0174-3

[28] Tappeiner C, Heiligenhaus A, Halter JP, Miserocchi E, Bandello F, Goldblum D. Challenges and concepts in the diagnosis and management of ocular

graft-versus-host disease. Frontiers in Medicine (Lausanne). 2023;**10**:1133381. DOI: 10.3389/fmed.2023.1133381

[29] Binotti WW, Bayraktutar B, Ozmen MC, Cox SM, Hamrah P. A review of imaging biomarkers of the ocular surface. Eye & Contact Lens. 2020;**46**(Suppl 2):S84-S105. DOI: 10.1097/icl.0000000000000684

[30] Jang JH, Lee K, Nam SH, Kim J, Kim JY, Tchah H, et al. Comparison of clinical outcomes between intense pulsed light therapy using two different filters in meibomian gland dysfunction: Prospective randomized study. Scientific Reports. 2023;**1**:6700. DOI: 10.1038/s41598-023-33526-z

[31] Novo-Diez A, López-Miguel A, Fernández I, Blanco-Vázquez M, Valencia-Sandonís C, Enríquez-de-Salamanca A, et al. Effect of a single vectored thermal pulsation treatment of Meibomian gland dysfunction patients under controlled environmental conditions. Scientific Reports. 2022;**1**:16761. DOI: 10.1038/s41598-022-20994-y

[32] Asghari B, Brocks D, Carrasquillo KG, Crowley E. OSDI outcomes based on patient demographic and Wear patterns in prosthetic replacement of the ocular surface ecosystem. Clinical Optometry (Auckl). 2022;**14**:1-12. DOI: 10.2147/opto.S337920

[33] Kuroda K, Toshida H, Sorita Y, Ichikawa K, Matsuzaki Y, Ohta T. Surgical punctal occlusion; combined lacrimal canaliculi cauterization and punctal suturing for severe dry eye. Journal of Ophthalmic & Vision Research. 2023;**2**:143-149. DOI: 10.18502/jovr.v18i2.13179

[34] Kate A, Deshmukh R, Donthineni PR, Sharma N, Vajpayee RB, Basu S. Management of corneal perforations in dry eye disease: Preferred practice pattern guidelines. Indian Journal of Ophthalmology. 2023;**4**:1373-1381. DOI: 10.4103/ijo.Ijo_2826_22

[35] Wakamatsu TH, Sant' Anna A, Cristovam PC, Alves VAF. Wakamatsu a and Gomes JAP: Minor salivary gland transplantation for severe dry eyes. Cornea. 2017;**36**(Suppl 1):S26-S33. DOI: 10.1097/ico.0000000000001358