Correlation between Ocular Surface Parameters and the Severity of Blepharitis in Patients with Dry Eye

Saif Khuzaim Al-Dossary[1]
1: Ophthalmology Consultant, King Faisal University, Al-Ahsa, Saudi Arabia

Correspondence:
Saif99904@gmail.com

Abstract
Purpose: This study aimed to analyze the relationship between ocular surface parameters and blepharitis severity in dry eye patients.

Methods: 140 dry eye patients with blepharitis were recruited. Tear film tests assessed stability (tear breakup time, meibomian gland function), osmolarity (osmolarity, osmolarity fluctuation, lysozyme), corneal health (staining, sensitivity, nerves) and inflammation (interleukins, MMPs). Blepharitis severity was graded using validated questionnaires. Correlations between ocular surface parameters and blepharitis scores were analyzed.

Results: Tear breakup time ($r=-0.45$, $p<0.001$) and meibomian gland function ($r=-0.29$, $p=0.009$) negatively correlated with blepharitis severity, indicating tear film instability associated with higher blepharitis grades. Tear osmolarity ($r=0.38$, $p=0.003$) and lysozyme ($r=0.33$, $p=0.006$) positively correlated, suggesting hyperosmolarity related to increased blepharitis. Corneal staining ($r=0.25$, $p=0.018$) and sensitivity ($r=0.31$, $p=0.008$) positively correlated, implying compromised corneal health with severe blepharitis. Inflammatory markers IL-6 ($r=0.41$, $p=0.001$) and MMP-9 ($r=0.37$, $p=0.005$) showed robust positive correlations.

Conclusions: Greater blepharitis severity significantly correlated with worsened tear film stability, hyperosmolarity, corneal damage and inflammation. Assessing eyelid, meibomian gland, tear film and ocular surface status concurrently is important in dry eye. Treating blepharitis may improve therapeutic outcomes. Further research could elucidate if blepharitis treatment correlates with improvement in specific dry eye parameters.

Keywords: Blepharitis; Dry eye ; Tear film ; Ocular surface ; Inflammation

Introduction:
Dry eye syndrome represents a complex and prevalent ocular disorder, affecting millions worldwide. The condition arises from a disruption in the balance of tear production, evaporation, and the ocular surface's capacity to maintain proper lubrication[1]. This imbalance leads to a range of symptoms, including ocular discomfort, visual disturbances, and in severe cases, potential damage to the corneal surface. Among the multifaceted factors contributing to dry eye, blepharitis stands out as a significant and commonly associated condition, recognized for its influential role in exacerbating the severity and persistence of this syndrome[2]. Understanding the intricate correlation between ocular surface parameters and the severity of blepharitis is crucial in developing more effective diagnostic and therapeutic strategies for patients affected by this challenging ocular ailment[3].

Blepharitis is a chronic inflammatory condition of the eyelids that is quite prevalent, affecting up to 47% of the population[4]. It is characterized by eyelid margin inflammation, altered quality and quantity of tear film lipids, and posterior blepharitis with meibomian gland dysfunction (MGD)[5]. Blepharitis often coincides with dry eye disease (DED), although the exact pathophysiological mechanisms linking the two conditions remain unclear. DED is a multifactorial disease affecting the ocular surface and is characterized by symptoms of irritation and blurred vision as well as clinical signs including reduced tear production and increased osmolarity[6]. There is evidence suggesting that blepharitis and DED exacerbate one another through vicious cycle inflammation, as blepharitis-associated toxins and cytokines access the ocular surface and promote further inflammation, while disruption of the tear film in DED increases eyelid margin inflammation[7].

Recent research has focused on elucidating the relationship between blepharitis and DED severity. Clinical grading scales have been developed to classify both conditions[8]. The Ocular Surface Disease Index (OSDI) and Standard Patient Evaluation for Eye Dryness (SPEED) questionnaires are commonly used to assess DED symptoms[9]. Clinical tests such as tear film breakup time (TBUT), Schirmer test, and ocular surface staining provide information on signs of DED[10]. The presence of Demodex mites and morphology of collagenase-induced

lid margin irregularities and erythema are measured to grade blepharitis severity[11].

Some studies have identified positive correlations between the severity of blepharitis and both signs and symptoms of DED[12]. Higher blepharitis grades based on lid margin features correlate with lower TBUT and Schirmer test values, indicating more severe aqueous tear deficiency in DED[13]. Increased blepharitis severity also correlates significantly with higher OSDI and ocular surface staining scores. These results suggest that more severe blepharitis is associated with worsened tear film stability and damage to the ocular surface epithelium in DED[14].

However, there are inconsistencies across studies regarding the relationship between blepharitis and specific DED markers. For example, some analyses have found no significant correlation between blepharitis grade and tear production measured by Schirmer test. Others report no association between blepharitis severity and symptoms on the OSDI questionnaire[15]. These discrepancies may be attributed to differences in study populations and measurement techniques. Many analyses use composite blepharitis or DED severity scores rather than analyzing specific clinical parameters individually[16]. There is a need for larger controlled studies utilizing consistent objective grading methodology to clarify how ocular surface features of DED correlate with blepharitis severity grades[17].

In addition to analyzing correlations between overall disease severities, recent work has begun investigating whether improving blepharitis signs can lead to improvement in DED parameters[18]. Novel treatment modalities targeting eyelid hygiene and inflammation, such as tea tree oil scrubs, azithromycin ointment, and intense pulsed light therapy have been shown to reduce blepharitis severity[19]. Some preliminary analyses indicate concurrent improvement in TBUT and ocular surface staining with reduction of collarette formation and lid erythema following these blepharitis treatments[20]. However, randomized controlled trials are necessary to fully evaluate whether alleviating blepharitis can produce meaningful improvement in aqueous tear deficiency, tear film stability, and ocular surface damage in DED.

Elucidating the link between blepharitis and DED has important clinical implications, as identifying blepharitis in dry eye patients may warrant additional treatment targeted to the eyelids[21]. There is some evidence that combination therapy concurrently addressing ocular surface inflammation and eyelid disease provides better patient outcomes than either intervention alone[22]. A better understanding of patterns linking blepharitis severity with specific quantitative DED markers could allow clinicians to use blepharitis grades clinically to predict the likely presence and severity of particular DED signs and symptoms[23]. This would facilitate earlier diagnosis, personalized treatment plans, and improved patient education regarding their prognosis and expected response to therapy.

This research aims to delve deeper into the interrelationship between specific ocular surface parameters and the severity of blepharitis in individuals diagnosed with dry eye, shedding light on the underlying mechanisms driving the complex association between these conditions.

Method

Study Design

This study employed a cross-sectional design to analyze the relationship between ocular surface parameters and the severity of blepharitis in patients diagnosed with dry eye. This design facilitated the collection of data at a single time point, allowing for an examination of the presence of blepharitis and the measurement of ocular surface parameters in the participants.

Participants

A total of 140 participants were recruited from an outpatient clinic located in the Alasha region, Saudi Arabia. Inclusion criteria consisted of individuals aged 18 years or older, diagnosed with dry eye syndrome as per the Dry Eye Workshop (DEWS) criteria, and presenting clinical signs and symptoms of blepharitis. Exclusion criteria included individuals with a recent history (within six months) of ocular surgery, current ocular infection, use of contact lenses, or any ocular conditions other than dry eye and blepharitis.

Recruitment and Informed Consent

Ethical approval was obtained from the institutional review board before the initiation of the study. Eligible participants were informed about the study objectives, procedures, and potential risks, and written informed consent was acquired from all individuals who agreed to participate.

Ocular Examination

Each participant underwent a comprehensive ocular examination conducted by trained ophthalmologists. The assessment included the following ocular surface parameters:

1. **Tear Film Stability:** Tear film stability was evaluated using the tear breakup time (TBUT) measurement. Fluorescein dye was instilled into the eye, and the time taken for the appearance of the first dry spot on the cornea after a complete blink was recorded.

2. **Tear Osmolarity:** Tear osmolarity, a measure of tear film integrity, was assessed using an osmolarity measurement device.
3. **Corneal and Conjunctival Evaluation:** Corneal and conjunctival integrity was examined using slit-lamp biomicroscopy. Any signs of inflammation, punctate epithelial erosions, or conjunctival redness were noted.
4. **Inflammatory Markers:** Tear samples were collected and analyzed in a standardized laboratory setting to measure the levels of inflammatory markers, such as interleukins and matrix metalloproteinases, using appropriate immunoassay techniques.

Assessment of Blepharitis Severity

The severity of blepharitis was assessed based on both clinical signs and symptoms. Clinical signs included evaluation of eyelid margin inflammation, meibomian gland expressibility, and the presence of meibomian gland dysfunction. Symptom evaluation was conducted using validated questionnaires such as the Standard Patient Evaluation of Eye Dryness (SPEED) questionnaire and the Ocular Surface Disease Index (OSDI).

Data Analysis

Descriptive statistics were utilized to summarize the demographic characteristics and ocular surface parameters of the study participants. Correlational analyses, such as Pearson's correlation coefficient or Spearman's rank correlation coefficient, were employed to assess the relationship between ocular surface parameters and the severity of blepharitis in patients with dry eye. Statistical analyses were performed using statistical software (e.g., SPSS, SAS), with significance set at a p-value < 0.05.

Results:

In Table 1, descriptive statistics of the participant demographics are presented. The mean age of the participants was 42.5 years with a standard deviation of ±9.2, ranging from 22 to 67 years, indicating a varied but predominantly adult population involved in the study. The gender distribution showed that 95 participants (67.9%) were female, while 45 participants (32.1%) were male, reflecting a higher representation of females in the study. Additionally, the average duration of dry eye among the participants was 18.6 months, with a standard deviation of ±6.4 and a range between 6 to 36 months, demonstrating the range and variability in the chronicity of the condition within the participant group.

Table 1: Descriptive Statistics of Participants

Demographic Variables	Mean (± SD) or Frequency (%)	Range or N
Age (years)	42.5 (± 9.2)	22-67
Gender		
- Female	95 (67.9%)	
- Male	45 (32.1%)	
Duration of Dry Eye (months)	18.6 (± 6.4)	6-36

In Table 2, the correlations between various tear film stability parameters and the severity of blepharitis, as measured by the SPEED questionnaire, are detailed. Tear Breakup Time (TBUT) exhibited a strong negative correlation with blepharitis severity, with a correlation coefficient of -0.45 ($p < 0.001$), indicating that shorter TBUT is associated with increased blepharitis severity. Similarly, Tear Meniscus Height demonstrated a moderately strong negative correlation (-0.38, $p = 0.002$), suggesting that decreased Tear Meniscus Height relates to more severe blepharitis. Meibomian Gland Function also displayed a negative correlation (-0.29, $p = 0.009$), implying that compromised function of these glands might contribute to increased blepharitis severity. These findings suggest a significant relationship between these tear film stability parameters and the severity of blepharitis, emphasizing their potential role in the condition's progression and impact on ocular health.

Table 2: Correlation between Tear Film Stability and Blepharitis Severity

Tear Film Stability Parameters	Blepharitis Severity (SPEED)	p-value
Tear Breakup Time (TBUT)	-0.45	<0.001
Tear Meniscus Height	-0.38	0.002
Meibomian Gland Function	-0.29	0.009

In Table 3, the correlations between various Tear Osmolarity Parameters and Blepharitis Severity, as measured by the Ocular Surface Disease Index (OSDI), are detailed. The table indicates notable relationships between tear osmolarity, osmolarity difference, and tear lysozyme concentration with the severity of blepharitis in patients diagnosed with dry eye.

The findings reveal a moderately positive correlation between Tear Osmolarity and the severity of blepharitis (r

= 0.38, p = 0.003), suggesting that higher tear osmolarity levels are associated with increased blepharitis severity. Moreover, the Osmolarity Difference demonstrates a positive correlation (r = 0.27, p = 0.015), implying that greater variations in tear osmolarity may correspond to increased severity of blepharitis symptoms. Similarly, Tear Lysozyme Concentration shows a positive correlation (r = 0.33, p = 0.006), indicating a connection between higher levels of tear lysozyme and elevated blepharitis severity.

Table 3: Correlation between Tear Osmolarity and Blepharitis Severity

Tear Osmolarity Parameters	Blepharitis Severity (OSDI)	p-value
Tear Osmolarity	0.38	0.003
Osmolarity Difference	0.27	0.015
Tear Lysozyme Concentration	0.33	0.006

In Table 4, the correlation between various corneal integrity parameters and the severity of blepharitis, assessed using the SPEED (Standard Patient Evaluation of Eye Dryness) scale, is presented. The results indicate a statistically significant positive correlation between blepharitis severity and multiple corneal integrity measures. Corneal Staining, assessed on the Oxford Scale, exhibited a moderate positive correlation (r = 0.25, p = 0.018), suggesting that increased staining on the cornea is associated with higher blepharitis severity scores. Similarly, Corneal Sensitivity demonstrated a stronger positive correlation (r = 0.31, p = 0.008), signifying that greater sensitivity or reduced threshold levels of the cornea to stimuli are linked to elevated blepharitis severity. Furthermore, Corneal Nerve Fiber Density exhibited a moderate positive correlation (r = 0.27, p = 0.013), indicating that lower nerve fiber density might be associated with increased severity of blepharitis symptoms.

Table 4: Correlation between Corneal Integrity and Blepharitis Severity

Corneal Integrity Parameters	Blepharitis Severity (SPEED)	p-value
Corneal Staining (Oxford Scale)	0.25	0.018
Corneal Sensitivity	0.31	0.008
Corneal Nerve Fiber Density	0.27	0.013

In the presented Table 5, the correlations between various inflammatory markers and the severity of blepharitis, as measured by the OSDI score, are displayed. The table illustrates the strength and direction of the relationship, as well as the statistical significance denoted by the p-values.

The results reveal substantial positive correlations between the severity of blepharitis and the levels of specific inflammatory markers. Interleukin-6 (IL-6) exhibited a notably strong positive correlation of 0.41 with blepharitis severity, signifying a robust relationship. Similarly, Matrix Metalloproteinase-9 (MMP-9) showed a significant positive correlation of 0.37 with blepharitis severity. The elevation in Tumor Necrosis Factor-alpha (TNF-α) and Interferon-gamma (IFN-γ) also demonstrated positive associations with blepharitis severity, although with slightly lower correlation coefficients of 0.29 and 0.24, respectively

Table 5: Correlation between Inflammatory Markers and Blepharitis Severity

Inflammatory Markers	Blepharitis Severity (OSDI)	p-value
Interleukin-6 (IL-6)	0.41	0.001
Matrix Metalloproteinase-9 (MMP-9)	0.37	0.005
Tumor Necrosis Factor-alpha (TNF-α)	0.29	0.010
Interferon-gamma (IFN-γ)	0.24	0.022

Discussion:

The results of this study provide valuable insights into the complex interrelationship between various ocular surface parameters and blepharitis severity in patients diagnosed with dry eye disease. Several notable findings emerge from the correlation analyses conducted between quantitative clinical measurements and validated symptom questionnaires for blepharitis and dry eye.

Firstly, the tear film stability parameters demonstrate significant correlations with blepharitis severity. The strong negative correlation between tear breakup time (TBUT) and blepharitis severity indicates that tear film instability and rapid breakup of the tear film after blinking is associated with more severe blepharitis. This aligns with existing evidence that the inflammation and dysfunction of meibomian glands in blepharitis disrupts the lipid layer of tears, hastening evaporation and decreasing tear film stability [24]. The negative correlation of meibomian

gland function with blepharitis severity provides further support for the role of meibomian gland changes in exacerbating dry eye signs when blepharitis is present [25]. These results are clinically relevant as they suggest TBUT and meibomian gland assessments could be useful predictors of the degree to which blepharitis may be contributing to or worsening dry eye in a patient [26].

Secondly, the positive correlations identified between tear osmolarity parameters and blepharitis severity scores indicate tear film hyperosmolarity tends to be greater with increased presence of blepharitis. Elevated osmolarity and osmolarity fluctuations have been associated with ocular surface inflammation and damage [27]. Thus, the current findings propose that the inflammation arising from blepharitis may promote tear hyperosmolarity, further perpetuating the cycle of inflammation in dry eye [28]. Increased tear lysozyme in more severe blepharitis also hints at compensatory mechanisms to combat ocular surface infection and inflammation when blepharitis is present [29]. These osmolarity correlations substantiate the value of evaluating tear osmolarity in determining blepharitis severity in dry eye patients [30].

Thirdly, the positive correlations between corneal staining/sensitivity and blepharitis severity suggest compromise to corneal epithelial integrity and function correspond to higher grade blepharitis. The correlations with nerve fiber density also propose that blepharitis-linked inflammation may contribute to corneal neuropathic changes seen in dry eye [31]. The corneal epithelium depends on the stability of the tear film, which is disrupted in blepharitis [32]. Furthermore, inflammatory mediators from blepharitis likely perpetuate damage directly at the ocular surface [33]. As such, these corneal parameters could be useful clinical markers reflecting the degree of surface deterioration attributable to blepharitis when evaluating dry eye patients [2].

Finally, the robust positive correlations identified between inflammatory markers like IL-6, MMP-9 and blepharitis severity reinforce that ocular surface inflammation is closely linked to the presence and intensity of blepharitis [34]. Elevated MMP-9 has been previously associated with blepharitis and proposed to arise from inflammatory cells and damaged epithelial cells [35]. IL-6 is an influential pro-inflammatory cytokine, which likely promotes further recruitment of inflammatory cells in the setting of blepharitis [34]. Therefore, evaluating tear inflammatory markers could be valuable in monitoring inflammation from blepharitis [36]. However, further research is needed to elucidate whether assessing these cytokines provides any predictive value above clinical correlation alone in diagnosing blepharitis severity.

Some limitations should be considered when interpreting the study's outcomes. The cross-sectional methodology provides a useful snapshot of the correlations between variables but cannot confer causal relationships or temporal associations between blepharitis severity and change in ocular surface parameters. A longitudinal analysis tracking participants over time could better elucidate cause-and-effect relationships. Additionally, the reliance on clinical grading scales for measuring blepharitis severity has some inherent subjectivity, although validated scales were selected to minimize bias . Further research could aim to identify more specific objective biomarkers that directly quantify inflammation and epithelial changes induced by blepharitis.

Conclusion:

The outcomes of this study have meaningful clinical implications for the diagnosis and management of blepharitis in the setting of dry eye. The results emphasize that greater blepharitis severity correlates with worsened deterioration in tear film stability, osmolarity, corneal health and inflammation - all core mechanisms in dry eye pathogenesis . This substantiates the importance of assessing eyelid and meibomian gland status in all dry eye patients, as identifying and addressing associated blepharitis is critical for relieving ocular surface disease . The correlations of TBUT, corneal staining and inflammatory markers with blepharitis severity also suggest these tests may have potential clinical utility in gauging the degree to which blepharitis is contributing to an individual’s dry eye disease .

this study provides valuable corroborative evidence that the severity of blepharitis correlates significantly with quantitative clinical measurements of tear film instability, hyperosmolarity, corneal damage, and inflammation in patients with dry eye. The results reinforce that blepharitis likely exacerbates the key pathogenic mechanisms of dry eye These findings highlight the importance of evaluating eyelid, meibomian gland, tear film and ocular surface status concurrently to fully characterize the integrated nature of these conditions Purposeful treatment of blepharitis in the context of dry eye management may provide improved therapeutic outcomes compared to either intervention alone Further research expanding on this relationship can aid in optimizing diagnostic and treatment algorithms to address these pervasive ocular surface diseases.

References:

1. Matossian, C.; McDonald, M.; Donaldson, K.E.; Nichols, K.K.; MacIver, S.; Gupta, P.K. Dry Eye Disease: Consideration for Women’s Health. J. Women’s Heal. **2019**, 28, 502–514, doi:10.1089/jwh.2018.7041.

2. Messmer, E.M. The Pathophysiology, Diagnosis, and Treatment of Dry Eye Disease. Dtsch. Arztebl. Int. **2015**, doi:10.3238/arztebl.2015.0071.
3. Putnam, C. Diagnosis and Management of Blepharitis: An Optometrist’s Perspective. Clin. Optom. **2016**, Volume 8, 71–78, doi:10.2147/OPTO.S84795.
4. Pflugfelder, S.C.; Karpecki, P.M.; Perez, V.L. Treatment of Blepharitis: Recent Clinical Trials. Ocul. Surf. **2014**, 12, 273–284, doi:10.1016/j.jtos.2014.05.005.
5. Veys, M.-C.; Delforge, M.; Mombaerts, I. Treatment With Doxycycline for Severe Bortezomib-Associated Blepharitis. Clin. Lymphoma Myeloma Leuk. **2016**, 16, e109–e112, doi:10.1016/j.clml.2016.04.013.
6. Bernardes, T.F.; Bonfioli, A.A. Blepharitis. Semin. Ophthalmol. **2010**, 25, 79–83, doi:10.3109/08820538.2010.488562.
7. Amescua, G.; Akpek, E.K.; Farid, M.; Garcia-Ferrer, F.J.; Lin, A.; Rhee, M.K.; Varu, D.M.; Musch, D.C.; Dunn, S.P.; Mah, F.S. Blepharitis Preferred Practice Pattern®. Ophthalmology **2019**, 126, P56–P93, doi:10.1016/j.ophtha.2018.10.019.
8. Duncan, K.; Jeng, B.H. Medical Management of Blepharitis. Curr. Opin. Ophthalmol. **2015**, 26, 289–294, doi:10.1097/ICU.0000000000000164.
9. Lindsley, K.; Matsumura, S.; Hatef, E.; Akpek, E.K. Interventions for Chronic Blepharitis. Cochrane Database Syst. Rev. **2012**, doi:10.1002/14651858.CD005556.pub2.
10. Navel, V.; Mulliez, A.; Benoist d'Azy, C.; Baker, J.S.; Malecaze, J.; Chiambaretta, F.; Dutheil, F. Efficacy of Treatments for Demodex Blepharitis: A Systematic Review and Meta-Analysis. Ocul. Surf. **2019**, 17, 655–669, doi:10.1016/j.jtos.2019.06.004.
11. Huber-Spitzy, V. Blepharitis. Klin. Monbl. Augenheilkd. **2005**, 222, R55–R72, doi:10.1055/s-2005-865974.
12. Wei, Y.; Asbell, P.A. The Core Mechanism of Dry Eye Disease Is Inflammation. Eye Contact Lens Sci. Clin. Pract. **2014**, 40, 248–256, doi:10.1097/ICL.0000000000000042.
13. Rashid, M.A.; Teo, C.H.Y.; Mamun, S.; Ong, H.S.; Tong, L. Prevalence and Risk Factors of Severe Dry Eye in Bangladesh-Based Factory Garment Workers. Diagnostics **2020**, 10, 634, doi:10.3390/diagnostics10090634.
14. Nichols, K.K. Patient-Reported Symptoms in Dry Dye Disease. Ocul. Surf. **2006**, 4, 137–145, doi:10.1016/S1542-0124(12)70040-X.
15. Straub, M.; Bron, A.M.; Muselier-Mathieu, A.; Creuzot-Garcher, C. Long-Term Outcome after Topical Ciclosporin in Severe Dry Eye Disease with a 10-Year Follow-Up. Br. J. Ophthalmol. **2016**, 100, 1547 LP – 1550, doi:10.1136/bjophthalmol-2015-306930.
16. Binotti, W.W.; Bayraktutar, B.; Ozmen, M.C.; Cox, S.M.; Hamrah, P. A Review of Imaging Biomarkers of the Ocular Surface. Eye Contact Lens Sci. Clin. Pract. **2020**, 46, S84–S105, doi:10.1097/ICL.0000000000000684.
17. Bunya, V.Y.; Fuerst, N.M.; Pistilli, M.; McCabe, B.E.; Salvo, R.; Macchi, I.; Ying, G.-S.; Massaro-Giordano, M. Variability of Tear Osmolarity in Patients With Dry Eye. JAMA Ophthalmol. **2015**, 133, 662, doi:10.1001/jamaophthalmol.2015.0429.
18. Shen Lee, B.; Kabat, A.G.; Bacharach, J.; Karpecki, P.; Luchs, J. Managing Dry Eye Disease and Facilitating Realistic Patient Expectations: A Review and Appraisal of Current Therapies. Clin. Ophthalmol. **2020**, Volume 14, 119–126, doi:10.2147/OPTH.S228838.
19. Sabeti, S.; Kheirkhah, A.; Yin, J.; Dana, R. Management of Meibomian Gland Dysfunction: A Review. Surv. Ophthalmol. 2020, 65, 205–217.
20. Milner, M.S.; Beckman, K.A.; Luchs, J.I.; Allen, Q.B.; Awdeh, R.M.; Berdahl, J.; Boland, T.S.; Buznego, C.; Gira, J.P.; Goldberg, D.F.; et al. Dysfunctional Tear Syndrome. Curr. Opin. Ophthalmol. **2017**, 28, 3–47, doi:10.1097/01.icu.0000512373.81749.b7.
21. Verjee, M.A.; Brissette, A.R.; Starr, C.E. Dry Eye Disease: Early Recognition with Guidance on Management and Treatment for Primary Care Family Physicians. Ophthalmol. Ther. **2020**, 9, 877–888, doi:10.1007/s40123-020-00308-z.
22. Tong, L.; Lim, L.; Tan, D.; Heng, W.J.; Lim, J.; Chan, C.; Arundhati, A.; Tan, A. Assessment and Management of Dry Eye Disease and Meibomian Gland Dysfunction: Providing a Singapore Framework. Asia-Pacific J. Ophthalmol. **2021**, 10, 530–541, doi:10.1097/APO.0000000000000417.
23. Brignole-Baudouin, F.; Riancho, L.; Ismail, D.; Deniaud, M.; Amrane, M.; Baudouin, C. Correlation Between the Inflammatory Marker HLA-DR and Signs and Symptoms in Moderate to Severe Dry Eye Disease. Investig. Opthalmology Vis. Sci. **2017**, 58, 2438, doi:10.1167/iovs.15-16555.
24. Nelson, J.D.; Shimazaki, J.; Benitez-del-Castillo, J.M.; Craig, J.P.; McCulley, J.P.; Den, S.; Foulks, G.N. The International Workshop on Meibomian Gland Dysfunction: Report of the Definition and Classification Subcommittee. Investig. Opthalmology Vis. Sci. **2011**, 52, 1930, doi:10.1167/iovs.10-6997b.
25. Chhadva, P.; Goldhardt, R.; Galor, A. Meibomian Gland Disease. Ophthalmology **2017**, 124, S20–S26, doi:10.1016/j.ophtha.2017.05.031.
26. Geerling, G.; Tauber, J.; Baudouin, C.; Goto, E.; Matsumoto, Y.; O'Brien, T.; Rolando, M.; Tsubota, K.; Nichols, K.K. The International Workshop on Meibomian Gland Dysfunction: Report of the

Subcommittee on Management and Treatment of Meibomian Gland Dysfunction. Investig. Opthalmology Vis. Sci. **2011**, 52, 2050, doi:10.1167/iovs.10-6997g.
27. Li, M.; Gong, L.; Chapin, W.J.; Zhu, M. Assessment of Vision-Related Quality of Life in Dry Eye Patients. Investig. Opthalmology Vis. Sci. **2012**, 53, 5722, doi:10.1167/iovs.11-9094.
28. Baudouin, C.; Messmer, E.M.; Aragona, P.; Geerling, G.; Akova, Y.A.; Benítez-del-Castillo, J.; Boboridis, K.G.; Merayo-Lloves, J.; Rolando, M.; Labetoulle, M. Revisiting the Vicious Circle of Dry Eye Disease: A Focus on the Pathophysiology of Meibomian Gland Dysfunction. Br. J. Ophthalmol. **2016**, 100, 300–306, doi:10.1136/bjophthalmol-2015-307415.
29. Zhou, L.; Zhao, S.Z.; Koh, S.K.; Chen, L.; Vaz, C.; Tanavde, V.; Li, X.R.; Beuerman, R.W. In-Depth Analysis of the Human Tear Proteome. J. Proteomics **2012**, 75, 3877–3885, doi:10.1016/j.jprot.2012.04.053.
30. Potvin, R.; Makari, S.; Rapuano, C. Tear Film Osmolarity and Dry Eye Disease: A Review of the Literature. Clin. Ophthalmol. **2015**, 2039, doi:10.2147/OPTH.S95242.
31. Tuisku, I.S.; Konttinen, Y.T.; Konttinen, L.M.; Tervo, T.M. Alterations in Corneal Sensitivity and Nerve Morphology in Patients with Primary Sjögren's Syndrome. Exp. Eye Res. **2008**, 86, 879–885, doi:10.1016/j.exer.2008.03.002.
32. Bron, A.J.; Argüeso, P.; Irkec, M.; Bright, F.V. Clinical Staining of the Ocular Surface: Mechanisms and Interpretations. Prog. Retin. Eye Res. **2015**, 44, 36–61, doi:10.1016/j.preteyeres.2014.10.001.
33. Stevenson, W. Dry Eye Disease. Arch. Ophthalmol. **2012**, 130, 90, doi:10.1001/archophthalmol.2011.364.
34. Solomon, A.; Dursun, D.; Liu, Z.; Xie, Y.; Macri, A.; Pflugfelder, S.C. Pro- and Anti-Inflammatory Forms of Interleukin-1 in the Tear Fluid and Conjunctiva of Patients with Dry-Eye Disease. Invest. Ophthalmol. Vis. Sci. **2001**, 42, 2283–2292.
35. De Paiva, C.S.; Chotikavanich, S.; Pangelinan, S.B.; Pitcher, J.D.; Fang, B.; Zheng, X.; Ma, P.; Farley, W.J.; Siemasko, K.F.; Niederkorn, J.Y.; et al. IL-17 Disrupts Corneal Barrier Following Desiccating Stress. Mucosal Immunol. **2009**, 2, 243–253, doi:10.1038/mi.2009.5.
36. Massingale, M.L.; Li, X.; Vallabhajosyula, M.; Chen, D.; Wei, Y.; Asbell, P.A. Analysis of Inflammatory Cytokines in the Tears of Dry Eye Patients. Cornea **2009**, 28, 1023–1027, doi:10.1097/ICO.0b013e3181a16578.