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ORIGINAL RESEARCH

Impact of Time of Day on Dry Eye Disease: Findings from a Large Dry Eye Clinic Cohort

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Introduction: Previous research on the influence of time of day on dry eye disease (DED) symptoms and tear film characteristics has yielded inconsistent results, despite frequent reports of diurnal fluctuation in patient-reported symptoms. This study aimed to clarify these temporal patterns by evaluating both subjective and objective measures of DED in a large clinical cohort.

Methods: A total of 1044 patients from a Norwegian dry eye clinic were assessed between September 2021 and December 2023. Associations between time of day and both subjective symptom scores and objective clinical parameters were evaluated using Pearson correlation, while diurnal rhythmicity was assessed using single-component cosinor analysis with a fixed 24-hour period.

Results: Patients reported increased symptom severity in the morning and evening. However, analyses demonstrated statistically significant but clinically negligible correlations between time of day and all measured objective tear film parameters. No meaningful diurnal variation was identified in quantitative clinical metrics.

Discussion: These findings reveal a persistent disconnect between subjective symptom patterns and objective clinical measures in DED. The lack of clinically meaningful diurnal variation in tear film parameters suggests that time of day may have limited relevance for objective assessment, while symptom variability may be driven by factors not captured by standard clinical testing. Further research is needed to better understand the mechanisms underlying this discrepancy.

Keywords: dry eye disease, ocular surface, time of day effects, diurnal variation, tear film stability, breakup time

Introduction

The tear film is the interface between the ocular surface and the external environment. The combination of the tear film and the cornea provides approximately two thirds of the refractive power of the eye.[1] Classically, the tear film is composed of three layers, with different components secreted by diverse glands and tissues. The innermost mucin layer, produced by conjunctival goblet cells, the corneal epithelium, the conjunctival epithelium and, to a lesser extent, the lacrimal gland, primarily protects the ocular surface from chemical, physical, and pathological insults.[2] The majority of the tear film by volume is the middle aqueous layer which contains water, electrolytes, metabolites and small molecules, soluble mucins, enzymes, and proteins providing hydration, nourishment, protection, immune defense, and removal of waste products for the ocular surface.[3] The outermost lipid layer, secreted primarily by the meibomian glands that line the eyelids' tarsal plates, is hypothesized to prevent evaporation of the aqueous layer[4,5] and may contribute to corneal oxygenation.[6]

Given the dynamic nature of the tear film, its properties may be influenced by systemic biological rhythms. Circadian rhythms are endogenous, approximately 24-hour cycles that regulate various physiological processes, including ocular surface homeostasis.[7] These rhythms are synchronized by melatonin secretion which is regulated by retinal environmental light exposure transmitted to the suprachiasmatic nucleus and pineal gland.[8] Melatonin secretion exhibits

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a distinct nocturnal peak that contributes to the regulation of sleep-wake timing and ocular surface properties. Beyond its systemic effects, melatonin receptors are expressed in the lacrimal gland, corneal epithelium, and conjunctiva, where they can modulate tear secretion.[9,10] Alterations in melatonin release due to artificial light exposure, sleep disruption, or shift work may therefore influence tear film composition and subjective symptoms of dryness or discomfort. Environmental lighting conditions fluctuate throughout the day, potentially compounding circadian modulation of ocular physiology. Increased screen exposure, low ambient humidity, and reduced blink frequency during waking hours can accentuate tear film instability, while lower nighttime light levels may alter symptom perception rather than tear dynamics. Therefore, biological rhythms and external factors shape both the diurnal profile of tear film parameters and self-reported ocular surface symptoms.[7,10]

Tear film composition has been shown to vary throughout the day, resulting in diurnal patterns in physical properties, including tear film breakup time (TFBUT), tear volume, pH, TFBUT, tear film osmolarity, and Schirmer test results.[11–15] Similar patterns have additionally been observed in patients with dry eye disease (DED), a chronic, complex multifactorial disease affecting up to 50% of the global population and 47% of those in Norway seeking optometric care.[16,17] Seasonal variations in DED symptoms have been reported in this Nordic country.[18] A clinical hallmark of the disease is increased tear film osmolarity.[19,20] It disproportionately affects women and the elderly, though male patients in general tend to have more meibomian gland dysfunction.[21,22] The common symptoms of DED include eye pain, redness and visual impairment.[23] Symptom-based questionnaires remain valuable for both diagnosing and monitoring DED, but current guidelines recommend they be used in conjunction with at least one objective clinical sign.[24]

Symptom questionnaires generally correlate poorly with objective tear film measures, raising concerns about the reliability of clinical DED severity assessments.[25] Traditionally, DED is diagnosed using a combination of a valid questionnaire and tests, the including Schirmer test, TFBUT, ocular surface staining, and tear osmolarity following patient complaints of dry eye-related symptoms.[26,27]

According to the Tear Film & Ocular Surface Dry Eye Workshop III report, DED is classified into three broad categories: tear film component deficiencies, eyelid anomalies, or ocular surface abnormalities.[17] However, up to one third of patients present with mixed-cause DED.[28] Because lifestyle factors (eg, screen use), hormonal fluctuations, inflammatory mediator levels, and tear film composition can vary not only between sleep and wakefulness but also vary throughout the day, assessing diurnal changes in the tear film of DED patients is crucial for optimizing disease management.[29] Current understanding of diurnal variation in DED is constrained by a reliance on small, underpowered studies, most involving few participants, which have yielded inconsistent and conflicting results. This underscores a critical gap in the current literature: the absence of large sample size, well-characterized cohort studies capable of definitively assessing diurnal fluctuations in both subjective symptoms and objective tear film parameters.

This study aimed to determine whether time of day influences both subjective symptom severity and objective clinical measures of dry eye disease, and to assess the extent to which any observed diurnal patterns are statistically and clinically meaningful within a large clinical cohort.

Methods

The data presented herein are extracted from the Norwegian Dry Eye Cohort 2023 (NDEC2023). NDEC2023 is a specialized, prospective observational cohort established at the Norwegian Dry Eye Clinic to investigate the pathophysiology of DED through biochemical analyses of Schirmer strips, clinical features, and treatment responses in patients diagnosed with various types of DED. The cohort comprises 1,044 patients (741 female and 303 male) referred to or presenting to the clinic due to dry eye related symptoms (Table 1).[30] The cohort enrolled patients between 2021 and 2023, with plans for longterm followup to enable the study of disease progression and therapeutic outcomes. It is predominantly composed of individuals of Northern European ancestry and is representative of patients receiving tertiary care for dry eye in a Scandinavian setting. NDEC2023 aims to facilitate translational research in ocular surface disease. As part of inclusion, information detailing symptoms, previous surgery, medications, comorbidities, previous treatments, slit lamp exam findings, tear film characteristics, ocular surface clinical findings, Keratograph results, symptoms (Ocular Surface Disease Index (OSDI), Dry Eye Questionnaire 5 (DEQ5), and in-house questionnaires), and time of the exam were recorded (data not shown). All examinations were performed by DED expert physicians (Fredrik Fineide and/or Tor

Table 1 Cohort Demographics

Characteristic	Value
Age (mean ± SD)	52.8 ± 16.77 years
Gender, n (%)	741 female (71%)
	303 male (39%)
Duration of Symptoms Prior to First Visit	6.98 ± 8.27 months
ODSI Score (mean ± SD)	39.11 ± 22.45
DEQ5 Score (mean ± SD)	12.85 ± 4.29

Notes: Characteristics are presented on the left with values on the right ± standard deviation as applicable.

Utheim). Patients signed consent forms authorizing the use of their questionnaire and tear film parameter data in this cohort. For this analysis, time of day was divided into morning (6:00–12:00), afternoon (12:01–18:00), and evening (18:01–24:00). The study was approved by the Regional Ethics Committee of Southeast Norway (reference ID 6892) and adhered to the Declaration of Helsinki.

Only data from each patient's initial visit were included in the analysis. Each patient contributed a single time-point measurement. Patients were not excluded based on comorbid conditions, including Sjögren syndrome (n=36), rheumatoid arthritis (n=14), systemic lupus erythematosus (n=2), rosacea (n=33), or hypothyroidism (n=98). Contact lens users (n=142) were also included. Additionally, patients were not excluded on the basis of prior or ongoing treatments before their first visit, including Monoprex (n=290), Softacort (n=135), Ikervis (n=251), Restasis (n=53), heat mask therapy (n=222), Blephademodex (n=11), Ilidex Extra (n=1), intense pulsed light (IPL) therapy alone (n=640) or in combination with other treatments (n=129), doxycycline (n=19), scleral lenses (n=8), and punctal plugs (n=105 OD, n=102 OS).

Diurnal variation was examined using single component cosinor analysis with a fixed 24 hour period, implemented via cosinor.online.[31] The model fitted the equation $Y(t) = M + A \cdot cos(2\pi t/24 + \varphi)$, where M represents the mesor (rhythm adjusted mean), A the amplitude (half the peak to trough difference), and φ the acrophase (timing of the peak). Time of day was expressed in hours from midnight. Parameter estimates with 95% confidence intervals were derived from the fitted cosine and sine coefficients. Model significance was assessed using the overall F-statistic, comparing the fitted rhythm to a no rhythm null model ($\alpha = 0.05$). Goodness of fit was evaluated using the coefficient of determination (R^2) and percent rhythm, representing the proportion of variance explained by the rhythmic component.

The data were analyzed with SPSS Statistics Version 30 (IBM corp., Armonk, NY, USA) to calculate the Pearson correlation coefficient, t-statistic, and p-value ($\alpha < 0.05$ was considered significant).

Patients were not involved in the design or conduct of this research.

Results

Overall, no consistent relationship was observed between time of day and any subjective or objective measure of dry eye severity. Although patients reported more pronounced symptoms in the morning and evening (Figure 1A), their subjective DEQ5 and OSDI scores did not display any relationship between the score and time of day (Figure 1B and C). We additionally compared DEQ5 and OSDI scores to tear quantitative tear film quality metrics (number of expressible meibomian glands, average meibum quality, osmolarity, Schirmer test results, NIBUT, and FBUT) and likewise found statistically significant, but very small ($r < 0.13$) correlations between symptoms and quantitative metrics (data not shown). Pearson's correlation coefficient compared to time of day, t-statistic, and p-value were additionally recorded for Meibomian dropout score, and redness score, (Supplementary 1).

No significant rhythmicity was detected for DEQ5 or OSDI scores ($F(2,978) = 2.18$, $p = 0.1137$; $F(2,993) = 2.09$, $p = 0.1244$, respectively). The models estimated mesors of 12.38 (95% CI: 11.42–13.34) for DEQ5 and 35.48 (95% CI: 30.48–40.49) for OSDI, with amplitudes of 0.77 (95% CI: –0.15–1.68) and 5.07 (95% CI: –0.41–10.56). Predicted

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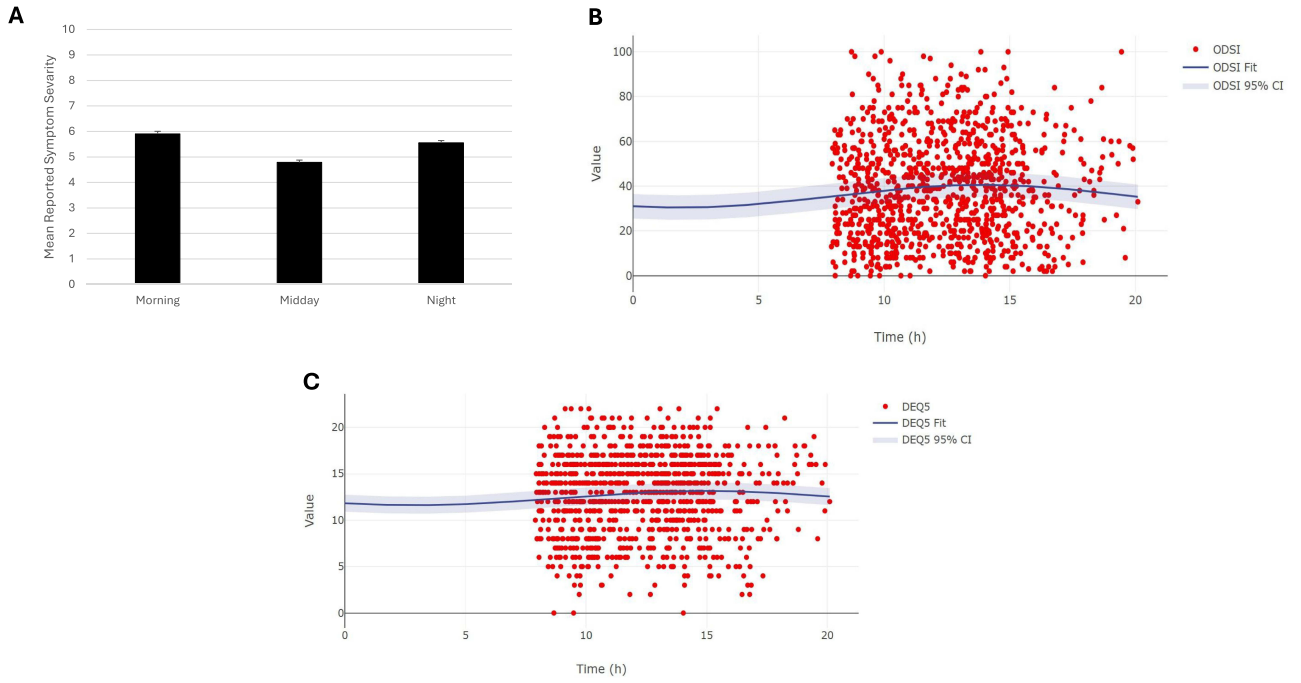

Figure 1 (**A**) Bar graph of patient reported symptom severity (on a scale of 1–10) by time of day (morning, midday, or night). Values are given ± standard error of the mean. (**B**) Cosinor plot of ocular surface disease index questionnaire (OSDI). OSDI scores are bounded 0 to 100 and DEQ5 Scores are bounded 0–22. OSDI scores >13. (**C**) Cosinor plot of dry eye questionnaire (DEQ5) scores plotted against time of exam and DEQ5 scores >6 were considered indicative of dry eye disease.

acrophases occurred at 14.9 h (DEQ5) and 13.9 h (OSDI), with corresponding bathyphases at 2.9 h and 1.9 h. The wide confidence intervals for amplitude, both spanning zero, indicate uncertainty in any underlying oscillation. Model fit was poor (R^2 = 0.0044 and 0.0042; percent rhythm ≈ 0.4%), and correlations between fitted and observed data were weak (R = 0.07 and 0.07). These results suggest that any diurnal variation in DEQ5 or OSDI scores is minimal and indistinguishable from random variability.

We additionally observed no change in the number of expressible meibomian glands (Figure 2A) or meibum quality relative to the time of exam (Figure 2B). We observed significant, but exceptionally weak, correlations between the time of day and tear film osmolarity (Figure 3A and B), Schirmer test results (Figure 3C), NIBUT (Figure 4A), and FBUT (Figure 4B). We measured an average of 5.33 ± 2.33 (oculus dexter, OD), and 5.06 ± 2.36 (oculus sinister, OS) expressible meibomian glands out of the central 8 glands with a mean meibomian quality score of 1.03 ± 0.76 (OD), and 1.16 ± 0.79 (OS) measured on a Likert scale from 0–3.

Cosinor analyses were additionally conducted for the number of expressible glands, average meibomian quality, FBUT, and NIBUT in both eyes (OD/OS). None of the models showed a significant 24 hour rhythm (all $p \geq 0.0559$), and all explained ≤ 0.6% of the variance (R^2 = 0.0010–0.0062). Estimated amplitudes were small across all variables, and in every case the 95% confidence interval for amplitude included zero, indicating no reliable oscillatory component. The strongest apparent rhythm was observed for MQavg (OD/OS) (p = 0.0559), but even this model accounted for only 0.6% of variability. Correlations between fitted cosines and observed data were uniformly low (R = 0.03–0.08). Overall, no meaningful diurnal variation was detected in any parameter for either eye.

Schirmer test results of both eyes showed a very slight, but statistically significant, negative correlation with the time of day with means of 18.5 ± 10.9 (OD) and 17.0 ± 10.2 (OS). As with the osmolarity results, the correlations observed were so small as to be clinically insignificant. This inference is reinforced by the inconsistency in quantitative data with the number of expressible central meibomian glands, tear film osmolarity in the right eye, and redness in the right eye displaying slight negative correlations with time of day while the total number of expressible meibomian glands, meibum quality, tear film osmolarity in the left eye, NIBUT, and FBUT display slight positive correlations.

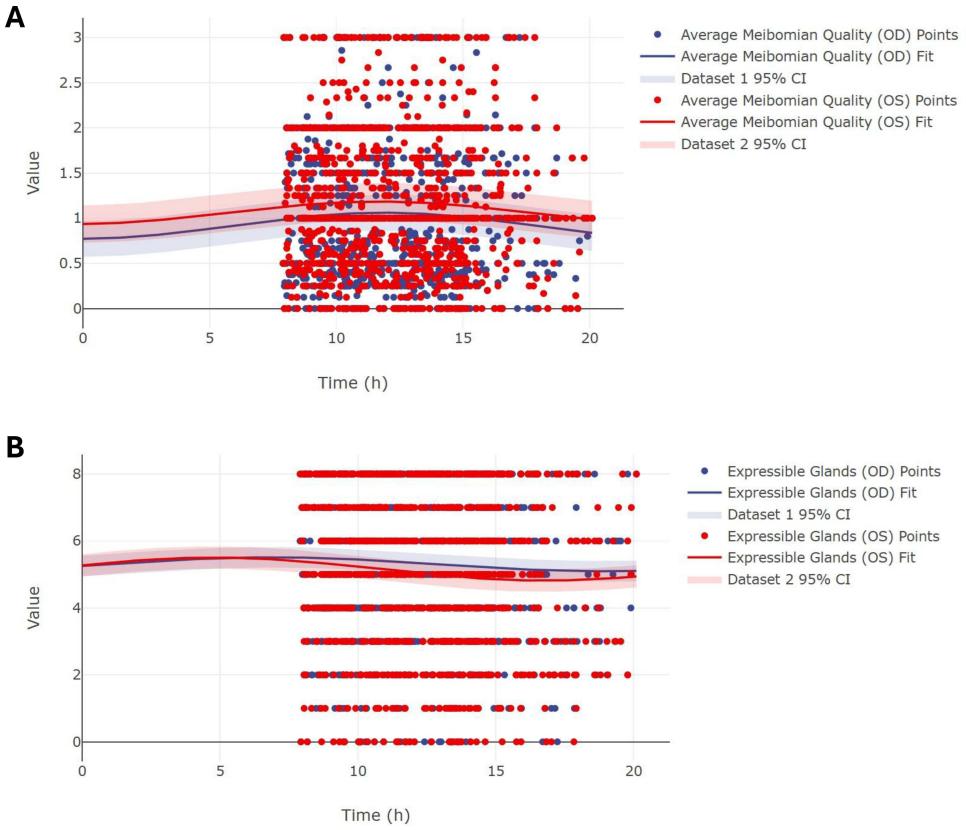

Figure 2 (**A**) Cosinor plot of the number of the central 8 meibomian glands that are expressible during the first visit versus time of the first visit in hours since midnight. (**B**) Cosinor plot of mean meibomian quality (meibomian quality score divided by the number of expressible meibomian glands) plotted against time of day in hours since midnight. OD indicates the right eye and OS indicates results from the left eye.

A 24 hour cosinor model identified statistically significant diurnal variation in Schirmer test results for both eyes (OD: F = 6.10, p = 0.0023; OS: F = 7.35, p = 0.0007). Estimated mesor values were 19.56 (95% CI: 17.18–21.93) for OD and 17.78 (95% CI: 15.57–20.00) for OS, with corresponding amplitudes of 2.54 (95% CI: 0.75–4.33) and 2.38 (95% CI: 0.94–3.83). The acrophases occurred at approximately 4.1 h and 4.7 h, with troughs at 16.1 h and 16.7 h after midnight for OD and OS, respectively. However, despite statistical significance, the explained variance was minimal (R^2 = 0.012 and 0.014; percent rhythm = 1.2% and 1.4%), indicating a very small oscillatory component and limited physiological relevance.

Cosinor analysis of tear osmolarity (OSM) in both eyes (OD and OS) revealed no significant 24 hour rhythmicity (OD: p = 0.3598; OS: p = 0.2229). Although the estimated amplitudes were 40.9 mOsm/L for OD and 13.8 mOsm/L for OS, the 95% confidence intervals for both included zero, indicating that the oscillatory component was not statistically supported. Model fit was weak in both cases (R^2 = 0.027 and 0.038; percent rhythm ≤ 3.8%), and correlations between fitted and observed values were low (R = 0.16–0.20). These findings indicate that no meaningful diurnal variation in tear osmolarity was detected in either eye.

In line with prior studies,[32,33] patients in this cohort reported worsening symptoms in the morning and evening as indicated by their OSDI and DEQ5 scores. However, we found no corresponding correlations between time of day and tear film metrics. While the correlations between time of day and meibomian gland expressibility (both central and total) and meibum quality were statistically significant, they were too weak to be attributed clinical value as determined by the low magnitude of correlations (low Pearson's r values) and minimal explained variance (R^2). Likewise, osmolarity measurements were statistically significantly correlated with both FBUT and NIBUT, but similarly very weak. We did note a single exception: the osmolarity of the left eye is slightly negatively correlated with time of day (r = −0.15), but

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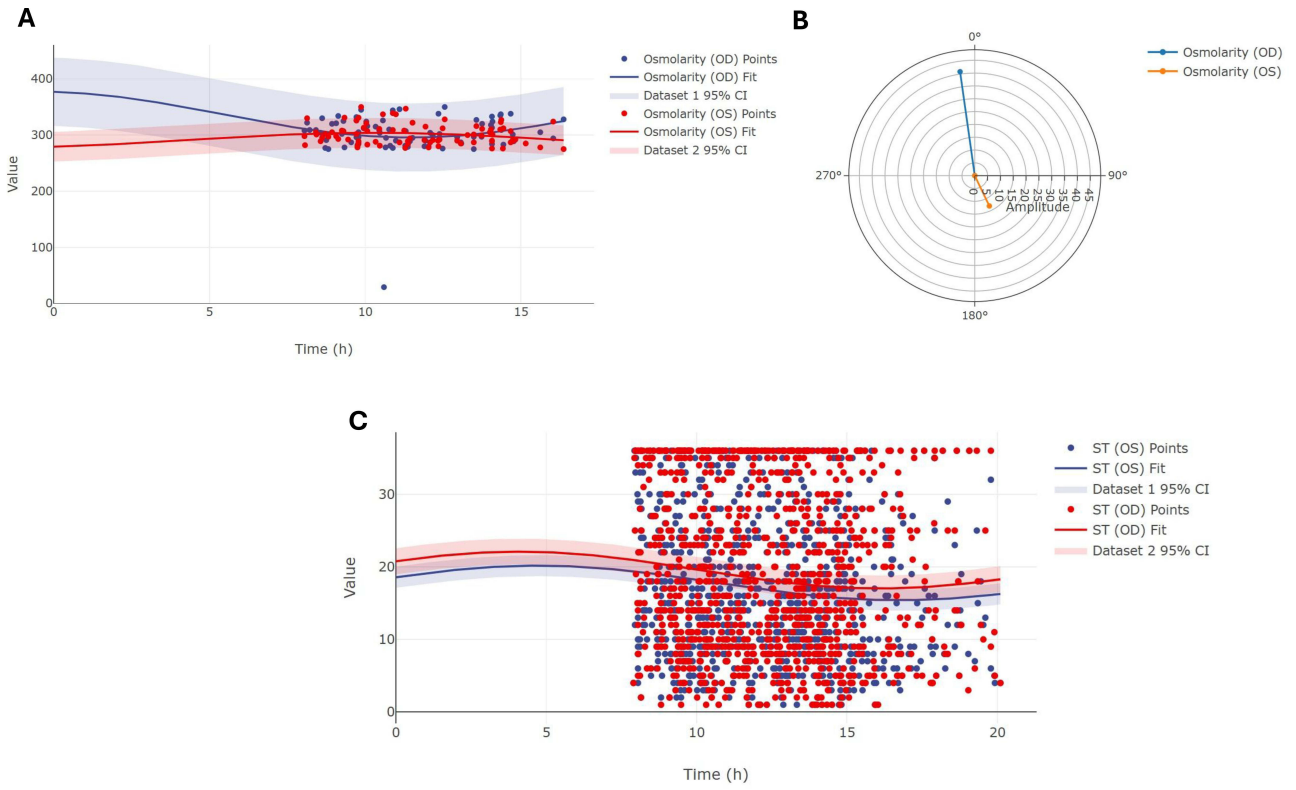

Figure 3 (**A**) Cosinor fit of tear film osmolarity plotted against the time of measurement. (**B**) Polar plot of tear film osmolarity showing peak osmolarity and time of peak for each eye. OD indicates the right eye (blue) and OS indicates results from the left eye (Orange). (**C**) Cosinor fit of Schirmer test results measured in mm versus time of exam. OD indicates the right eye and OS indicates results from the left eye.

this is likely due to random error given that we did not observe a similar correlation with the right eye, and indeed observed and opposite correlation in the right eye (r = 0.05).

Discussion

This study found no significant diurnal variation in tear film metrics among Norwegian patients with DED, despite subjective reports of fluctuating symptoms. Our study population included more females than males, reflecting the known gender distribution of the broader DED population.[34] Average age of participants was also consistent with typical demographic trends for the disease. Despite reporting severe dry eye symptoms, as indicated by high DEQ5 and OSDI scores, this severity was not mirrored in clinical measures of meibomian gland function, expressibility, tear film osmolarity, or Schirmer test results. Participants exhibited approximately half of the central meibomian glands as expressible, with meibum quality scores suggesting mild rather than severe dysfunction. Measured osmolarity values fell below the DEWS III threshold for distinguishing normal from mild to moderate DED.[17] Although osmolarity data were not available for all patients. Schirmer test results were generally well above the DEWS II threshold for reduced tear production.[24] Collectively, these findings suggest that while patients experience severe symptoms, they maintain adequate tear volume, production and reasonable protection against evaporative loss.

Several previous observational studies showed an increase in tear film osmolarity throughout the day, while others demonstrated a decrease in osmolarity over the course of a day, though the sample size in each of these studies was less than 50 individuals.[35–37] Another study with a similarly small sample size found no diurnal variation in tear film osmolarity (N=20).[38] Likewise, NIBUT has repeatedly found no diurnal variation in similarly sized studies (N = 20, 13, 20, and 17 respectively).[13,29,39,40] Redness similarly showed no variation with the time of day in a study by Walker et al[33] The inconsistency of results suggested that prior significant findings may be the result of sample bias. It should be noted, however, that the present study does not control for season, patient age, or patient sex.

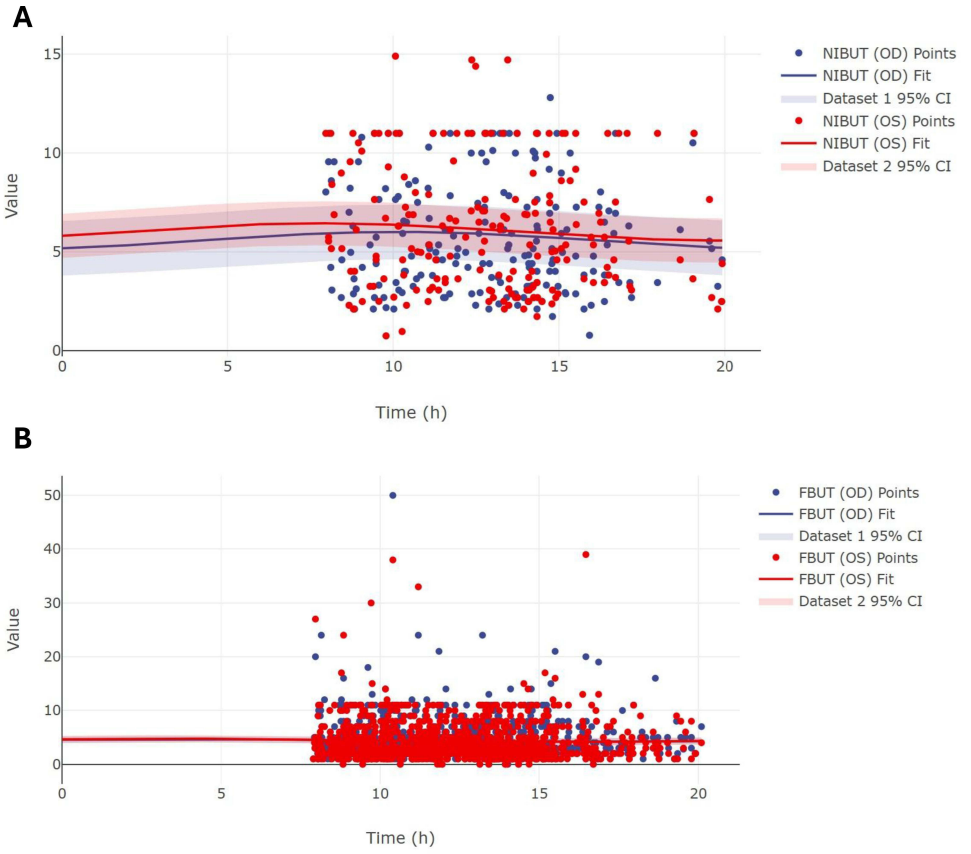

Figure 4 (**A**) Cosinor Fit of the non-invasive tear breakup time (NIBUT) measured in seconds versus time of exam. (**B**) Cosinor Fit of the functional tear breakup time (FBUT) measured in seconds versus time of exam. OD indicates the right eye and OS indicates results from the left eye.

Interestingly, while patients tended to report worsening DED symptoms in the morning and evening, none of the quantitative tear film metrics reflected this reported trend. In fact, tear osmolarity in the left eye appeared to slightly improve with time, though, as noted above, this result is likely a reflection of random error. While this discrepancy between patient reports and quantitative data may be in part due to our practice of recording some symptoms categorically, specifically the questions about when patients experienced the most severe symptoms and meibomian quality. These findings indicate that tear film osmolarity and meibomian gland function may not be causal to patient symptoms. This finding raises questions about the possibility of undiagnosed or asymptomatic DED patients who display altered tear osmolarity, but do not experience associated symptoms.

The observed discrepancy between subjective symptoms and objective signs of DED underscores the multifactorial nature of the condition and the limitations of relying on a single metric of assessment. Patients may report significant discomfort despite minimal clinical findings, or show quantifiable tear film instability without prominent symptoms. This disconnect likely reflects contributions from neural, inflammatory, and psychosocial factors that influence symptom perception independently of ocular surface status. Alterations in corneal nerve sensitivity, central sensitization, and environmental or behavioral influences can amplify or attenuate symptom perception. Therefore, our findings reinforce the need for a multimodal diagnostic approach integrating both subjective metrics, such as DEQ-5 or OSDI, and objective measures including TFBUT, osmolarity, and staining patterns.

These results highlight the importance of personalized clinical management strategies in DED. Rather than basing treatment decisions solely on objective or subjective parameters, clinicians should weigh patient reported symptoms and objective measures when selecting or modifying therapies. Cases characterized by disproportionate symptoms may justify evaluation for neuropathic ocular pain or comorbid mood disorders, which may require alternative therapeutic approaches such as anti-inflammatory agents. Likewise, when objective abnormalities are present without symptoms,

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early intervention is essential to prevent progression. As patient perception of dryness often reflects accumulated or chronic ocular surface damage rather than early disease activity, clinicians should implement objective testing for DED earlier in order to identify subclinical dysfunction before symptoms become pronounced or irreversible changes occur. These findings underscore the need for a more nuanced, patient-centered approach to DED management that integrates both the physiological mechanisms and the subjective experiences of those suffering with DED.

Recall bias in the present dataset cannot be ruled out, especially given that patients experienced symptoms for an average of seven months before their first visit. Recall bias, known to influence symptom reporting in chronic diseases such as rheumatoid arthritis,[41,42] may similarly affect self-reported ocular discomfort. Nevertheless, patient self-reported symptoms were significantly, but exceptionally weakly correlated ($r < 0.05$) with time of day indicating that patient symptoms recall was minimally influenced by time of day (data not shown).

Ocular surface staining results were collected but are excluded from this analysis, as the measure primarily reflects accumulated epithelial damage rather than rapid changes in tear film quality or quantity. Our aim was to evaluate parameters that could vary meaningfully over the course of the day, and we therefore focused on metrics more sensitive to short-term fluctuations. A separate analysis of the staining data is ongoing.

Seasonal normalization was not applied in the present analysis because the influence of seasonal variation on ocular surface parameters is the focus of an upcoming study. The current investigation was designed to isolate and characterize diurnal rhythmicity, independent of broader environmental or temporal trends. A dedicated analysis addressing the impact of seasonal factors will be presented separately to allow for a more complete understanding of their interaction with tear film dynamics and symptom variability.

Additionally, this study was limited by the lack of control for environmental conditions (eg, humidity, temperature, and screen exposure), individual medication use, and patient lifestyle factors such as sleep patterns and daily activities, all of which may influence tear film dynamics and symptom perception and could confound the assessment of diurnal variation in dry eye disease. As this study employed a cross-sectional design, in which each patient was assessed at a single time point during their initial clinic visit, observed differences across times of day reflect between-subject variation rather than within-subject diurnal changes.

Conclusion

Our sampling of Norwegian DED patients did not reveal any diurnal variation in tear film osmolarity, TFBUT (measured either invasively or noninvasively), eye redness, Schirmer strip results, meibum quality, or the quantity of expressible central or total meibomian glands. While patients reported their DED symptoms to be the worst in the morning and evening, these reports do not coincide with quantitative measures of tear film osmolarity, TFBUT, or meibomian gland function. This suggests that further exploration of the relationship between the clinical measures of DED severity and patient reported symptoms is warranted. These findings additionally suggest that the timing of diagnostic testing or clinical evaluation may have limited impact on objective tear film measurements, indicating that DED assessments can be performed consistently throughout the day without substantially affecting clinical interpretation.

AI Use Disclosure

An AI-based language model (ChatGPT, version 5.0 Pro) was used solely to assist with English-language editing and grammatical refinement. The AI did not contribute to study design, data analysis, or interpretation. All authors retain full responsibility for the final content.

Ethical Statement

The study was approved by the Regional Ethics Committee of South-East Norway (reference ID 6892) and adhered to the Declaration of Helsinki. Data access was approved by the Regional Ethics Committee of South-East Norway and Norwegian Dry Eye Clinic Administration. All patients consented to data collection and access and signed written informed consent forms. This study did not involve animal research.

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Disclosure

AZK, TPU and FAF report ownership interests in the Norwegian Dry Eye Clinic. TPU also reports personal fees from Santen, Thea and Bausch and Lomb. The authors report no other conflicts of interest in this work.

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