ARTICLE

Prevalence of tear film hyperosmolarity in 1150 patients presenting for refractive surgery assessment

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Purpose: To present an analysis of tear film hyperosmolarity in a large, consecutive population and evaluate the correlation of ocular and systemic conditions with tear film osmolarity (TFO).

Setting: Private practice, Sydney, Australia.

Design: Single-center, retrospective, consecutive cohort.

Method: Patients undergoing screening for laser refractive surgery from October 2017 to October 2020 were retrospectively reviewed. 1404 patients (n = 1357 standard, n = 47 postrefractive) undergoing screening for laser refractive surgery from October 2017 to October 2020 were reviewed. Routine examination included TFO and Ocular Surface Disease Index (OSDI) questionnaire. TFO was conducted prior to further tests, and patients refrained from topical eyedrops minimum 2 hours before the appointment.

Results: 1404 patients (n = 1357 standards, n = 47 postrefractive) patients were reviewed. Mean highest TFO in the standard population was 299.12 ± 11.94 mOsm/L, with 82.3% of eyes <308 mOsm/L indicating normal tear film homeostasis. The mean intereye TFO difference was 8.17 ± 8.60 mOsm/L, with 65.2% of eyes ≤8 mOsm/L. Mean highest TFO in the postrefractive subgroup was 299.72 ± 11.00 mOsm/L, with a mean intereye difference of 9.02 ± 6.92 mOsm/L. Postrefractive surgery patients indicated higher mean OSDI values of 15.28 ± 14.46 compared with the remainder of the population 9.69 ± 10.56 (P = .012). Significant correlation was demonstrated between TFO scores and OSDI normal classification in the standard population only (P = .005, r = 0.077). The use of contact lens correlated inversely with TFO and OSDI scores (P = .000, r = −0.136, and P = .000, r = −0.152, respectively).

Conclusions: To the authors' knowledge, this study represents the largest available cohort of TFO scores in a standard population presenting for refractive surgery. Although most patients were found to fall within normal ranges, a reasonable percentage were diagnosed with tear hyperosmolarity and therefore at risk for dry eye disease.

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In recent years, dry eye disease (DED) has been recognized as an important public health concern. DED has been attributed to a number of causes including ocular and systemic disease, medication, environmental factors, and surgical intervention.[1–3] The worldwide prevalence of dry eye varies significantly with estimates between 5% and 50%. These estimates are impacted by classification and the cohort within the respective analyses.[3,4]

Dry eye assessment tools identify defects and aid classification of disease. The positive identification of early or subclinical disease is especially relevant to potential refractive and cataract patients.[5] The loss of tear film homeostasis has been recognized as a core mechanism in DED pathophysiology. Although no single gold standard test is currently available, this definition suggests a significant role for tear film osmolarity (TFO) assessment in the detection of DED; indeed, several studies suggest that TFO may represent the single best objective metric currently in use.[6] Similar to most dry eye tests, however, the literature suggests variability in test outcomes with diversity in test protocols between studies considered the main driver of variability in measurements.[7–10]

The cutoff value of 308 mOsm/L has been proposed as a threshold in differentiating mild hyperosmolarity and thereby subclinical DED. The cutoff for marked hyperosmolarity is 316 mOsm/L.[7,11] Intereye asymmetry represents an additional feature of DED diagnosis by osmolarity, with an 8 mOsm/L or greater difference considered an indication of tear film instability. Functionally, tear film hyperosmolarity has been shown to increase

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variability in objective biometry measurements suggesting a potential impact on refractive outcomes in these patients if heading to cataract surgery.[8]

Most TFO research has focused on patients with moderate to marked dry eye. Although clinicians may be aware of the cutoff values for TFO, minimal information regarding the incidence of hyperosmolarity in the standard population is available. Furthermore, the relationship between TFO and subjective dry eye parameters and clinical variables remains inconclusive. Therefore, analysis of a broad range of patients is necessary to promote our understanding of the condition. Our study presents a new analysis of the largest current sample of TFO measurements in patients undergoing dry eye assessment prior to considering refractive surgery to provide insight into a standard population and postrefractive subgroup. Furthermore, the analysis involves using the Ocular Surface Disease Index (OSDI) questionnaire results as a comparator to TFO measurements (Supplementary material, http://links.lww.com/JRS/A437).

METHODS

This retrospective study was conducted at a private ophthalmology practice in Sydney, Australia. All patient files that underwent a screening consultation for laser refractive surgery from October 2017 to October 2020 were retrospective assessed. Patients were subjected to a routine examination including history and visual acuity, refraction, topography, dry eye testing, biomicroscopy, and fundus assessment. Patients were also asked to complete the OSDI questionnaire (Allergan). Separately, patients were asked whether they felt that their eyes were dry or whether they used artificial lubricants for dry eyes.

Preexisting ocular, systemic conditions and medications that may have impacted TFO were recorded for analysis. Preexisting ocular conditions noted were contact lens use, history of previous refractive surgery, and recent episode of ocular inflammation. Systemic conditions noted were thyroid dysfunction (hyperthyroidism and hypothyroidism), diabetes, autoimmune disorders, and history of previous cancer treatment. Medications included vitamin supplements (fish oil, vitamin D, and multivitamins), oral contraception, thyroid medications, hormone replacement therapy, general anti-inflammatory medications (aspirin or nonsteroid anti-inflammatory drugs), diabetic medication, and the use of artificial tears.

Dry eye testing was conducted with the TearLab Osmolarity System (TearLab). In brief, the TearLab Osmolarity test card was attached to the Osmolarity Test Pen before being placed gently against the lower eyelid margin to collect tear fluid. Following the application of a lot-specific calibration curve, TFO was calculated and then displayed as a quantitative numerical value, which was recorded in the patient file. The test was then repeated for the second eye with a new test card. A consultation protocol was introduced to maintain consistency across tests. The TearLab Osmolarity pen and test cards were colocated in a temperature and humidity-controlled location, and calibration was undertaken with each new batch of test cards as per the manufacturer's recommendation with the control fluid vial. Osmolarity assessment was conducted at the unit prior to any further tests, and patients were previously instructed to refrain from using topical eyedrops for at least 2 hours before the appointment. Standard protocol for the refractive consultation required soft contact lenses and rigid gas permeable lenses to be removed for 3 days or 3 weeks respectively prior to the consultation. This was not achieved in all cases due to a lack of alternative optical aids for some patients. Patient data that did not meet the protocol were removed from the review prior to the analysis.

Statistical analysis was performed using SPSS software (v. 24.0, IBM). Descriptive statistical methods were used to report the basic demographic details. Pearson correlation was used to investigate the association between TFO and selected variable, whereas chi-square tests were used to test the distribution of categorical variables. The individual's highest TFO value was included only in comparative analyses. Multivariate analysis was undertaken to understand the contribution of variables toward the tear osmolarity score. P values of <0.05 were considered statistically significant.

Review by the institution's low and negligible risk review committee determined that full approval was not required due to the retrospective and anonymous nature of the data collection and analysis. Patients had previously signed a privacy form indicating their consent for deidentified information to be used for audit and research purposes. The research adhered to the tenets of the Declaration of Helsinki.

RESULTS

For this study, 1404 (n = 1357 standard population and n = 47 postrefractive) patients were assessed at a single center. The average age of the standard population 39.00 ± 12.93 years (range 18 to 85 years) compared with the postrefractive group 51.89 ± 10.96 (range 29 to 73 years). The overall mean preoperative spherical equivalent was −2.78 ± 3.48 diopter sphere (range −25.63 to 9.63 diopter sphere), and mean keratometry was 43.52 ± 1.45 D (range 35.40 to 48.20 diopter).

TFO was recorded in 2808 eyes of 1404 patients. In the standard population, the mean TFO was 299.12 ± 11.94 mOsm/L (range 270 to 395 mOsm/L), with the mean of the highest individual TFO value 303.21 ± 12.10. Overall, 82.6% of all eyes had values below 308 mOsm/L, indicating normal tear film homeostasis. 6.7% of eye exhibited a value over 316 mOsm/L which is a marker of moderate to severe hypersomolarity. The mean intereye TFO difference was 8.17 ± 8.60 mOsm/L (range 0 to 101 mOsm/L) (Table 1). An intereye difference of >8 mOsm/L is indicative of an unstable tear film, with 31.6% of difference values above this mark. Of note, 42.11% of the patients with intereye difference of greater than 8 mOsm/L retained a value of 308 mOsm/L or under in the highest scoring eye.

Forty-seven eyes (3.4%) exhibited a prior history of laser refractive surgery (Table 1). In comparison to nonsurgery patients, the TFO value in the highest eye was 304.23 ± 10.43, which was not significantly different. Almost 85% (84.7%) of all eyes in this cohort were considered to have normal TFO values (<308 mOsm/L). The mean difference between eyes was higher in this cohort; however, this did not reach statistical significance (9.02 ± 6.92 mOsm/L). The patients in this cohort were significantly older than the standard cohort, and both mean and spherical equivalent and keratometry values were lower ($P < .001$).

Age correlated with highest TFO value and difference between eyes ($r = 0.155$, $P < .01$, and $r = 0.082$, $P = .002$). There was a significant difference in mean highest TFO scores and the difference between eyes between patients younger and older than 40 years (Table 2).

Of note, 57.1% of the standard population wore contact lenses either full or part time. The use of the contact lens correlated inversely with TFO and OSDI scores ($P = .000$, $r = -0.136$, and $P = .000$, $r = -0.152$, respectively). The

Table 1. Mean Values for Cohort Including the Postrefractive Surgery Subgroup.

Variables	Normal (n = 1357)	Ranges	Postrefractive (n = 47)	Ranges	*P* value
Age (y)	39.00 ± 12.93	18, 85	51.89 ± 10.96	29, 73	<.001
Preop SE (DS)	−2.86 ± 3.50	−25.5, 9.38	−0.64 ± 1.80	−6.38, 3.75	<.001
Mean keratometry (D)	43.52 ± 1.45	36.35, 48.20	41.38 ± 2.80	34.60, 45.85	<.001
Mean TFO (total)	299.12 ± 11.94	270, 395	299.72 ± 11.00	284, 328	.632
Mean TFO highest individual value	303.21 ± 12.10	—	304.23 ± 10.43	—	.566
Mean I-E difference	8.17 ± 8.60	0, 101	9.02 ± 6.92	1, 27	.574
Mean OSDI scores	15.28 ± 14.47	0, 89	9.69 ± 10.56	0, 58	.012
% > 308 TFO	17.4		15.3		NA
% > 316 TFO	6.7		4.2		NA
% Using contact lenses	58.4		17.0		NA
% Using artificial tears	22.6		14.9		NA

DS = diopter sphere; I-E = intereye; NA, not available; OSDI = Ocular Surface Disease Index; preop = preoperative; SE = spherical equivalent; TFO = tear film osmolarity

highest TFO was significantly different between contact lens wearers and those not wearing contact lenses (301.81 ± 11.22 vs 305.12 ± 12.85, $P = < 0.001$). Similarly, the mean difference in TFO scores between eyes in contact lens wearers was significantly lower (7.67 ± 8.31 vs 8.87 ± 8.81, $P = .01$).

With respect to systemic disease, thyroid dysfunction was recorded in 3.2% of the population representing the largest reported risk factor. However, a prior diagnosis of thyroid disease or other systemic disease did not seem to impact the TFO value or difference between eyes ($P > .05$). A previous diagnosis of cancer correlated with a diagnosis of dry eye in either eye ($P = .023$) in the standard population. No other systemic conditions or medications were identified to have significant correlation with TFO or OSDI scores in the normal population or postrefractive subgroup.

Patients with diabetes on average had higher TFO values compared with patients without diabetes (mean high TFO 308.39 ± 11.96 vs 303.11 ± 12.03, $P = .016$), albeit diagnosis of diabetes did not impact the difference between eyes (8.20 ± 8.58 vs 7.23 ± 6.46, $P = .531$). Of interest, the highest TFO score correlated significantly with a diagnosis of diabetes mellitus ($P = .006$) in a standard population.

The mean OSDI values for both cohorts were 9.69 ± 10.56 and 15.28 ± 14.47, respectively ($P = .012$). Table 3 describes the breakdown of OSDI values and corresponding mean TFO outcomes. Figure 1 highlights the distribution of OSDI scores correlated with highest individual TFO value. Most (74.1%) patients identified as normal compared with only half of the postrefractive group (52.1%). Paradoxically, the mean TFO for the postrefractive cohort decreased through the increasing subjective classification, albeit the variability may reflect the low numbers per group. An OSDI score in the standard population correlated significantly with age, spherical equivalent, and an abnormal TFO score ($r = 0.124$, $P = <0.001$; $r = 0.076$, $P = .005$; and $r = 0.085$, $P = .002$, respectively). There were no statistically significant correlations between the OSDI value and age, spherical equivalent, or abnormal TFO score for the postrefractive cohort, although this is again likely to reflect the small cohort size. There was no correlation with mean keratometry in either cohort. On questioning, 38.5% of the standard cohort described a previous experience of dry eye compared with 23.4% of the postrefractive cohort ($P = .036$).

DISCUSSION

To our knowledge, our study represents the largest current sample to date of TFO scores in a normal population presenting for refractive surgery assessment. TFO is readily measured in the clinical setting and is routinely used as part of the wider battery of tests to diagnose DED.[9,10,12] The predictability of TFO remains high with a positive predictive value of between 85% and 98.4%, although both the reported specificity and sensitivity of the test have been shown to be variable, ranging from 59% to 96%.[13–16] The reported variability of readings has been attributed to tear film instability and evaporation rate, which in itself remains a reflection of DED.[17] Peng et al. used modeling to indicate that increasing tear film irregularity would lead to significant variation in local tear osmolarity, further reinforcing the possible impact on readings.[18] Environmental factors

Table 2. Mean Values for Cohort per Age Subgroup.

Variables	≤40 years (n = 841)	>40 years (n = 563)	*P* value
Age (y)	30.58 ± 5.39	53.04 ± 8.92	< .001
Mean highest individual TFO	301.92 ± 10.66	305.17 ± 13.62	< .001
Mean I-E difference	7.58 ± 7.64	9.08 ± 9.67	.002
% > 308 highest TFO	22.2	33.0	.005
OSDI	8.53 ± 9.51	12.05 ± 12.34	<.001

I-E = intereye; OSDI = Ocular Surface Disease Index; TFO = tear film osmolarity

Table 3. Breakdown for OSDI Classification Responses and Corresponding Mean TFO Scores.

OSDI classification	Standard population, %	Mean highest TFO ± SD	Range	Refractive population, %	Mean highest TFO ± SD	Range
Normal (0-12)	74.1	302.78 ± 11.75	270, 395	52.1	305.84 ± 10.63	288, 328
Mild dry eye (13-22)	16.8	304.21 ± 13.31	280, 388	22.9	302.60 ± 10.90	289, 319
Moderate dry eye (23-32)	5.8	304.40 ± 12.28	282, 340	14.6	303.50 ± 12.41	284, 320
Severe dry eye (33-100)	3.3	306.20 ± 12.23	281, 337	10.4	299.60 ± 7.67	219, 311

OSDI = Ocular Surface Disease Index; TFO = tear film osmolarity.

such as temperature, humidity, and airflow may influence the assessment.[19] It is therefore recommended to conduct the measurement in a single, controlled area to optimize reading consistency.

We found an average TFO value of 299.12 ± 11.94 mOsm/L in a large standard cohort of patients undergoing preoperative assessment for refractive surgery. The mean value is below the existing literature for normal or control populations, which suggest a value between 302 mOsm/L and 305.6 mOsm/L, albeit in modest sample sizes.[20,21] Of note, 82.6% of our patients in the standard population remained below the standard cutoff point for hyperosmolarity (308 mOsm/L), which suggests that tear film homeostasis is common in younger, healthy patients. Of interest to a clinical diagnosis of DED, the mean intereye difference of our cohort was 8.17 ± 8.60 mOsm/L, which represents a marker of unstable tear film. Although only 31.6% of patients recorded a difference above 8 mOsm/L, over half of the patients had at least 1 eye above the standard threshold for hyperosmolarity, confirming the likelihood that patients with hyperosmolarity will exhibit significant asymmetry between eyes. This is an important finding for patients presenting for consideration of laser refractive surgery. As surgery has been shown to lead to iatrogenic dry eye, this suggests that a considerable number of patients may be at risk for developing symptoms postoperatively or exhibiting variable wound healing.[22,23] The standard test protocol and significant sample size of our cohort suggest that this may be a significant finding within the refractive population seeking surgery. Further population studies would be ideal in providing greater understanding.

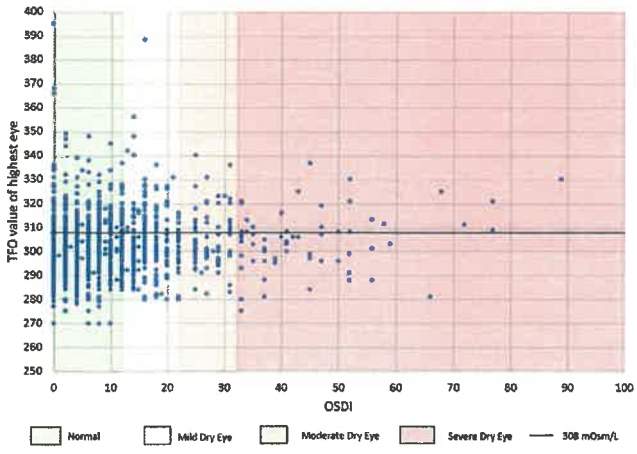

Figure 1. Distribution of OSDI scores correlated with highest individual TFO value. OSDI = Ocular Surface Disease Index; TFO = tear film osmolarity

A multitude of studies have investigated the effect of various systemic and ocular conditions on TFO.[6,24–26] Of these, autoimmune disorders such as Sjögren syndrome, rheumatoid arthritis, and diabetes have been shown to have higher TFO than control comparative cohorts.[27–29] Potvin et al. previously detailed the reported association between TFO and ocular conditions. Perhaps unsurprisingly, common to most ocular conditions with hyperosmolarity is a likely inflammatory component. Patients with thyroid eye disease, graft-vs-host diseases, and ocular rosacea have all been shown to exhibit high TFO scores in comparison to controls.[30] Our cohort further supports a difference in TFO variables between patients with diabetes, indicating that increased vigilance is required for patients with diabetes who may proceed to ocular surgery. Patients with diabetes in our study were not subdivided into groups based on whether appropriate glycemic control was maintained. However, given the mean age and that patients were presenting for elective laser refractive surgery screening, it was reasonable to assume that their disease was well controlled. We did not find significant differences in other systemic conditions, suggesting that mild cases or those that seem to be well controlled with medication are unlikely to exhibit significant clinical changes in tear homeostasis.

Various medications have been identified in making an impact on TFO values. Previously, patients using aspirin for antiaggregant purposes were identified to have a significantly lower prevalence of symptomatic dry eye while vitamin supplements such as vitamin D or omega-3 were similarly found to reduced TFO scores in patients.[24,25,31] We did not find a significant correlation with vitamin supplements or additional medication, while confirming only incremental changes in tear film stability in patients within the normal range of health.[26] Other medications such as the birth control pill have not shown an effect on tear osmolarity, consistent with the literature.[32]

Wearing contact lens provides the potential for increased osmolarity though enhanced evaporation and change of electrolyte concentrations across the precorneal tear film.[33] Early studies tended to show increases in TFO in contact lens patients in comparison to nonwearers; however, more recent findings support no significant change.[34–37] Paradoxically, we found that a history of contact lens wear resulted in a significantly lower TFO value compared with nonwearers. Both groups maintained a mean value within the normal range of osmolarity, suggesting a mild but not

clinically important impact. We did not record duration or type of contact lens wear or duration of contact lens removal prior to consultation, factors that may have further influenced analysis. In addition, the compensatory use of artificial tears in contact lens wearers could have led to this paradoxical effect of a lower TFO value among lens wearers.

Of note, 3.3% of our cohort had undergone previous refractive surgery. Denoyer et al. found that TFO was raised 1 month postsurgery in a cohort of laser-assisted in situ keratomileusis (316.3 ± 1.6 mOsm/L, respectively).[22] Kacerovska and coauthors identified a similar marked increase in TFO at 1 month in a LASIK cohort (320 ± 1.47 mOsm/L).[38] The mean TFO value of postrefractive eyes in our cohort was 299.72 ± 11.00 mOsm/L, which corresponded to the standard cohort. The minimum period from the initial refractive surgery in our population was 6 months, which may suggest that TFO changes after corneal refractive surgery may be transient. This supports analysis by Beheshtnejad et al. who identified TFO values returning to baseline levels at four months.[39]

Age seemed to impact mean TFO values and the mean difference between eyes, indicating increasing hyperosmolarity with time. We categorised the population based on age to reflect the potential surgery population and the plausible impact on the accuracy of outcomes (i.e., <40 years to represent a corneal refractive population and >40 years a lens-based procedure). Although both populations on average retained normal TFO values, the difference between eyes across groups suggests that patients more appropriate to lens-based procedures may have subtle hyperosmolarity concerns. This may impact the number of patients requiring tear film optimization prior to cataract surgery, although further studies to determine the impact of optimizing the tear film on refractive and safety outcomes are required.

We found a positive correlation between TFO and subjective assessment (OSDI) in the standard population but not in the postrefractive surgery cohort. That most TFO values remained below the threshold for hyperosmolarity in all OSDI classifications, however, suggests additional factors outside clinical dry eye signs contributing to the patient's level of ocular surface disease comfort. Of note, a greater percentage of patients in the standard group reported a previous experience of dry eye compared with the postrefractive cohort, although we suspect that routine contact lens wear, significantly higher in the standard cohort, may represent the main consideration in the patient response (58.4% vs 17.0%).

Our study was limited in that TFO values were not retested in the practice; therefore, we cannot make assumptions regarding test validity or repeatability. However, test protocols were in place to maintain consistency. Patients identified with tear film hyperosmolarity proceeding to surgery were pretreated with a regimen to ensure optimal tear film and corneal surface prior to final testing and surgery. The results of the analysis for the postrefractive subgroup were limited by the small sample population. Subsequently, the authors were unable to conduct analysis for patients with a prior history of laser refractive surgery separated by procedure types or approximate time since procedure. The results should therefore be considered with this background in mind.

The impact of our findings may resonate with cataract and refractive surgeons in particular, as almost one-fifth of routine patients exhibited tear film hyperosmolarity representing a possible risk for reduced postoperative outcomes and ocular comfort after surgery. Future population studies to confirm TFO in other groups may be valuable as would be postsurgical follow-up to determine whether an abnormal TFO value represents a significant risk factor in a suboptimal surgery outcome.

The study found that although most patients can be expected to fall within normal ranges, a reasonable percentage will be diagnosed with tear hyperosmolarity and therefore at risk for DED. Furthermore, osmolarity may be altered by contact lens wear and systemic conditions; however, the difference is unlikely to be significant if patient health is well controlled.

WHAT WAS KNOWN

- Tear film osmolarity is increasingly utilized as a diagnostic tool for dry eye.
- Dry eye has been shown to impact the refractive outcomes after cataract and corneal laser refractive procedures.

WHAT THIS PAPER ADDS

- This analysis provides the largest cohort of tear film osmolarity outcomes in a standard population presenting for surgery
- A small but appreciable percentage of patients will have tear film hyperosmolarity at presentation and represent a risk for suboptimal refractive outcomes without pretreatment.

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