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ORIGINAL RESEARCH

Prevalence of Dry Eye Disease and Ocular Surface Abnormalities in Eyes with Corneal Transplantation: A Cross-Sectional Study

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Purpose: To evaluate tear film and ocular surface parameters and estimate the prevalence of dry eye disease (DED) in eyes following corneal transplantation.

Patients and Methods: This cross-sectional study assessed 104 eyes of 81 patients who had undergone penetrating keratoplasty (PK; 81 eyes), deep anterior lamellar keratoplasty (DALK; 9 eyes), or endothelial keratoplasty (EK; 14 eyes) for ≥ 3 months. Comprehensive ocular surface evaluations included the Ocular Surface Disease Index (OSDI), tear osmolarity, tear meniscus height (TMH), fluorescein tear breakup time, Oxford fluorescein staining, eyelid margin morphology, Schirmer I test, meibomian gland expressibility, and meibum quality.

Results: Among post-PK/DALK eyes, more than 50% demonstrated at least one significant ocular surface abnormality, whereas this was observed in at least 25% of post-EK eyes. Elevated tear osmolarity was detected in approximately 20% of eyes in both groups. Based on TFOS DEWS II criteria, 32% of post-PK/DALK eyes and 57% of post-EK eyes met the diagnostic threshold for DED. Post-PK/DALK eyes with a follow-up time of ≤ 6 months exhibited significantly higher Oxford staining scores compared to those with follow-up > 6 months ($P = 0.011$). In unilateral PK/DALK cases, operated eyes showed greater ocular surface staining ($P < 0.001$) and a greater proportion of tear hyperosmolarity ($P = 0.001$) compared to unoperated fellow eyes.

Conclusion: DED is common after corneal transplantation. While more pronounced in the early postoperative period, ocular surface epitheliopathy may persist long-term after surgery. These findings underscore the need for proactive long-term ocular surface monitoring and management to optimize surgical outcomes.

Keywords: dry eye, keratoplasty, ocular surface, tear film, tear osmolarity

Introduction

Corneal transplantation is the most commonly performed and highly successful allogeneic procedure for treating corneal blindness worldwide.[1] Traditionally, more attention has been directed toward the prevention and treatment of endothelial graft rejection and disabling astigmatism, which are considered the leading causes of anatomical and functional graft failure, respectively. However, ocular surface diseases can also play a significant role in delaying visual rehabilitation and causing substantial morbidity, ultimately leading to non-rejection-related graft failure.[2] Studies have reported that at least 25% of full-thickness corneal graft failures are attributed to ocular surface problems.[3,4] Corneal transection during transplantation inevitably compromises corneal sensory innervation, especially in penetrating keratoplasty (PK) and deep anterior lamellar keratoplasty (DALK). These procedures involve a 360° full-thickness (PK) or near full-thickness (DALK) corneal incision, severing corneal nerves and resulting in complete denervation of the transplanted cornea.[5]

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This iatrogenic neurotrophic state, combined with various surgical, donor-related, and recipient-related factors, can impair ocular surface function, contribute to the signs and symptoms of dry eye disease (DED), and adversely affect surgical outcomes.[2]

Recently, tear film hyperosmolarity has been recognized as a key pathophysiological mechanism of DED, regardless of its underlying cause, perpetuating a cycle of ocular surface inflammation and tear film instability.[6,7] Thus, measuring tear osmolarity is considered a reliable metric for diagnosing DED.[8] Nonetheless, interpretation of tear osmolarity results requires caution, as variability in tear osmolarity measurements may arise from factors such as inadequate operator training, device inaccuracy, environmental and behavioral factors, ocular comorbidities, or the natural diurnal variation of tear film osmolarity.[9–11] Currently, data on tear film and ocular surface health following corneal transplantation remain limited.[12–25] While some studies have focused exclusively on postoperative corneal epithelial integrity,[12,14,17,25] others have evaluated additional tear film parameters but were limited by small sample sizes, short follow-up durations, or a limited range of diagnostic tests.[13,15,16,18–24] Tear osmolarity has also not yet been assessed in post-keratoplasty eyes. Therefore, this study aims to comprehensively evaluate tear film and ocular surface parameters, including tear osmolarity, and to estimate the prevalence of DED in eyes undergoing keratoplasty. Additionally, the study explores whether any clinical variables are significantly associated with ocular surface abnormalities following keratoplasty.

Materials and Methods

This was a cross-sectional study approved by the Ethics Committee of Ramathibodi Hospital, Mahidol University (No. MURA2020/1759) and adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants before study enrollment.

Study Population

Patients who underwent uneventful corneal transplantation surgery, either PK, DALK, or endothelial keratoplasty (EK), with a postoperative follow-up of at least three months were eligible for inclusion in this study. Inclusion criteria required patients to be 18 years or older at the time of surgery and to have a clear corneal graft without neovascularization. Exclusion criteria included large-diameter grafts ($\geq$ 8.75 mm), a history of other ocular surgeries, except for cataract surgery, contact lens use, preexisting anatomical or functional abnormalities of the nasolacrimal drainage, eyelids, conjunctiva, or limbus, active ophthalmic disease, systemic conditions known to affect ocular surface function, pregnancy or lactation, and hypersensitivity to any eye drops used in the study protocol. A total of 81 patients were ultimately enrolled in the study.

Surgical Techniques

All corneal transplantation surgeries were performed by three experienced corneal surgeons at Ramathibodi Hospital, Bangkok, Thailand, using standard surgical techniques. Briefly, in the PK group, a donor cornea was punched out using a Hessburg-Barron vacuum donor punch (Katena, Denville, NJ, USA), with the endothelial side facing up. The graft size was 0.5 mm larger than the recipient trephination size, except keratoconus cases, where the graft size was kept the same or 0.25 mm larger to compensate for myopia. The recipient cornea was trephined up to 80% depth using a 7.0- to 8.0-mm Barron vacuum trephine (Katena, Denville, NJ, USA). Care was taken to avoid reaching 100% depth of the cornea to prevent injury to the iris and lens. The anterior chamber was entered using a 15-degree blade. The circumferential cut was completed using curved corneal scissors. The corneal graft was then secured to the host rim with 16 interrupted 10–0 nylon sutures. For DALK, the big bubble technique was used to bare Descemet's membrane.[26] An iris spatula and corneal scissors were used to dissect the deep stroma into four quadrants, cutting each down from the margin of the trephination. The corneal donor button, with Descemet's membrane and endothelium removed, was then sutured onto the recipient eye's bare Descemet's membrane using a technique similar to that employed in PK. For both PK and DALK, the maximum recipient trephination size was 8.0 mm and the maximum graft size was 8.5 mm.

In the EK group, the Descemet stripping automated endothelial keratoplasty (DSAEK) and Descemet membrane endothelial keratoplasty (DMEK) techniques, along with the postoperative management, have been described previously.[27,28] For DSAEK, Descemet's membrane and diseased endothelium were stripped from the planned graft

area using a reverse-Sinskey hook and a DSAEK stripper. Venting incisions to improve graft adherence were not required, as per protocol since 2005. A 4.5 mm clear corneal incision was made using a 3.0 mm wide slit knife for graft insertion. The precut donor cornea was punched to a diameter of 7.5–8.5 mm, and the posterior lenticule was inserted into the recipient's anterior chamber using a Busin glide (Moria, Doylestown, PA, USA). Once the posterior lenticule was properly unfolded and well centered, it was fully pressed up against the recipient stroma using air. One or two interrupted 10–0 nylon sutures were used to close the corneal incision. For DMEK, after graft preparation, a 7.5–8.5 mm donor Descemet membrane was loaded into the curved glass injector system (DMEK surgical disposable set, DORC International® Zuidland, The Netherlands) and injected into the anterior chamber through a 2.75 mm clear corneal incision. The tapping technique, together with intracameral short bursts of balanced salt solution (BSS) was used to unfold and position the graft. The anterior chamber was initially filled with air before being replaced with 20% SF6 gas at the end of surgery. An inferior peripheral iridectomy was performed before donor insertion in all EK cases to prevent pupillary block.

Study Protocol

For all patients, data were collected on demographic characteristics, medical history, ocular history, indications for keratoplasty, intraoperative and postoperative complications, postoperative medications, and postoperative best spectacle-corrected visual acuity (BSCVA). A history of ocular herpes virus infection was documented separately, as it may independently influence tear film and ocular surface outcomes through mechanisms such as corneal nerve damage, chronic inflammation, or recurrent disease, potentially confounding the interpretation of post-keratoplasty ocular surface abnormalities. After completing data collection, a trained interviewer administered the Ocular Surface Disease Index (OSDI) questionnaire (Allergan, Irvine, CA, USA) to assess dry eye symptoms. To minimize the impact on tear film and ocular surface physiology for subsequent tests, a comprehensive ocular surface examination was then performed in order of increasing invasiveness: tear osmolarity, tear meniscus height (TMH), fluorescein tear breakup time (FTBUT), ocular surface fluorescein staining using the Oxford grading scale, eyelid margin morphology, Schirmer I test, meibomian gland expressibility, and meibum quality. In patients undergoing unilateral keratoplasty, the contralateral eye was also assessed for comparison.

Tear Osmolarity

Tear osmolarity was measured once in each eye using the TearLab Osmolarity System (OcuSense, San Diego, CA, USA) with disposable test cards provided by the manufacturer. Patients were instructed not to instill any eye drops within two hours before the examination. The system was calibrated at the start of each testing day according to the manufacturer's recommendations. With the patient looking in primary gaze, the osmolarity test card tip was placed on the inferior tear meniscus in the central portion of the temporal third of the lower eyelid. Avoiding contact with the conjunctiva or any pressure to the globe, the tip was kept still until a beep sounded after a few seconds, indicating successful tear collection. The handset was immediately re-docked in the base unit to ensure the sample was analyzed within 30 seconds, minimizing the risk of loss or unreliable results. Tear osmolarity was considered normal if it was < 308 mOsm/L and abnormal if it was ≥ 308 mOsm/L or if there was an interocular difference of > 8 mOsm/L, based on the TFOS DEWS II report.[8]

Tear Meniscus Height (TMH)

Inferior TMH was assessed with fluorescein. Fluorescein dye was carefully applied by wetting a fluorescein-impregnated strip with sterile, non-preserved saline, shaking off any excess liquid, and gently touching the lower conjunctival fornix with the fluid at the tip of the strip. To minimize the effects of reflex tearing and the temporary increase in TMH caused by fluorescein instillation, the inferior TMH was measured at two minutes after application. With the slit-lamp observation and illumination system aligned frontally to the inferior tear meniscus, patients were instructed to look at a fixed target located to maintain primary gaze. A vertical, short, 1-mm-wide slit beam with moderate illumination was focused on the central third of the inferior tear meniscus at 6 o'clock to prevent direct light exposure to the pupil during assessment. The inferior TMH was measured as the distance between the dark edge of the lower eyelid and the upper

limit of the stained tear meniscus and recorded in millimeters using a microscope scale.[29] A TMH of ≤ 0.2 mm was considered abnormal.[8]

Fluorescein Tear Breakup Time (FTBUT)

FTBUT was used to evaluate tear film stability. Patients were asked to blink naturally several times to distribute the fluorescein throughout the tear film and then hold their eyes open. The cornea was observed under the slit-lamp using a cobalt blue filter. A dry spot was indicated by the appearance of a black spot or line. The time interval between the last complete blink and the appearance of the first random dry spot was recorded in seconds as the FTBUT. The test was repeated three times in each eye, and the average of the results was used. An average FTBUT of < 10 seconds was considered abnormal.[8]

Ocular Surface Fluorescein Staining

Ocular surface fluorescein staining was rapidly assessed after the FTBUT measurement. The presence of any staining of the cornea and/or interpalpebral conjunctiva was recorded and graded using the Oxford Scheme 6-point scale (from 0 to 5). The total score ranged from 0 to 15,[30] with a score > 3 considered abnormal.

Eyelid Margin Morphology

Modified from the new grading scales for meibomian gland dysfunction (MGD) signs,[31] eyelid margin morphology was scored as 0 (absent) or 1 (present) for the following parameters: lid margin telangiectasia, plugging of meibomian gland orifices, lid margin irregularity, and lid margin thickening.

Schirmer I Test

The Schirmer I test without anesthesia was performed by folding the Schirmer paper strip (5 x 35 mm) at the notch and hooking the folded end over the temporal third of the lower eyelid margin for five minutes, ensuring the cornea was not touched. The score was reported in millimeters based on the length of the wetting from the notch. A Schirmer I score of < 10 mm/5 minutes was considered abnormal.[8]

Meibomian Gland Expressibility and Meibum Quality

Firm digital pressure was applied to the central five meibomian glands in the upper or lower tarsus through the skin surface of the eyelid. Meibomian gland expressibility was assessed on a scale of 0 to 3, according to the number of glands expressible: 0, all glands; 1, three to four glands; 2, one to two glands; and 3, no glands. Meibum quality was then assessed in each of the eight glands of the central third of the lower eyelid on a scale of 0 to 3 for each gland: 0, clear; 1, cloudy; 2, cloudy with debris (granular); and 3, thick, like toothpaste (total score range, 0–24).[32] Meibomian gland expressibility of grade ≥ 2 and a meibum quality score of ≥ 8 were considered abnormal.[32]

Statistical Analysis

Statistical analyses were performed with the statistical software package STATA version 18 (StataCorp, College Station, Texas, USA). For continuous data, normally distributed variables were expressed as mean and standard deviation (SD); non-normally distributed variables were expressed as median and range. Frequency and percentage were used for categorical data. The results of eyes with PK or DALK, which involved a 360° corneal incision, were compared with those of eyes with EK, which required significantly smaller incisions. The outcomes of eyes with a follow-up time of 6 months or less were compared with those of eyes with a follow-up time of greater than 6 months, where follow-up time referred to the interval between corneal transplantation and ocular surface evaluation. In patients who underwent unilateral keratoplasty, the results of the operated eyes were compared with those of the contralateral unoperated eyes of the same patients. Comparisons of tear film and ocular surface parameters between groups were performed using an independent *t*-test or Mann–Whitney *U*-test for continuous data and the Chi-square test or Fisher's exact test for categorical data, depending on the data distribution. As tear osmolarity in post-keratoplasty eyes has never been reported, associations between abnormal tear osmolarity and baseline characteristics or other tear film and ocular surface

parameters were analyzed using multiple logistic regression. A P value of less than 0.05 was considered statistically significant.

Results

Characteristics of the Study Population

Of the 104 post-keratoplasty eyes from the 81 enrolled patients, 81 eyes (77.9%) underwent PK, 9 (8.7%) underwent DALK, 8 (7.7%) underwent DSAEK, and 6 (5.8%) underwent DMEK. Baseline characteristics of the 104 eyes, categorized by type of corneal transplantation, are summarized in Table 1. Among the 90 post-PK/DALK eyes, the most common indication for corneal transplantation was infectious corneal scars (21 eyes, 23.3%), followed by bullous keratopathy secondary to laser or intraocular procedures (18 eyes, 20.0%), secondary graft failure (18 eyes, 20.0%), and Fuchs' endothelial corneal dystrophy (FECD) (8 eyes, 8.9%). Thirty-three eyes (36.7%) had undergone prior PK(s). Of the 14 post-EK eyes, 13 eyes (92.9%) underwent EK for FECD, while 1 eye (7.1%) received DSAEK for congenital hereditary endothelial dystrophy (CHED). Nearly all patients in the EK group were female. One eye (7.1%) had a history of prior DSAEK. The median durations between keratoplasty and ocular surface examination were 52 months for post-PK/DALK eyes and 50 months for post-EK eyes. Postoperative topical medications included preservative-free sodium hyaluronate artificial tears (104 eyes, 100%), corticosteroids containing preservatives (91 eyes, 87.5%), and anti-glaucoma agents that were either preserved or preservative-free (54 eyes, 51.9%). Artificial tears were typically administered every 4 to 6 hours, while topical corticosteroids were used once or twice daily. The percentages of eyes using each type of postoperative medication, categorized by corneal transplantation type, are provided in Table 1.

Tear Film and Ocular Surface Parameters Categorized by the Type of Corneal Transplantation

Table 2 presents the tear film and ocular surface parameters of 90 eyes that underwent PK or DALK and 14 eyes that underwent DSAEK or DMEK. In the PK/DALK group, 29 eyes (32.2%) had an OSDI score of ≥ 13, and all of these eyes

Table 1 Demographics and Baseline Characteristics of the 104 Post-Keratoplasty Eyes, Categorized by Type of Corneal Transplantation

Variables	Large-Incision Keratoplasty (PK or DALK)	Small-Incision Keratoplasty (DSAEK or DMEK)
Number of eyes, n (%)	90 (86.5)	14 (13.5)
Age (years), mean ± SD (range)	65.1 ± 15.5(22–87)	69.2 ± 12.6(33–83)
Sex: male/ female, n (%)	44/45(50/ 50)	1/13(7.1/ 92.9)
History of prior corneal transplant(s), n (%)		
• 1	24 (26.7)	1 (7.1)
• 2	7 (7.8)	0 (0.0)
• ≥ 3	2 (2.2)	0 (0.0)
History of ocular infection caused by herpesviruses, n (%)	20 (22.2)	0 (0.0)
Combined corneal transplantation and cataract surgery, n (%)	34 (37.8)	5 (35.7)
Duration between keratoplasty and examination (months), median (range)	52 (3–242)	50 (3–264)
Postoperative topical medication(s) use, n (%)		
• Artificial tears	90 (100)	14 (100)
• Corticosteroids	77 (85.6)	13 (92.9)
• Anti-glaucoma drug(s)	49 (54.4)	5 (35.7)

Abbreviations: DALK, deep anterior lamellar keratoplasty; DMEK, Descemet membrane endothelial keratoplasty; DSAEK, Descemet stripping automated endothelial keratoplasty; PK, penetrating keratoplasty; SD, standard deviation.

Table 2 Tear Film and Ocular Surface Parameters of Eyes Following Large-Incision Keratoplasty and Small-Incision Keratoplasty

Variables		Large-Incision Keratoplasty (PK or DALK) (90 Eyes)	Small-Incision Keratoplasty (DSAEK or DMEK) (14 Eyes)
OSDI score	Median (range)	10.2 (0–44.4)	24.8 (0–38.6)
	≥ 13, n (%)	29 (32.2)	8 (57.1)
Tear osmolarity (mOsm/L)	Mean ± SD (range)	294.8 ± 15.6 (275–346)	296.6 ± 18.8 (277–338)
	≥ 308 mOsm/L, n (%)	18 (20.0)	3 (21.4)
Tear meniscus height (mm)	Median (range)	0.2 (0–1)	0.25 (0.1–0.5)
	≤ 0.2 mm, n (%)	65 (72.2)	7 (50.0)
Average FTBUT (seconds)	Median (range)	4.3 (0.8–11.6)	4.0 (1.5–9.3)
	< 10 seconds, n (%)	89 (98.9)	14 (100)
Oxford staining score	Median (range)	6 (0–15)	3 (0–15)
	> 3, n (%)	51 (56.7)	4 (28.6)
Eyelid margin morphology, n (%) • Normal • ≥ 1 abnormal sign(s)		 2 (2.2) 88 (97.8)	 0 (0) 14 (100)
Schirmer I score (mm)	Median (range)	8 (0–29)	6 (4–35)
	< 10 mm, n (%)	51 (56.7)	8 (57.1)
Meibomian gland grading	Gland expression, n (%) • Grade 0–1 • Grade 2-3	 30 (33.3) 60 (66.7)	 7 (50) 7 (50)
	Meibum quality • mean ± SD (range) • Score ≥ 8, n (%)	 15.8 ± 6.4 (2–24) 78 (86.7)	 14.9 ± 7.1 (3–24) 12 (85.7)

Abbreviations: DALK, deep anterior lamellar keratoplasty; DMEK, Descemet membrane endothelial keratoplasty; DSAEK= Descemet stripping automated endothelial keratoplasty; FTBUT, fluorescein tear breakup time; OSDI, Ocular Surface Disease Index; PK, penetrating keratoplasty; SD, standard deviation.

also exhibited either an average FTBUT < 10 seconds, tear osmolarity ≥ 308 mOsm/L, or significant positive ocular surface staining, thereby fulfilling the diagnostic criteria for DED as proposed by the TFOS DEWS II.[8] In the EK group, 8 eyes (57.1%) met the TFOS DEWS II diagnostic criteria for DED. Compared to the EK group, the PK/DALK group demonstrated lower OSDI scores, a higher proportion of eyes with TMH ≤ 0.2 mm, and greater postoperative Oxford staining scores (Figure 1). No significant associations were observed between any of the abnormal tear film and ocular surface parameters and baseline characteristics in either group. Due to the small number of eyes having undergone DSAEK or DMEK, subgroup analyses were limited to only eyes that had undergone PK or DALK.

Comparison of tear film and ocular surface parameters between post-PK/DALK eyes with a follow-up time of 6 months or less (13 eyes) and those with a follow-up time of more than 6 months (77 eyes) is presented in Table 3. The number of eyes with an Oxford staining score > 3 was significantly higher in eyes with a follow-up time of 6 months or less compared to those with a follow-up time exceeding 6 months ($P = 0.028$). There were no significant differences in other tear film and ocular surface parameters between the two groups. When the cutoff between the early and late

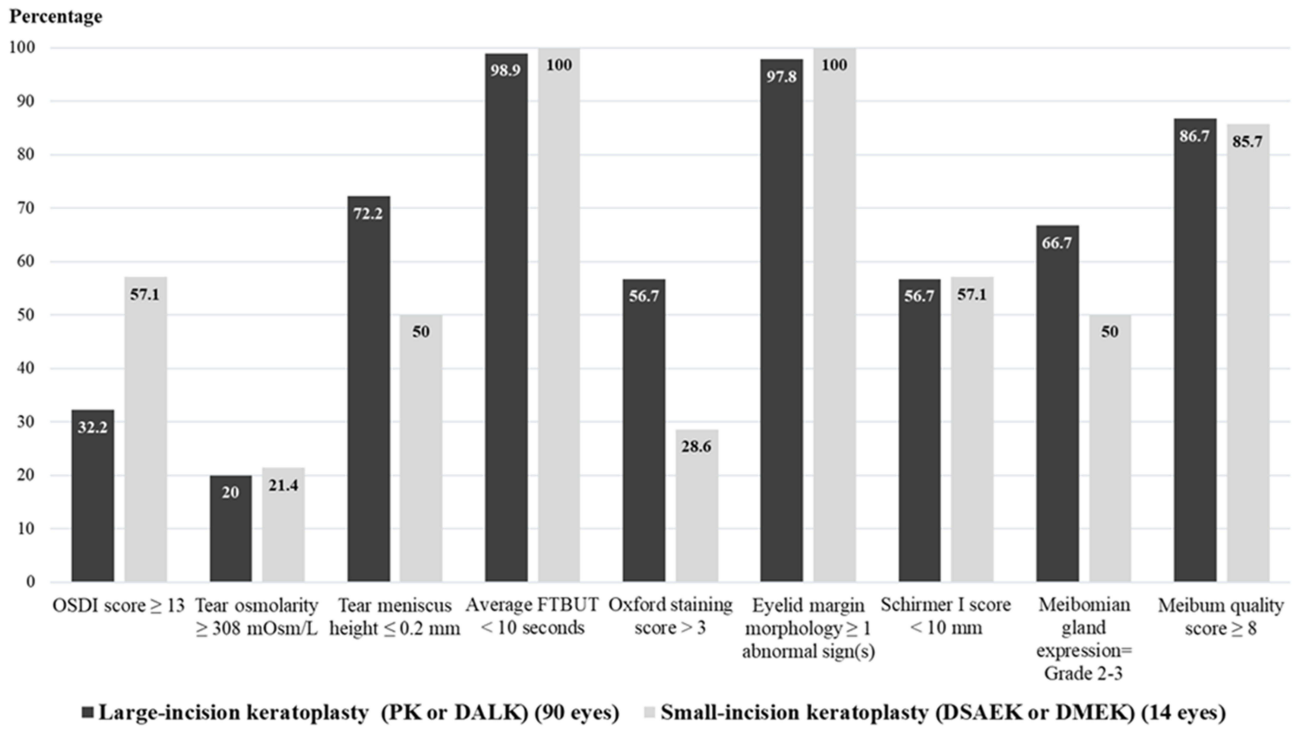

Figure 1 Proportions of eyes with abnormal tear film and ocular surface parameters following large-incision keratoplasty (PK or DALK) and small-incision keratoplasty (DSAEK or DMEK). Comparisons are descriptive and not based on statistical testing due to the imbalance in group sizes.

postoperative periods was set at 12 months instead of 6 months, the significant difference in Oxford staining scores was no longer observed.

In patients undergoing unilateral PK or DALK, tear film and ocular surface parameters of the operated eyes were compared with those of the unoperated fellow eyes of the same patients (Table 4). Operated eyes exhibited significantly higher Oxford staining scores compared to unoperated fellow eyes ($P < 0.001$). The proportion of eyes with tear osmolarity ≥ 308 mOsm/L was significantly higher in operated eyes than in unoperated fellow eyes ($P = 0.001$), although

Table 3 Tear Film and Ocular Surface Parameters of Post-PK/DALK Eyes with a Follow-Up Time (the Interval Between Keratoplasty and Ocular Surface Examination) of 6 Months or Less and Those with a Follow-Up Time of More Than 6 Months

Variables		**Follow-Up of ≤ 6 Months (13 Eyes)**	**Follow-Up of > 6 Months (77 Eyes)**	***P*-value**
OSDI score	Median (range)	12.5 (0–22.9)	9.1 (0–44.4)	0.434
	≥ 13, n (%)	5 (38.5)	24 (31.1)	
Tear osmolarity (mOsm/L)	Mean ± SD (range)	296.9 ± 14.7 (278–333)	294.4 ± 14.6 (275–346)	0.565
	≥ 308 mOsm/L, n (%)	3 (23.1)	15 (19.5)	
Tear meniscus height (mm)	Median (range)	0.15 (0–0.3)	0.2 (0.05–1)	0.083
	≤ 0.2 mm, n (%)	11 (84.6)	54 (70.1)	

(*Continued*)

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Table 3 (Continued).

Variables		Follow-Up of ≤ 6 Months (13 Eyes)	Follow-Up of > 6 Months (77 Eyes)	*P*-value
Average FTBUT (seconds)	Mean ± SD (range)	4.6 ± 1.9 (2.3–8.3)	4.4 ± 2.2 (0.8–11.6)	0.737
	< 10 seconds, n (%)	13 (100)	76 (98.7)	
Oxford staining score	Median (range)	6 (0–12)	6 (0–15)	**0.028**
	> 3, n (%)	11 (84.6)	40 (52.0)	
Eyelid margin morphology, n (%) • Normal • ≥ 1 abnormal sign(s)		0 13 (100)	2 (2.6) 75 (97.4)	1.000
Schirmer I score (mm)	Median (range)	5 (0–17)	8 (0–29)	0.170
	< 10 mm, n (%)	8 (61.5)	43 (55.8)	
Meibomian gland grading	Gland expression, n (%) • Grade 0–1 • Grade 2-3	 5 (38.5) 8 (61.5)	 25 (32.5) 52 (67.5)	0.753
	Meibum quality • mean ± SD (range) • Score ≥ 8, n (%)	 16.5 ± 6.3 (3–24) 11 (84.6)	 15.6 ± 6.4 (2–24) 67 (87.0)	0.668

Notes: Bold text indicates statistical significance at the $P < 0.05$ level.
Abbreviations: FTBUT, fluorescein tear breakup time; OSDI, Ocular Surface Disease Index; SD, standard deviation.

Table 4 Tear Film and Ocular Surface Parameters of Operated Eyes and Unoperated Fellow Eyes of the Same Patients with Unilateral PK or DALK

Variables		Operated Eyes (PK or DALK) (55 Eyes)	Unoperated Fellow Eyes (55 Eyes)	*P*-value
Tear osmolarity (mOsm/L)	Mean ± SD (range)	293.2 ± 13.3 (275–336)	291.2 ± 10.5 (275–310)	0.365
	≥ 308 mOsm/L, n (%)	9 (16.4)	2 (3.6)	**0.001**
	Interocular difference (mOsm/L), • mean ± SD (range) • > 8 mOsm/L, n (%)	11.4 ± 8.3 (0–31) 32 (58.2)		-
Tear meniscus height (mm)	Median (range)	0.2 (0.05–1)	0.2 (0.1–0.8)	1.000
	≤ 0.2 mm, n (%)	37 (67.3)	36 (65.5)	
Average FTBUT (seconds)	Median (range)	4.5 (1.5–9.2)	5.1 (1.5–13.8)	0.194
	< 10 seconds, n (%)	55 (100)	49 (89.1)	
Oxford staining score	Median (range)	6 (0–15)	1 (0–5)	**0.000**
	> 3, n (%)	35 (63.6)	6 (10.9)	

(*Continued*)

Table 4 (Continued).

Variables		Operated Eyes (PK or DALK) (55 Eyes)	Unoperated Fellow Eyes (55 Eyes)	*P*-value
Eyelid margin morphology, n (%) • Normal • ≥ 1 abnormal sign(s)		 2 (3.6) 53 (96.4)	 5 (9.1) 50 (90.9)	0.079
Schirmer I score (mm)	Median (range)	10 (0–29)	9 (0–28)	0.600
	< 10 mm, n (%)	25 (45.5)	31 (56.4)	
Meibomian gland grading	Gland expression, n (%) • Grade 0–1 • Grade 2-3	 19 (34.5) 36 (65.5)	 17 (30.9) 38 (69.1)	0.680
	Meibum quality • mean ± SD (range) • Score ≥ 8, n (%)	 15.0 ± 6.4 (2–24) 47 (85.5)	 13.8 ± 6.4 (2–24) 45 (81.8)	0.234

Notes: Bold text indicates statistical significance at the $P < 0.05$ level.
Abbreviations: DALK, deep anterior lamellar keratoplasty; FTBUT, fluorescein tear breakup time; PK, penetrating keratoplasty; SD, standard deviation.

no significant difference in average tear osmolarity values between the two groups was found ($P = 0.365$). Operated eyes also tended to exhibit at least one abnormal eyelid sign more frequently than unoperated fellow eyes, however, this difference did not reach statistical significance ($P = 0.079$). The remaining tear film and ocular surface parameters showed no significant differences between the operated and unoperated fellow eyes.

Associations Between Abnormal Tear Osmolarity and Baseline Characteristics or Other Tear Film and Ocular Surface Parameters

Given the lack of previous reports on tear osmolarity in post-keratoplasty eyes, we analyzed associations between abnormal tear osmolarity (≥ 308 mOsm/L) and baseline characteristics, as well as other tear film and ocular surface parameters. Elevated tear osmolarity of ≥ 308 mOsm/L was negatively associated with TMH ($P = 0.004$, odds ratio = 0.001, 95% confidence level (CI) 0.00–0.24; Table 5). A multivariable logistic regression model was then constructed to examine all variables with a P value < 0.15 in combination. In this model, none of the baseline characteristics or other tear film and ocular surface parameters, including TMH, were significantly associated with elevated tear osmolarity.

Discussion

This study is unique in comprehensively investigating tear film and ocular surface parameters, including tear osmolarity, and in estimating the prevalence of DED in post-keratoplasty eyes. The key findings were that, based on the diagnostic criteria recommended by the TFOS DEWS II and MGD reports,[8,32] over half of the eyes undergoing either PK/DALK or EK for at least 3 months and up to 22 years had some degree of ocular surface abnormalities, including tear film instability (FTBUT < 10 seconds), decreased tear volume (TMH ≤ 0.2 mm), reduced aqueous tear production (Schirmer I score < 10 mm), ocular surface epithelial damage (Oxford staining score > 3; observed only in the PK/DALK group), and signs of MGD (abnormal eyelid margin morphology, poor meibomian gland expressibility, and a meibum quality score ≥ 8); and approximately 20% had tear film hyperosmolarity (≥ 308 mOsm/L). DED was diagnosed in 32.2% of PK/DALK eyes and 57.1% of EK eyes.

Previous studies reported that within the first 3–4 months after PK, 33–63% of patients developed various forms of epithelial keratopathy, such as coarse punctate epithelial keratopathy, hurricane keratopathy, epithelial defects, and filamentary keratopathy.[12,14,25] Another study found that 10 of 11 patients with persistent corneal epithelial defect

Table 5 Associations Between Abnormal Tear Osmolarity and Baseline Characteristics or Other Tear Film and Ocular Surface Parameters in 104 Post-Keratoplasty Eyes

Variables	Tear Osmolarity ≥ 308 mOsm/L (21 Eyes)	Tear Osmolarity < 308 mOsm/L (83 Eyes)	*P*-value	Odd Ratio	95% CI
Baseline characteristics					
Tear osmolarity (mOsm/L), mean ± SD (range)	319.1 ± 11.3 (308–346)	288.9 ± 8.3 (275–306)	-	-	-
Age (years), mean ± SD	68.4 ± 12.5	65.4 ± 15.8	0.411	1.01	0.98–1.05
Sex: male/ female, n (%)	7/14 (33.3/66.7)	39/44 (47.0/53.0)	0.260	1.77	0.65–4.84
Number of prior transplant(s), median (range)	1 (1–3)	1 (1–5)	0.924	0.97	0.50–1.86
History of ocular infection caused by herpesviruses, n (%)	7 (33.3)	13 (15.7)	0.066	2.69	0.91–7.95
Type of corneal transplantation, n (%) • PK or DALK • DSAEK or DMEK	 18 (85.7) 3 (14.3)	 72 (86.7) 11 (13.3)	0.695	1.20	0.51–2.14
Combined corneal transplantation and cataract surgery, n (%)	10 (47.6)	29 (34.9)	0.284	1.69	0.64–4.46
Duration between keratoplasty and examination (months), median (range)	46 (3–232)	55.5 (3–264)	0.806	1.00	0.99–1.01
Postoperative topical medication(s) use, n (%) • Artificial tears • Corticosteroids • Anti-glaucoma drug(s)	 21 (100) 19 (90.5) 12 (57.1)	 83 (100) 69 (83.1) 42 (50.6)	 - 0.405 0.592	 - 1.93 1.30	 - 0.40–9.23 0.50–3.42
Other tear film and ocular surface parameters					
OSDI score, median (range)	12.5 (0–31.8)	9.1 (0–44.4)	0.278	1.02	0.98–1.07
Tear meniscus height (mm), median (range)	0.1 (0–0.3)	0.2 (0.05–1)	0.004	0.001	0.00–0.24
Average FTBUT (second), median (range)	3.7 (0.8–8.0)	4.5 (1.5–11.6)	0.143	0.84	0.65–1.07
Oxford staining score, median (range)	6 (0–15)	3 (0–15)	0.057	1.11	1.00–1.25
Eyelid margin morphology, n (%) • Normal • ≥ 1 abnormal sign(s)	 0 (0) 21 (100)	 2 (2.4) 81 (97.6)	1.000	-	-
Schirmer I score (mm), median (range)	4 (0–35)	9 (0–29)	0.141	0.95	0.88–1.02
Meibomian gland grading • Gland expression, n (%) ○ Grade 0–1 ○ Grade 2–3 • Meibum quality, mean ± SD	 7 (33.3) 14 (66.7) 17. 7 (5.1)	 30 (36.1) 53 (63.9) 15.1 (6.7)	 0.810 0.097	 1.13 1.07	 0.41–3.11 0.98–1.16

Abbreviations: CI, confidence interval; DALK, deep anterior lamellar keratoplasty; DMEK, Descemet membrane endothelial keratoplasty; DSAEK, Descemet stripping automated endothelial keratoplasty; FTBUT, fluorescein tear breakup time; OSDI, Ocular Surface Disease Index; PK, penetrating keratoplasty; SD, standard deviation.

following PK (90.9%) experienced the onset of the condition within the first 3 months after surgery.[17] Our study also demonstrated significantly higher Oxford staining scores in post-PK/DALK eyes with a follow-up time of 6 months or less, compared to those with a follow-up time exceeding 6 months. Thus, these results suggest that ocular surface epithelial damage typically arises and may be more pronounced in the early postoperative period; however, significant ocular surface epitheliopathy can still frequently occur months to years after surgery. Additionally, in our study, postoperative abnormal tear film and ocular surface parameters were not significantly associated with either preoperative baseline characteristics or postoperative topical medications. Meanwhile, prior studies have reported associations

between older recipient age, certain preoperative diagnoses, preexisting anterior blepharitis or decreased corneal sensation, and the use of postoperative topical antibiotics with a higher prevalence of punctate epithelial keratopathy in the early period following PK.[12,14,25] This difference might be attributed to the relatively advanced age, favorable preoperative diagnoses, and uniform postoperative regimens among our study population, which may have limited the variability needed to detect such associations.

We also demonstrated that eyes that underwent DSAEK or DMEK appeared to present with more dry eye symptoms, greater tear volume, and less epithelial damage compared with those that received PK or DALK. Having more dry eye symptoms in the post-EK group supports the previous evidence of preserved corneal sensation in DSAEK,[19,33] in contrast to the profound reduction in corneal sensation observed after PK and DALK.[5,13,16,19,21] This paradox—more symptoms but less objective ocular surface damage—highlights the role of corneal innervation in symptom perception. The more intact corneal nerves in EK procedures likely provide both protective reflexes and trophic factors that contribute to faster recovery of tear film function and better long-term maintenance of ocular surface health after surgery. In contrast, the extensive nerve disruption from PK and DALK may blunt symptom reporting despite more ocular surface damage, due to impaired sensory feedback. In addition to the neurotrophic state, the irregular graft surface commonly observed around sutures following PK has also been implicated in delayed corneal epithelial healing. This surface irregularity may disrupt uniform tear film distribution, alter the composition or dynamics of tear components, and potentially inhibit the centripetal migration of corneal epithelial cells.[2,13] It has also been postulated that surface irregularity, as reflected by a higher surface regularity index in post-PK patients, together with irritation by sutures and corneal wound healing, may stimulate reflex tear secretion.[18,19] Conversely, the improved surface regularity seen in post-EK patients might reduce the stimulus for reflex tearing.[19] This hypothesis could help explain the comparable Schirmer I scores between the PK/DALK and EK groups in our study, despite the EK group exhibiting a slightly greater TMH.

Another notable observation from our study is that, among patients who underwent unilateral PK or DALK, the operated eyes demonstrated significantly more ocular surface damage and were more likely to exhibit at least one abnormal eyelid sign compared to their unoperated fellow eyes, although this difference was not statistically significant. These findings align with those of a prior study.[24] The continuous use of topical corticosteroids postoperatively may have mitigated eyelid inflammation, contributing to the lack of statistically significant differences between the two eyes. Nevertheless, unlike the prior report,[24] our study did not find a significant difference in FTBUT between operated and unoperated fellow eyes. The discrepancy may be attributed to differences in age and indication for surgery between the study populations. The older age of our patients (65.1 ± 15.5 years), compared to those in the previous study (38 ± 14 years), likely contributed to the overall lower baseline FTBUT observed in our cohort. An average FTBUT < 10 seconds was noted in 89 eyes (98.9%) and < 5 seconds in 56 eyes (62.2%). Consequently, the anticipated difference in FTBUT between the operated and unoperated fellow eyes may have been obscured due to the already compromised tear film stability in both eyes. More interestingly, the operated eyes showed a higher proportion of tear osmolarity ≥ 308 mOsm/L than their unoperated counterparts. The hyperosmolar tears indicate a disturbance in tear film homeostasis in post-keratoplasty eyes, emphasizing that the underlying neurotrophic state may induce dry eye pathology even when not all clinical symptoms and signs are overtly apparent.

Furthermore, abnormal tear osmolarity of ≥ 308 mOsm/L was not correlated with other DED signs in this study. This finding is not unexpected, as previous research in patients with moderate to severe DED has shown that tear osmolarity, as measured by the TearLab system, exhibits only weak correlations with other clinical signs such as conjunctival and corneal staining scores, TBUT, and Schirmer scores and shows no correlation with OSDI scores.[34] Moreover, changes in tear osmolarity have not been consistently associated with changes in either signs or symptoms of DED.[34,35] This may be partly attributed to the known high variability in osmolarity measurements obtained using the TearLab system, which may limit its reliability as a standalone diagnostic tool.[10] To minimize variability from operator or technical errors, all tear osmolarity measurements in this study were conducted by a single, well-trained investigator under the same environmental conditions. This approach was adopted to enhance the reliability and consistency of the data collected using the TearLab system.

The strengths of the present study included its relatively large sample size and extended follow-up time, which enabled a more comprehensive assessment of long-term ocular surface outcomes after keratoplasty. To the best of our knowledge, this is the first study to evaluate tear osmolarity specifically in eyes that underwent various types of corneal transplantation, providing novel insights into tear film homeostasis and dry eye status across different surgical techniques. Importantly, this study excluded unusually large grafts and high-risk corneas with neovascularization, thereby ensuring that the findings more directly reflect genuine post-keratoplasty ocular surface abnormalities rather than being confounded by surgical technique or preexisting ocular surface risk factors. Beyond triggering an intense host immune response, large-diameter trephinations may lead to greater corneal nerve transection and ocular surface disturbance.[36] Likewise, persistent or newly developed corneal neovascularization can increase ocular surface inflammation and the risk of ocular surface complications, such as epithelial breakdown and tear film instability. Both factors could otherwise bias the interpretation of dry eye-related findings.

The limitations of this study included its cross-sectional design, which allowed only between-group comparisons stratified by follow-up duration but did not permit evaluation of longitudinal changes within the same patients from the early (eg $\leq$ 6 months) to the late (eg > 6 months) postoperative period, nor assessment of causality. However, patients with corneal blindness requiring corneal transplantation often present with poor preoperative tear film and ocular surface conditions.[23] Therefore, direct comparisons of ocular surface assessments before and after surgery may not accurately isolate the true impact of keratoplasty on tear film and ocular surface in these eyes. The heterogeneity of the study population and the unequal group sizes also restricted the ability to perform statistical comparisons between the PK/DALK and EK groups and limited the generalizability of some conclusions. Additionally, the small sample size in the EK group precluded reliable subgroup analyses. Furthermore, although a thorough ocular surface examination was performed, some techniques, such as FTBUT and TMH measurements, were operator-dependent. Nonetheless, these methods are widely used in clinical practice and have demonstrated good diagnostic accuracy and correlation with other DED tests.[8,37] Regarding variables associated with abnormal tear osmolarity, while multivariate logistic regression was chosen for this study due to its suitability for binary outcomes, other machine learning models (eg, random forests, support vector machines, or gradient boosting methods), may offer additional value by capturing nonlinear relationships among variables and improving predictive accuracy and variable importance ranking. However, given the relatively modest sample size of our study, such models would risk overfitting and may not yield reliable or generalizable results. Lastly, the influence of unmeasured or uncontrolled confounding factors, including suture status, preservatives in postoperative topical eye drops, prolonged corticosteroid use, the widespread use of preservative-free sodium hyaluronate artificial tears, and variations in artificial tear administration frequency, cannot be fully ruled out. Future studies with larger cohorts of eyes that have undergone EK may benefit from incorporating additional informative assessments, such as corneal sensitivity testing, infrared meibography, in vivo confocal microscopy, anterior segment optical coherence tomography (OCT), and corneal topography. Longitudinal studies with repeated pre- and postoperative measurements at multiple time points are also warranted to better characterize the temporal evolution of ocular surface changes after keratoplasty. Furthermore, applying advanced machine learning approaches to larger, multicenter datasets represents an important future direction to refine the prediction of abnormal tear osmolarity and enhance understanding of the multifactorial determinants of ocular surface abnormalities in this population.

Conclusions

In summary, this study highlights that a substantial proportion of eyes undergoing keratoplasty experience dry eye symptoms and signs, with at least one-third of patients meeting the TFOS DEWS II diagnostic criteria for DED. The symptom-sign disparity between keratoplasty types, with EK eyes reporting more symptoms despite less ocular surface damage, whereas PK/DALK eyes showed the opposite pattern, underscores the critical role of corneal innervation in post-transplant ocular surface health. Notably, abnormalities in tear film and ocular surface parameters may persist beyond the early postoperative period. As DED and ocular surface abnormalities can directly or indirectly contribute to both rejection-related and non-rejection-related graft failures, these findings emphasize the necessity of proactive, long-term monitoring and vigorous management of ocular surface health in post-keratoplasty patients to optimize surgical outcomes.

Data Sharing Statement

The authors confirm that the data supporting the findings of this study are presented within the article. Any additional raw data supporting the conclusions of this study are available on request from the corresponding author due to privacy/ethical restrictions.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing interests in this work.

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