Journal of Zhejiang University-SCIENCE B (Biomedicine & Biotechnology)
ISSN 1673-1581 (Print); ISSN 1862-1783 (Online)
www.jzus.zju.edu.cn; www.springerlink.com
E-mail: jzus@zju.edu.cn

Assessments of tear meniscus height, tear film thickness, and corneal epithelial thickness after deep anterior lamellar keratoplasty*

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Received Feb. 22, 2017; Revision accepted May 1, 2017; Crosschecked Feb. 7, 2018

Abstract: Objective: To assess the lower tear meniscus height (LTMH), central tear film thickness (CTFT), and central corneal epithelial thickness (CCET) after deep anterior lamellar keratoplasty (DALK). Methods: This was a retrospective cross-sectional study of 20 patients who had DALK in one eye over a three-month period. LTMH, CTFT, and CCET of the operated eyes and the unoperated fellow eyes were measured using high-definition optical coherence tomography (HD-OCT). Correlations between three OCT assessments and age, time following surgery, graft size, bed size, and the number of residual sutures were analyzed. Results: Compared to patients with keratoconus, patients with other corneal conditions had significantly higher CCET in the fellow eye (P=0.024). For all patients, CCET in the operated eye was significantly negatively correlated with the number of residual sutures (R=−0.579, P=0.008), and was significantly positively correlated with time following surgery (R=0.636, P=0.003). In the fellow eye, a significant positive correlation was found between age and CCET (R=0.551, P=0.012), and a significant negative correlation between age and CTFT (R=−0.491, P=0.028). LTMH was found to be significantly correlated between operated and fellow eyes (R=0.554, P=0.011). There was no significant correlation between LTMH and age, bed/graft size, time following surgery, or residual sutures (all possible correlations, P>0.05). Conclusions: Patients with keratoconus tend to have a thinner central corneal epithelium. Corneal epithelium keeps regenerating over time after DALK. DALK did not induce a significant change in tear volume compared with the fellow eye. Postoperative tear function might depend on an individual's general condition, rather than on age, gender, bed/graft size, time following surgery, or residual sutures.

Key words: Tear meniscus height; Corneal epithelial thickness; Tear film; Deep anterior lamellar keratoplasty (DALK); High-definition optical coherence tomography (HD-OCT); Keratoconus
https://doi.org/10.1631/jzus.B1700095 **CLC number:** R779.65

1 Introduction

Dry eye is one of the common postoperative complications of corneal transplantation and may be associated with multiple mechanisms (Lin et al., 2014). During corneal-related surgery, the afferent nerve fibers of the cornea are severed, which may interrupt the cornea-trigeminal nerve-brainstem-facial nerve-lacrimal gland reflex arc and result in decreased tear secretion (Xie, 2016). The morphological changes of the transplanted cornea, such as corneal epithelium redistribution, the changed shape of the cornea and the sutures, may affect tear film distribution and increase tear evaporation. Inflammatory responses together with tear deficiency may lead to further ocular surface damage including epithelial defect, impaired wound healing, infection, and even graft failure (Darwish et al., 2007; Lin et al., 2014). Therefore, early identification and treatment of tear dysfunction and the associated corneal epithelial dysfunction are essential to prevent severe postoperative complications.

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As an alternative to conventional penetrating keratoplasty (PKP), deep anterior lamellar keratoplasty (DALK) has been widely performed to treat corneal opacity induced by keratoconus, corneal infection, corneal dystrophy, ocular trauma, and ocular surface burn, in which the lesion reaches the corneal stroma without endothelial impairment (Yao et al., 2002; Hara et al., 2013). The Descemet's membrane and endothelium of the host cornea are preserved during DALK, causing less surgical damage, fewer complications including fewer or no endothelial rejection, and better clinical outcome than after PKP (Yao, 2008). However, quantitative evaluations of tear function and corneal epithelium after DALK have not yet been fully established. Traditional objective assessments of tear function such as the Schirmer test, tear break-up time, tear osmolarity, and corneal fluorescein staining have been widely applied in clinical practice, but the accuracy and repeatability of these methods are questionable (Nichols et al., 2004; Savini et al., 2008; Bunya et al., 2015). Brush cytology, impression cytology, ultrasound, and in vivo confocal microscopy are traditional methods to evaluate the corneal epithelium, but they require direct or indirect contact with the cornea (Francoz et al., 2011; Cui et al., 2014). During recent years, tear meniscus measurement using anterior segment optical coherence tomography (OCT) has been shown to be more reliable, with high sensitivity and specificity in the diagnosis of dry eye (Czajkowski et al., 2012; Arriola-Villalobos et al., 2015). In particular lower tear meniscus height (LTMH) has been used in recent corneal surgery-associated dry eye studies (Czajkowski et al., 2012; Xie et al., 2014; Arriola-Villalobos et al., 2015). The high-definition (HD) property of current OCT technology has also shown good reliability and repeatability in the evaluation of central corneal epithelial thickness (CCET) and central tear film thickness (CTFT) (Francoz et al., 2011; Werkmeister et al., 2013; Cui et al., 2014; Liang et al., 2016).

In this retrospective cross-sectional study, we used HD-OCT to evaluate and compare LTMH, CTFT, and CCET between the operated and unoperated fellow eyes in patients after DALK. Correlations between three OCT assessments and age, time following surgery, graft size, bed size, and the number of residual sutures were also analyzed.

2 Materials and methods

2.1 Patients

We retrospectively and cross-sectionally investigated patients who had keratoconus, corneal infection, corneal dystrophy, ocular trauma, or other ocular surface diseases and who underwent primary graft by DALK in one eye by the same experienced surgeon (YFY) between 2012 and 2015. Patients who completed regular follow-up over three months after DALK were included. Patients were excluded if they: did not receive a graft by a primary procedure; had other ocular surgeries in either eye; developed ocular disease other than the primary disease in either eye; developed postoperative complications such as infection, rejection, or recurrence of primary ocular disease; had meibomian gland dysfunction, blepharitis, or other ocular surface disorders in either eye prior to surgery; wore contact lenses. Patients who had bilateral corneal dystrophy, Stevens-Johnson syndrome, or other ocular surface diseases which caused irregular corneal epithelium distribution in the fellow eye were also excluded. A total of 20 patients were finally included in this study. Age, gender, time following surgery, graft size, bed size, and the number of residual sutures were documented and analyzed. This study was approved by the institutional review board of Sir Run Run Shaw Hospital, School of Medicine, Zhejiang University, Hangzhou, China.

2.2 DALK procedures

All DALK procedures were performed by the same surgeon (YFY) using Yao's hooking-and-detaching technique which had been introduced previously (Yao, 2008; Wu et al., 2012). A trephine 7.25 to 8.25 mm in diameter was used to perform trephination, and then a pocket was created from a small area of Descemet's membrane exposed at 12 o'clock in the recipient bed around the trephined margin by hooking the stromal fibers with a concave forceps tip. A single layer of full stroma extending to the full bed was then detached from the Descemet's membrane by injecting viscoelastic material between the stroma and the Descemet's membrane. Complete exposure of the Descemet's membrane was then created in the full bed. A donor corneal button, which was obtained from a cryopreserved eye stored at −20 °C without Descemet's membrane stripping, was sutured by 16 bites of

interrupted 10-0 nylon sutures into the recipient bed. The sutures were removed during postoperative follow-up visits based on refractive status and corneal topography (Yao et al., 2002; Yao, 2008; Wu et al., 2012). Eyes after surgery were treated with 0.1% (1 g/L) fluorometholone (Santen Pharmaceutical Co., Osaka, Japan) and 0.5% (5 g/L) levofloxacin (Santen Pharmaceutical Co., Osaka, Japan) four times daily; the fluorometholone was applied for at least 6 months and was tapered off during follow-up visits.

2.3 HD-OCT

HD-OCT (Cirrus, Carl Zeiss, Meditec Inc., Dublin, Calif., USA) was used to measure the LTMH, CTFT, and CCET of operated and fellow eyes in patients after DALK. This spectral domain OCT system had a 780-nm wavelength light source, the axial resolution was 5 μm in tissue, and the transverse resolution was 15 μm. The scan speed was 68000 A-scans per second. All measurements were performed between 8:00 a.m. to 10:00 a.m. in an examining room by an experienced doctor (WJX). All patients were asked to avoid using any eyedrops at least one hour prior to the OCT examination. During examination, the patients were instructed to look at a light target in the OCT system and blink normally. The images of the central cornea and lower tear meniscus were captured immediately after a full blink. Raw images were optically corrected automatically in the OCT processing system, and the LTMH, CTFT, and CCET were measured using cursors provided by the OCT system (Figs. 1 and 2). In the OCT image, tear film was defined as the first hyper-reflective line of the cornea, and basement membrane was defined as the second hyper-reflective layer (Diez-Feijóo and Durán, 2015). CCET was measured from a point located just beneath the central tear film to the basement membrane perpendicular to the anterior surface at the point of measurement (Francoz et al., 2011; Liang et al., 2016). Since the tear film is very thin, it was difficult to measure the thickness directly using the cursor, and therefore we subtracted CCET from the distance between the air-tear and the basement membrane-Bowman's interfaces to calculate the CTFT (Fig. 1). All measurements were performed three times and the mean value was recorded.

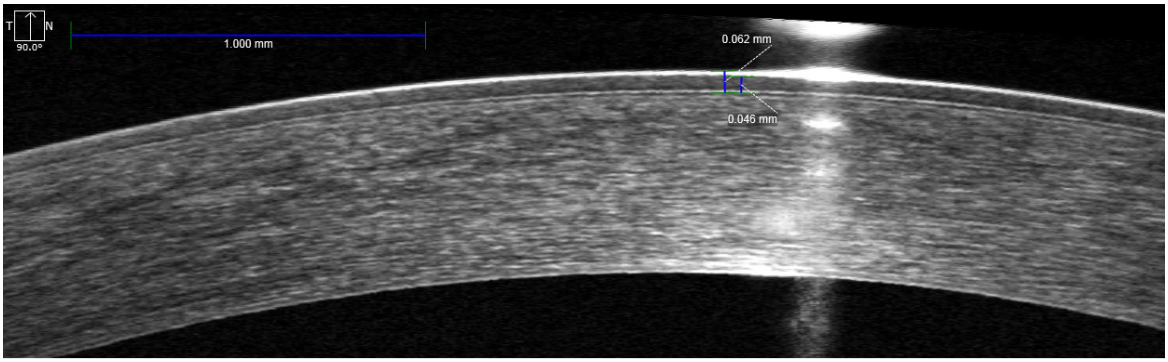

Fig. 1 Measurement of central corneal epithelial thickness (CCET) and central tear film thickness (CTFT) using HD-OCT

Fig. 2 Measurement of the lower tear meniscus height (LTMH) using HD-OCT

2.4 Statistical analysis

The Statistical Package for Social Sciences (SPSS Version 19.0; Cary, NC, USA) was used to perform the statistical analysis. The results are expressed as mean±standard deviation (SD). The Kolmogorov-Smirnov test was used to test the normality of the data. Paired *t*-test was used to compare LTMH, CTFT, and CCET between operated and fellow eyes; independent *t*-test was used to compare LTMH, CTFT, CCET and other normally distributed variables between males and females and between keratoconus and other primary diseases, while the Mann-Whitney *U*-test was used for non-normally distributed variables. Correlations of LTMH, CTFT, and CCET between operated and fellow eyes were tested using the Pearson's correlation coefficient; correlations between LTMH, CTFT, CCET and other demographic or clinical data were analyzed using Pearson's correlation coefficient (for normally distributed variables) or Spearman's correlation coefficient (for non-normally distributed variables). The significance level was set to $P<0.05$.

3 Results

Of the 20 patients (10 men and 10 women) included in this study, 13 had keratoconus as the primary disease and the 7 had other corneal conditions such as herpes simplex keratitis (n=4), ocular surface burn (n=2), and phlyctenular keratoconjunctivitis (n=1). The fellow eyes of non-keratoconic patients were all healthy and could be considered as normal controls. Table 1 summarizes the demographic and clinical data of the 20 patients. There were no significant differences in the demographic or clinical data between the male and female groups. Compared to the patients with keratoconus, patients with other corneal conditions were older and had higher CCET in the fellow eye (independent *t*-test, $P<0.001$ and $P=0.024$). No significant difference in CCET of the operated eye was found between keratoconus and other conditions ($P>0.05$), and no significant difference in CTFT or LTMH in either eye was found between keratoconus and other conditions (all $P>0.05$). No significant differences in LTMH, CTFT, or CCET between operated and fellow eyes or between male and female were found in all 20 patients (all $P>0.05$).

Fig. 3 shows the significant correlations between the variables. CCET in the operated eye was significantly negatively correlated with the number of residual sutures ($R=-0.579$, $P=0.008$; Fig. 3a), and was significantly positively correlated with the time following surgery ($R=0.636$, $P=0.003$; Fig. 3b). In the fellow eye, a significant positive correlation was found between age and CCET ($R=0.551$, $P=0.012$; Fig. 3c), and a significant negative correlation was found between age and CTFT ($R=-0.491$, $P=0.028$; Fig. 3d). A significant correlation of LTMH was found between operated and fellow eyes ($R=0.554$, $P=0.011$; Fig. 3e). No significant correlations of CCET or CTFT were found between the operated and fellow eyes (both $P>0.05$). There were no significant correlations between LTMH and age, bed/graft size, time following surgery, or residual sutures (all $P>0.05$).

Table 1 Demographic and clinical data

Group	Age (year)	Gender (male, female)	Time following DALK (month)	Graft size (mm)	Bed size (mm)	Residual sutures
Total (n=20)	33.1±15.1	10, 10	16.7±15.5	8.2±0.5	7.9±0.5	6.7±6.3
Keratoconus (n=13)	24.8±6.6	6, 7	14.8±17.9	8.2±0.3	7.8±0.3	8.4±6.2
Others (n=7)	48.4±14.5**	4, 3	20.1±9.9	8.4±0.7	7.9±0.7	3.4±5.7

Group	CCET (μm)		CTFT (μm)		LTMH (μm)	
	Operated eye	Fellow eye	Operated eye	Fellow eye	Operated eye	Fellow eye
Total (n=20)	44.1±12.8	46.2±6.4	13.2±1.5	14.3±3.0	342.4±226.9	336.0±139.8
Keratoconus (n=13)	43.6±15.7	43.9±6.7	13.3±1.5	15.2±3.2	361.8±220.8	370.1±137.9
Others (n=7)	45.0±4.8	50.4±2.5*	13.0±1.6	12.5±1.6	306.1±251.2	272.7±129.0

Data are expressed as mean±SD. DALK: deep anterior lamellar keratoplasty; CCET: central corneal epithelial thickness; CTFT: central tear film thickness; LTMH: lower tear meniscus height. * $P=0.024$, ** $P<0.001$, compared with the keratoconus group using independent *t*-test

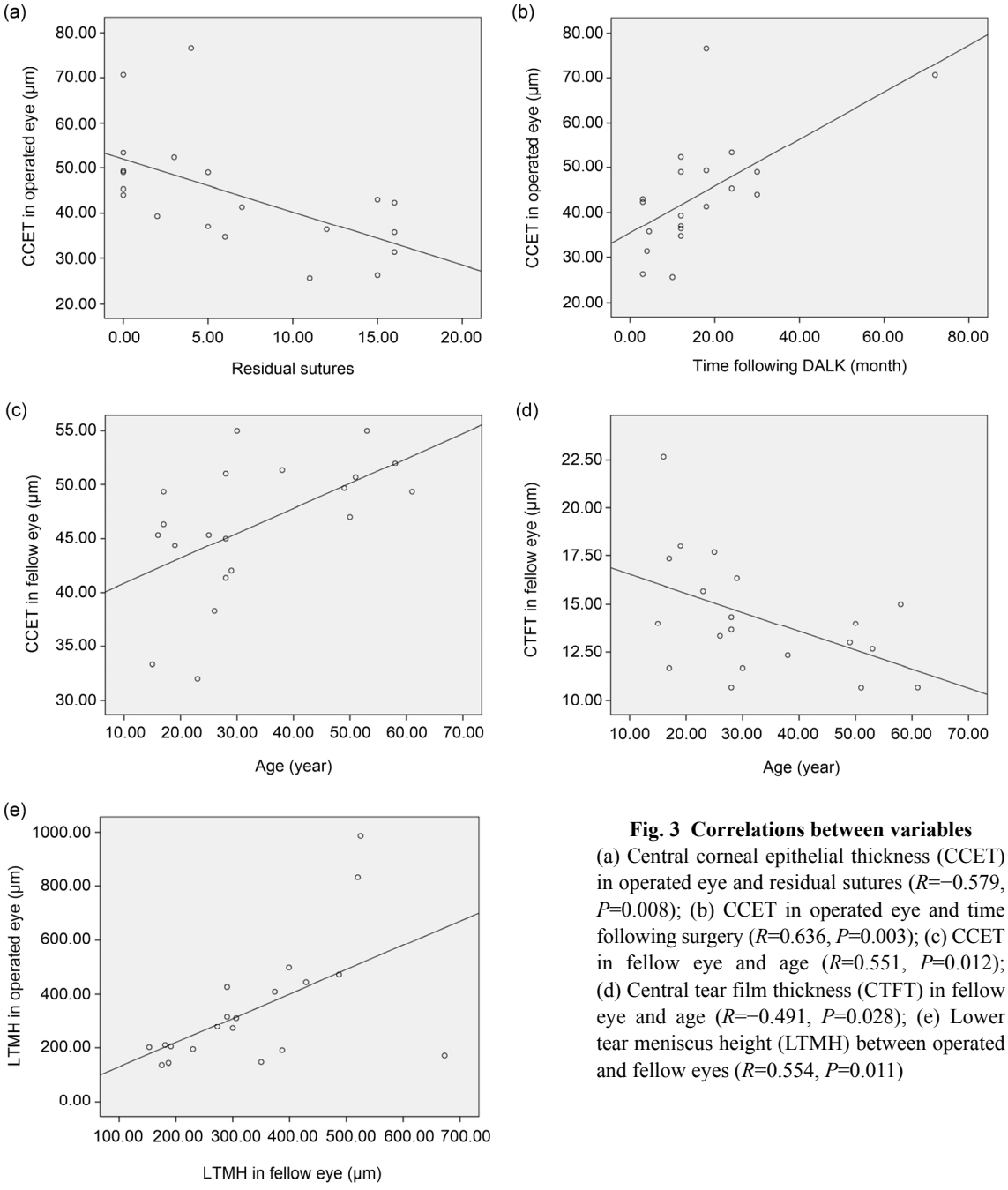

Fig. 3 Correlations between variables

(a) Central corneal epithelial thickness (CCET) in operated eye and residual sutures (R=−0.579, P=0.008); (b) CCET in operated eye and time following surgery (R=0.636, P=0.003); (c) CCET in fellow eye and age (R=0.551, P=0.012); (d) Central tear film thickness (CTFT) in fellow eye and age (R=−0.491, P=0.028); (e) Lower tear meniscus height (LTMH) between operated and fellow eyes (R=0.554, P=0.011)

4 Discussion

As a fast and non-invasive method, HD-OCT can objectively assess the tear film thickness and lower tear meniscus, which are considered sensitive indices for monitoring tear function (Yokoi et al., 2004; Campbell, 2005; Xie et al., 2014; Schmidl et al., 2015). Compared with other traditional invasive tear evaluation methods, HD-OCT is more likely to have a high degree of acceptance among patients in clinics; it may also be a more sensitive way of detecting tear deficiency prior to the appearance of significant dry eye symptoms (Xie et al., 2014). Therefore, HD-OCT has the potential to become a routine eye evaluation method for DALK and other corneal surgeries. In our study, we found a significant negative correlation

between age and CTFT in the fellow eye, which indicated that older age is a risk factor for tear film instability (Xie, 2016).

Similar to other corneal surgeries, such as laser in situ keratomileusis (LASIK), the impaired sub-basal and stromal nerves induced by corneal transplantation usually cause postoperative corneal hypoesthesia, which has traditionally been thought to affect reflex tear secretion and cause postoperative tear dysfunction (Kung et al., 2014; Levitt et al., 2015). Although nerve regeneration and corneal sensation recovery usually start at 6–12 months after corneal transplantation, they do not fully recover to preoperative values even several years after surgery (Tervo et al., 1985; Darwish et al., 2007; Zhang et al., 2013; Xu et al., 2017). Our study indicated that the epithelium and tear volume over three months after DALK could be maintained at the same level as the fellow eye, despite limited nerve regeneration and corneal sensation restoration. A similar phenomenon has also been reported in some LASIK studies (Tao et al., 2010; Zhang et al., 2012; Hu et al., 2015). One explanation is that the regenerated nerves are very thin and difficult to observe using current confocal microscopic methods (Trabucchi et al., 1994; Darwish et al., 2007). A histochemical study has also proved that the architecture and the density of corneal nerves do not fully regenerate in the graft cornea (Tervo et al., 1985). Another explanation is that the residual nerves located at the periphery of the host cornea are sufficient to complete the neural feedback loop to generate adequate tear production (Darwish et al., 2007). If this is the case, a smaller size of graft/bed would theoretically preserve more host corneal nerves and result in better tear production, although in our study, the bed/graft size had no correlation with the CTFT or LTMH. The third explanation is that other factors, such as mechanical stimulation caused by sutures and the ridge at the graft-host corneal junction, or the chemical stimuli from the inflammation induced by surgery, would generate additional reflex tear secretion (Situ and Simpson, 2010; Lin et al., 2014). According to our results, the number of residual sutures had no correlation with tear measurements after DALK. Future studies may be needed to evaluate if the position of the sutures or the height of the ridge at the junction influences tear volume.

Lin et al. (2014) investigated tear function after DALK and PKP compared with normal controls. They found that postoperative LTMH was significantly higher than normal controls at 1 and 3 months after DALK and throughout the follow-up after PKP. They concluded that the LTMH recovered faster in the DALK group compared with the PKP group, and proposed that the increased LTMH after surgery might be due to postoperative mechanical and chemical stimuli; the different inflammatory reactions to DALK and PKP may cause the difference in tear function between the two groups. According to our results, DALK did not induce a significant change of LTMH or CTFT in the operated eye compared with the fellow eye over three months after surgery. This corresponds with our clinical experience i.e. that few patients after DALK show significant signs of tear dysfunction or report significant sensation of dryness during the follow-up period. The mean time following DALK in our study was (16.7±15.5) months; future investigation of tear measurements at less than three months following surgery may be needed as corneal oedema was significant at the graft-host junction during the early stages after DALK. Further comparison of OCT measurements between DALK and PKP may help us to investigate the mechanisms of corneal epithelium regeneration and tear function recovery after keratoplasty.

Kanellopoulos and Asimellis (2014) found increased central epithelial thickness in dry eye patients; however, several studies found no significant difference in CCET between dry eye and normal groups, and no significant correlation was found between CCET and dry eye assessments such as ocular surface disease index, tear breakup time, or Schirmer test (Francoz et al., 2011; Cui et al., 2014; Liang et al., 2016). We also found no significant correlation between CCET and the other two tear measurements. This may be because the central cornea is less sensitive to inflammation than the peripheral regions, and it is mildly affected by tear dysfunction (Cui et al., 2014). Further studies to assess the peripheral corneal epithelium may be needed, although we found that it was difficult to identify the basement membrane at the peripheral cornea, and the measurement of peripheral epithelial thickness would induce more variation than at the central cornea.

As the technique has improved, DALK has been used routinely in recent years for treating a wide range of corneal diseases with normal endothelial

function (Watson et al., 2004; Yao, 2008), the most common indication for DALK being keratoconus as shown in our study (Shimmura and Tsubota, 2006). Although other primary corneal conditions such as corneal infection, trauma or ocular surface diseases might cause more impairment to tear function than keratoconus (before the complication stage), our study indicated that tear measurements were not significantly different between keratoconus and other conditions, either before (indicated by the fellow eye) or after DALK; future studies with larger sample size may be needed to verify this result. Previous studies using the OCT method (Li et al., 2012; Xu et al., 2016) found that keratoconic eyes had significantly lower epithelial thickness compared to normal eyes, and they suggested that epithelial thinning may play an important role in compensating for the irregular stroma and help to reduce the irregularity of the anterior corneal surface during the keratoconus process. We also found that the CCET in the fellow eye was significantly lower in keratoconus compared with other corneal conditions (which could be considered as normal controls); this result verified that patients with keratoconus tend to have a thinner central corneal epithelium (Li et al., 2012; Xu et al., 2016).

After DALK, the CCET in the operated eye was significantly negatively correlated with the number of residual sutures, and was significantly positively correlated with time following surgery. These results indicated that the longer the time period after surgery, the thicker the epithelium and that residual sutures might prohibit central epithelial recovery. However, the number of residual sutures was significantly negatively correlated with time following surgery, and this was due to the fact that sutures were removed during postoperative follow-up visits. Because of the interaction effect, the influence of time or the number of sutures on CCET recovery or redistribution could not be fully revealed by this study. Further studies which control one of these two factors may answer this question. We found that after DALK, central corneal epithelium showed no significant difference between operated and fellow eyes or between keratoconus and other conditions. Patients with keratoconus were younger than patients with other conditions. As we have discussed previously, keratoconic eyes would have a thinner epithelium and this might explain the significant positive correlation between age and CCET in the fellow eye for these 20 patients.

According to our results, age, gender, time following surgery, or residual sutures had no significant correlation with tear volume indicated by LTMH measurement. The only factor that showed correlation with the postoperative LTMH was LTMH in the fellow eye. Generally, the ocular surface findings in one eye are likely to be similar to those in the other eye (Murdoch et al., 1998). The high correlation between eyes despite surgical intervention in one eye indicated that the tear function after DALK might depend on an individual's general condition such as ocular anatomy, environment, and nutrition. Postoperative tear function could be predicted by the fellow eye or by the original status of the operated eye.

To the best of our knowledge, this is the first study to assess corneal thickness along with tear film thickness and tear meniscus height after DALK using HD-OCT. However, there are some limitations to this study. First, it was designed as a retrospective cross-sectional study; therefore preoperative OCT measurements were not performed on the operated eye. Further prospective studies with a larger sample size are needed to verify these results and to investigate the change in OCT assessments before and after surgery. Second, although there was a sharp demarcation between tear film layer and epithelial layer in our OCT images, the exact location of the tear-epithelium interface might not be identified with 5 μm resolution using this OCT system. Some previous studies which measured epithelial thickness included the tear film (Li et al., 2012; Cui et al., 2014; Lee and Ahn, 2016), and some did not (Francoz et al., 2011; Liang et al., 2016). Werkmeister et al. (2013) measured the CTFT using a custom-built ultrahigh-resolution (1.2 μm) OCT system, and the mean value in their study was (4.79±0.88) μm, which was thinner than our results ((13.2±1.5) μm in the operated eye and (14.3±3.0) μm in the fellow eye); this indicated that the tear film and epithelium layers might overlap to some extent in the OCT image. However, we suggest that the first hyperreflective layer should not be included when measuring the epithelium, although to exclude it might underestimate the epithelial thickness. The location of the tear-epithelium interface may be fully identified in the future as the resolution of commercially available OCT continually improves.

5 Conclusions

Patients with keratoconus tend to have a thinner central corneal epithelium. DALK did not induce a significant change in tear volume nor in the tear measurements found between keratoconus and other corneal conditions. Corneal epithelium keeps regenerating after DALK. The postoperative LTMH in the operated eye correlated with LTMH in the fellow eye, and LTMH was not dependent on age, gender, bed/graft size, time following surgery, or residual sutures.

Compliance with ethics guidelines

Wen-jia XIE, Ye-sheng XU, Xia ZHANG, and Yu-feng YAO declare that they have no conflict of interest.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5). Informed consent was obtained from all patients for being included in the study.

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中文概要

题　目：前部深板层角膜移植术后泪新月高度、泪膜厚度及角膜上皮厚度的评估

目　的：评估前部深板层角膜移植（DALK）术后的下泪新月高度（LTMH）、中央泪膜厚度（CTFT）及中央角膜上皮厚度（CCET）。

创新点：首次利用高清光学相干断层扫描成像技术（HD-OCT）定量测量DALK术后的CCET、CTFT和LTMH，并发现各个参数之间及与其他临床数据的相关性。

方　法：回顾性横断面分析20例单眼DALK术后3月以上的患者。使用HD-OCT定量分析并比较术眼和对侧未手术眼的LTMH、CTFT和CCET。对各个OCT参数之间及与年龄、术后时间、植片直径、植床直径和残余缝线数量进行相关性分析。

结　论：本研究显示，圆锥角膜患者的中央角膜上皮倾向变薄；DALK术后角膜上皮随着时间推移而持续再生；与对侧未手术眼相比，DALK并不引起显著的泪液量变化。因此，术后的泪液功能可能取决于患者的整体状况而非年龄、性别、植片/植床直径、术后时间或残余缝线。

关键词：泪新月高度；角膜上皮厚度；泪膜；前部深板层角膜移植（DALK）；高清光学相干断层扫描成像技术（HD-OCT）；圆锥角膜