

Evaluation of lipid layer tear film changes after femtosecond small incision lenticule extraction

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Abstract

Background: Dry eye disease is common after refractive procedures due to tear film instability. There are several causative factors for tear film instability, but the state of individual components of the tear film is not assessed much in published literature. This article quantifies the lipid layer thickness (LLT) of the tear film using surface interferometry before and after the small incision lenticule extraction (SMILE) refractive procedure.

Objectives: This study aimed to evaluate the effects of femtosecond SMILE on the postoperative stability of the LLT of the tear film.

Design: This was a prospective, interventional, non-case-control study.

Methods: A total of 160 eyes of 80 patients were enrolled in the study. The follow-up period was 6 months after surgery. A noninvasive surface interferometer was used to measure the thickness of the lipid layer before surgery and was repeated at 3 and 6 months after surgery. The main outcome measure was the change in average LLT at 3 and 6 months after SMILE and its statistical significance.

Results: There were 48 women and 32 men. Age ranged from 21 to 42 years (mean = 27 ± 6.4). Mean LLT at baseline was [oculus dextrus (OD) = $53.38 (\pm 7.24)$ nm; oculus sinister (OS) = $52.21 (\pm 6.95)$ nm], at 3 months [OD = $54.38 (\pm 5.75)$ nm; OS = $53.26 (\pm 5.70)$], and at 6 months [OD = $53.31 (\pm 5.66)$ nm; OS = $52.39 (\pm 5.94)$]. Mean LLT showed mild improvement at 3 months after surgery (OD = 53.38 – 54.38 mm, $p = 0.0417$; OS = 52.21 – 53.26 mm, $p = 0.0398$). There was no significant change in LLT from the baseline before surgery to levels 6 months after surgery ($p = 0.8914$ OD; $p = 0.7368$ OS).

Conclusion: The SMILE refractive procedure did not alter the LLT that remained stable and adequate at 6 months postoperative follow-up.

Keywords: dry eye, lipid layer thickness, LipiView, small incision lenticule extraction

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Introduction

Small incision lenticule extraction (SMILE) is a novel refractive procedure for the correction of myopia and myopic astigmatism. SMILE offers a minimally invasive technique of using a femtosecond laser to create an intrastromal lenticule that can be removed through a small incision of 3–4 mm. Involvement of the anterior cornea is spared in SMILE. In the absence of a corneal flap and smaller incision site, there is less damage to

the subbasal nerve plexus and corneal stromal nerves.^{1,2} This allows most of the epithelium and Bowman's membrane to remain intact. SMILE, which has less impact on corneal nerves, is presumed to induce less postoperative dry eye, supporting the association between corneal denervation and postoperative dry eye.³

The main concerns for refractive surgeons and patients undergoing corneal refractive surgery are

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the predictability and long-term stability of attempted correction, quality of the visual outcome, safety of the procedure, postoperative dryness, long-term corneal biomechanical stability, and minimization of intra- and post-operative complications. With rising number of refractive surgery cases, dry eye is becoming an increasing challenge for refractive surgeons to overcome, with a significant proportion of patients experiencing dry eye symptoms to varying degrees.^{4,5}

Dry eye is a common ocular surface disease that plays a significant role in the ocular comfort and visual performance of patients, with the potential to have a considerable impact on their quality of life.⁶⁻¹¹ Dry eye symptoms range from mild ocular irritation to severe discomfort, photophobia, and decreased vision. Clinical signs of dry eye include evidence of decreased aqueous tear production, decreased tear volume on the ocular surface, increased rate of tear evaporation, and increased tear osmolarity. The lipid layer of the human tear film serves as a barrier to retard the evaporation of aqueous tears.^{12,13} As the thickness dynamics of the tear film (tear film thinning and breakup) are closely related to ocular surface disease, studies of the thickness of the tear film and lipid layer facilitate understanding of dry eye disease. The challenge is to evaluate changes in the lipid layer thickness (LLT) of the tear film after femtosecond SMILE and the effects of SMILE on dry eye syndrome. Interferometric approaches have emerged as one of the most promising and contemporary methods to investigate the thickness of the precorneal tear film *in vivo* owing to its considerable advantages of being noninvasive, accurate, and rapid.¹⁴⁻¹⁶ LipiView[®] II is a noninvasive interferometer used to quantitatively measure the tear film LLT.¹⁷⁻¹⁹ It was used in this study to evaluate the stability of lipid layer tear film in patients with myopia and myopic astigmatism following SMILE refractive surgery.

Material and methods

This prospective, interventional, and non-case-control study aimed to evaluate tear film stability after the SMILE refractive procedure. We enrolled 80 patients treated with SMILE refractive surgery from May 2020 to March 2021, at Kuwait Specialized Eye Center in Kuwait. The study group included 160 eyes from 80 patients. Inclusion criteria were a minimum age of 18 years, preoperative myopic spherical refraction from

-1.0D to -10.0D, cylindrical refraction up to -3.50D, best-corrected visual acuity (BCVA) of 20/30 or better, and minimum calculated postoperative residual stromal bed of 350 μ m. Exclusion criteria were annual refractive changes of more than -0.50D, history of corticosteroids and antiglaucoma drugs affecting tear secretion and tear film stability, dry eye syndrome, corneal irregularity suspected for keratoconus, corneal haze, recurrent corneal erosion syndrome, herpetic keratitis, corneal dystrophy, active disease in the eye and eye adnexa, progressive retinal changes, diabetes, autoimmune or other systemic diseases, pregnancy, and lactation. Contact lens wear was not an exclusion criteria in this study. Contact lens wearer patients were asked to stop contact lens use 7 days before the preoperative assessment. Patients with evidence of meibomian gland disease (MGD) were advised hot compress and tobramycin-dexamethasone ointment. They were scheduled for SMILE procedure after the lid margins got healthy. All patients underwent a standard preoperative examination that included subjective uncorrected visual acuity (UCVA), BCVA, autorefractometry, keratometry readings K1 and K2, slit-lamp evaluation, and dilated fundus examination. Intraocular pressure was measured using the Goldmann applanation tonometry. Lipid layer tear film measurements were performed using a LipiView II ocular surface interferometer (TearScience Inc, Morrisville, NC, USA). Corneal topography with corneal thickness measurements was obtained using a Sirius corneal topography and aberrometry system (Costruzioni Strumenti Oftalmici, Italy). Temperature of the examination room was maintained between 21 and 23°C with corresponding relative humidity between 30% and 50%.

LLT was assessed before surgery and was repeated at 3 and 6 months after surgery. The LipiView[®] II (TearScience Inc) ocular surface interferometer was used in this study, with dynamic meibomian imaging measures LLT with nanometer accuracy. It is a noninvasive method that uses interferometry to measure the thickness of the lipid layer between blinks and performs a quantitative assessment in interferometric color units (ICUs). The LLT is presented in ICUs, in which one ICU corresponds to approximately 1 nm.

For SMILE, a VisuMax 500-kHz femtosecond laser (Carl Zeiss Meditec AG, Jena, Germany)

Table 1. Changes in LipiView readings in small incision lenticule extraction (SMILE) cases over 6 months.

Number	LipiView readings at baseline (<i>n</i> = 160 eyes)		LipiView readings at 3 months (<i>n</i> = 160 eyes)		LipiView readings at 6 months (<i>n</i> = 160 eyes)	
	OD	OS	OD	OS	OD	OS
Mean (SD)	53.38 (7.24)	52.21 (6.95)	54.38 (5.75)	53.26 (5.70)	53.31 (5.66)	52.39 (5.94)

OD, oculus dextrus; OS, oculus sinister; SD, standard deviation.

was used. This femtosecond laser system delivers focused patterns of femtosecond pulses with a wavelength of 1043 nm and frequency of 500 kHz to create an intrastromal refractive lenticule at a precise predecided depth and position. Standard mode pulse energy settings of 130 nJ with energy offset 26 (1 offset = 5 nJ) were used. After surgery, all patients received topical antibiotics and steroids for 2 weeks. Lubricating drops were prescribed for at least 1 month. Follow-up appointments after the surgery were performed after 1 week, 1 month, 3 months, and 6 months. The following examinations were performed: UCVA, BCVA, autorefractometry, K1 and K2 readings, LipiView interferometer, intraocular pressure, corneal topography, and slit-lamp examination. The main outcome measure was the change in average LLT at 3 and 6 months after SMILE and its statistical significance. Gatifloxacin 0.5% ophthalmic drops (Zymaxid; Allergan plc, Coolock, Dublin, Ireland) and prednisolone acetate 1% ophthalmic suspension (Pred Forte; Allergan plc, Coolock, Dublin, Ireland) were used postsurgery for 10 days. The study participants were advised to use preservative free lubricant eye drops, three to five times a day based on patient's dry eye signs and symptoms. Systane Ultra [polyethylene glycol (PEG)/propylene glycol (PG) with hydroxypropyl guar (HP) guar (Alcon, Fort Worth, TX, USA)] and Artelac Advanced (Bausch & Lomb GmbH, Germany) were used by the study participants for 1–2 months after surgery. All our patients were instructed to stop lubricant eye drops (if they were using any) 24h before they come for follow-up and assessment of LLT.

Statistical analysis

A standard statistical analysis was performed using MedCalc Statistical Software version 18.5 (MedCalc Software bvba, Ostend, Belgium); descriptive statistics [mean (standard deviation)] and percentages were used as needed. The paired sample *t* test was used for intragroup comparisons

of the parameters that were normally distributed. The significance level was set at $p < 0.05$.

Results

A total of 160 eyes of 80 patients were assessed in this study. There were 48 women and 32 men. Age ranged from 21 to 42 years (mean = 27 ± 6.4). Mean corneal thickness of the study participants was oculus dextrus (OD) = 545.7 (± 26.5) and oculus sinister (OS) = 546.4 (± 24.6). Mean spherical equivalent of the study participants was OD = 5.35 (range = 2.13–9.23) and OS = 5.72 (range = 2.24–9.42).

Table 1 shows the LLT of the tear film at baseline and 3 and 6 months postoperatively. Mean LLT at baseline was [OD = 53.38 (± 7.24) nm; OS = 52.21 (± 6.95)], at 3 months [OD = 54.38 (± 5.75) nm; OS = 53.26 (± 5.70)], and at 6 months [OD = 53.31 (± 5.66) nm; OS = 52.39 (± 5.94) nm]. Table 2 shows the comparative data of LLT at baseline and 3 months. As observed in Table 2, the mean LLT of the right eye improved to 54.38 nm from 53.38 nm, and for the left eye, LLT improved to 53.26 nm from 52.21 nm. The change in LLT at 3 months was statistically significant ($p = 0.0147$ and $p = 0.0398$, respectively) in the right and left eyes. Table 3 shows the comparison between LLT at 3 and 6 months after the SMILE procedure. As observed in the table, LLT values decreased from 54.38 nm at 3 months to 53.31 nm at 6 months in the right eye and from 53.26 nm at 3 months to 52.39 nm at 6 months in the left eye. The change, however, was not clinically significant ($p = 0.2408$ and $p = 0.0602$ in the right and left eyes, respectively). Table 4 shows the comparative levels of LLT at baseline, before surgery, and LLT levels 6 months after the SMILE. As evident in the table, there was not much change in the LLT levels in the right eye at 53.38 and 53.31 nm, before and after 6 months, respectively, after the SMILE procedure. In the left eye, mild changes in the LLT values were noted. It was 52.21 nm at baseline

Table 2. Comparison of lipid layer thickness (LLT) at baseline with LLT at 3 months.

Eye	LLT baseline, mean (SD)	LLT at 3 months, mean (SD)	<i>p</i> value
OD	53.38 (7.24)	54.38 (5.75)	0.0147 ^a
OS	52.21 (6.95)	53.26 (5.75)	0.0398 ^b

OD, oculus dextrus; OS, oculus sinister; SD, standard deviation.
^aThe result is significant at $p < 0.05$. The mean of group one minus group two is -1.00 ; 95% confidence interval (CI) from -1.80 to -0.20 .
^bThe result is significant at $p < 0.05$. The mean of group one minus group two is -1.05 ; 95% CI from -2.05 to -0.05 .

Table 3. Comparison of lipid layer thickness (LLT) at baseline with LLT at 6 months.

Eye	LLT at baseline, mean (SD)	LLT at 6 months, mean (SD)	<i>p</i> value
OD	53.38 (7.24)	53.31 (5.66)	0.8914 ^a
OS	52.21 (6.95)	52.39 (5.94)	0.7368 ^b

OD, oculus dextrus; OS, oculus sinister; SD, standard deviation.
^aThe result is not significant at $p < 0.05$. The mean of group one minus group two is 0.06 ; 95% confidence interval (CI) from -0.85 to 0.97 .
^bThe result is not significant at $p < 0.05$. The mean of group one minus group two is -0.18 ; 95% CI from -1.21 to 0.86 .

Table 4. Comparison of lipid layer thickness (LLT) at 3 months with LLT at 6 months.

Eye	LLT at 3 months, mean (SD)	LLT at 6 months, mean (SD)	<i>p</i> value
OD	54.38 (5.75)	53.31 (5.66)	0.2408 ^a
OS	53.26 (5.75)	52.39 (5.94)	0.0602 ^b

OD, oculus dextrus; OS, oculus sinister; SD, standard deviation.
^aThe result is not significant at $p < 0.05$. The mean of group one minus group two is 1.06 ; 95% confidence interval (CI) from -0.72 to 2.84 .
^bThe result is not significant at $p < 0.05$. The mean of group one minus group two is 0.88 ; 95% CI from -0.04 to 1.79 .

and increased marginally to 52.39 nm after 6 months of refractive procedure. The difference in LLT values at 6 months when compared with the baseline levels was not statistically significant ($p=0.8914$ and $p=0.7368$ in the right and left eyes, respectively).

Discussion

The mechanism of dry eye syndrome after corneal refractive surgery is multifactorial: decreased trophic influence on the corneal epithelium, impaired corneal sensation due to effect on corneal nerves affecting blink reflex, and damage to the limbal goblet cells during suction and post-surgical inflammation. SMILE is a new technique that causes minimal damage to the cornea and

corneal nerves and ensures maximal maintenance of anatomical structures and biomechanical properties. The lipid layer is located in the outermost layer of the tear film, which helps the tear film to respread after blinking and to prevent water evaporation. Changes in its composition, distribution, and thickness are associated with the pathophysiology of dry eye disease. Previously published data indicate that approximately 75% of patients reporting severe symptoms have relatively thin lipid layers of 60 nm or less.²⁰ The presence of dry eye symptoms significantly increased the likelihood of a relatively thin lipid layer. LLT appears to correlate better to symptoms, particularly severe symptoms than other reported correlations with objective clinical tests for dry eye disease.²⁰ This study aimed to evaluate the change in the

LLT after the SMILE refractive procedure over a period of 6 months. Several methods have been used to assess the LLT. Hosaka *et al.*²¹ semi-quantitatively graded LLT, using DR-1 a dry eye monitor (Kowa, Nagoya, Japan). They graded it from grade 1 (somewhat gray color, uniform distribution) to grade 5 (corneal surface partially exposed), according to the interference color pattern. Bai *et al.*²² used a high-resolution microscope to measure the thickness of the LLT of the tear film. Interferometry has the potential to be a practical and useful addition to clinical practice in the management of dry eye disease.²⁰ The LipiView interferometer used in this study quantitatively measures the average LLT during the 20s between blinks. The main proprietary algorithms and high-speed computers in this system capture the reflected color from the lipid layer at a rate of approximately 14 million pixels/s to complete the evaluation. The spatially modulated light source eliminates unnecessary background images and stray light. The processed output is expressed as an interference color unit that correlates with the thickness of the lipid layer.

Dry eye symptoms are reported by up to 95% of after refractive surgical procedure and up to 60% of the patients 1 month postsurgery.²³ According to the results of Goto *et al.*,²⁴ LLT decreased significantly at 1 week after SMILE and returned to the preoperative level after 3 months. Chen *et al.*,²⁵ however, found that there was no significant change in LLT, total blink rate, and the incomplete blinking rate at 1 month after LASIK. The decreased corneal sensitivity after surgery may affect the corneal-blink reflex-lacrimal gland pathway resulting in a reduced blink rate and decreased reflex aqueous tear secretion. Battat *et al.*²³ reported that as blinking contributes to the expression of meibum from the meibomian glands in the eye lids, the lipid layer secretion is also dependent on the blink. Reduction in the blink rate and an incomplete blink may result in subsequent reduction in the meibomian gland lipid secretion and changes in LLT.²³ After SMILE procedure, there was a decrease in partial blink rate and partial blink frequency, but an increase in complete blink rate was reported in a study by Zhou *et al.*²⁶ The authors further reported temporary increase in tear film thickness and stability if warm compress was used to treat the meibomian gland disorder after SMILE procedure. Spherical equivalent (SE) also influences the dry eyes syndrome. In this study, preoperative mean SE was OD = 5.35 (range = 2.13–9.23) and OS = 5.72

(range = 2.24–9.42). After SMILE surgery, SE reduced to OD = 0.07 (± 0.63) and OS = 0.08 (± 0.42). Ilhan *et al.*²⁷ reported that adult patients with high myopia (SE < -6.0D) had a higher incidence of dry eye disease. In another study, Korb *et al.*²⁸ found no significant changes in LLT after refractive surgery, at least not in the measurement region of the LipiView interferometer. They hypothesize that secretion of meibomian lipid could hardly be obstructed by SMILE procedure in such a short period because it was mainly based on the function of the meibomian gland and duct, although LLT is not constant and is dynamic on blinking. In this study, we observed that LLT levels improved at 3 months after SMILE. This was in contrast to several studies that have not documented an improvement in LLT levels after the SMILE procedure. LLT levels returned to near baseline thickness at 6 months postoperatively. This study had a limited number of cases and was not powered to determine the reason for this improvement in LLT levels. Nevertheless, we hypothesize that LLT levels may have improved at 3 months postoperatively owing to the extensive use of lubricants by some patients or due to changes in blink pattern. Several studies have reported that the LLT can be increased after using some commonly available topical medications.^{29,30} Korb *et al.*²⁹ showed that there was a statistically significant increase in LLT after the instillation of emollient eye drops. He reported a much greater increase in LLT (107%) following the instillation of the original formulation of the emollient eye drop and a small (16%) increase following the instillation of the nonemollient. In a similar study by Jennifer *et al.*,³⁰ the authors reported that the emollient eye drop increased the LLT of the tear film by an average of 58%. Korb *et al.* in their study mentioned that the slight increase in the nanometers observed in their study participants might be attributable to the compensatory effect of the blink pattern. Furthermore, forceful blinking contributed to a significant increase in LLT, which indicates that an increase in the complete blink rate can improve lipid flow.²⁸

This study had some limitations. First, there were no healthy controls. It would be ideal to include healthy controls to assess if there is a significant difference in LLT between nonoperated and operated eyes. Second, we based our results on average LLT; we did not evaluate blinking pattern or tear break-up time (TBUT) that can influence the lipid layer. In the tear interference images

from the LipiView interferometer, blinking is important for the formation and distribution of the lipid layer, and it is well observed that LLT is changeable between blinks.

Conclusion

Dry eye disease is common after refractive procedures. Femto laser SMILE is a relatively new procedure that promises better structural integrity and a lower incidence of dry eye. LLT plays a critical role in maintaining a stable tear film; therefore, evaluation is important in determining the integrity of the tear film. This study concludes that the SMILE refractive procedure does not affect the level of LLT after 6 months of follow-up and that ocular surface interferometry is a fast, accurate and repeatable method of assessing the LLT. Larger multicenter studies with case-control cohorts are needed to better comprehend the fluctuations of LLT and its importance in the causation of dry eye after corneal refractive procedures.

Value statement

What was known

- Dry eye disease is common after refractive procedures due to tear film instability.
- The SMILE procedure has a less pronounced impact on the ocular surface compared with LASIK, reducing the incidence of dry eye disease.

What this article adds

- There are several causative factors for tear film instability, but the state of individual components of the tear film is not assessed much.
- This article quantifies the lipid layer thickness of the tear film using surface interferometry before and after the SMILE refractive procedure. The SMILE refractive procedure does not affect the level of LLT up to 6 months of follow-up postoperatively.

Declarations

Ethics approval and consent to participate

This study was conducted as per the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The Ethics

Board of Kuwait Specialized Eye Center approved the study (vide letter reference IRB/021/2020). Written informed consent was obtained from all participants included in the study.

Consent for publication

Not applicable.

Author contributions

Khalid Al Sabti: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Validation; Visualization; Writing – review & editing.

Snezhana Zechevikj: Conceptualization; Data curation; Formal analysis; Methodology; Resources; Software; Validation; Writing – original draft.

Seemant Raizada: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Resources; Software; Supervision; Validation; Writing – review & editing.

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Competing interests

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Availability of data and materials

None.

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