



ISSN: 0975-833X

Available online at <http://www.journalcra.com>

INTERNATIONAL JOURNAL
OF CURRENT RESEARCH

International Journal of Current Research
Vol. 11, Issue, 01, pp.755-759, January, 2019

DOI: <https://doi.org/10.24941/ijcr.34063.01.2019>

RESEARCH ARTICLE

DRY EYE DISEASE AFTER REFRACTIVE SURGERY

*Dr. Muwafaq Mustafa Abdul Razzaq, Dr. Abdulkarim Hamdoun Ahmed Hassan Al-Tai,
and Dr. Bassil Saleh Abdul Qader Ashour

Mousl Health Directorate, Iraq

ARTICLE INFO

Article History:

Received 19th October, 2018
Received in revised form
29th November, 2018
Accepted 08th December, 2018
Published online 31st January, 2019

Key Words:

Lasik, Dry eye,
Fiber.

ABSTRACT

To compare small incision lenticule extraction (SMILE) versus LASIK for post-refractive dry eye disease. Its Prospective, comparative, nonrandomized clinical study. thirty patients scheduled for bilateral myopic SMILE and 30 age-, sex-, and refraction-matched patients scheduled for bilateral myopic LASIK were enrolled and followed for 6 months after the surgery. Complete evaluation of dry eye disease was performed at 1 and 6 months postoperatively, which included vision-related quality of life (Ocular Surface Disease Index [OSDI]), clinical examinations (tear film breakup time [TBUT]), Schirmer I test, corneal staining), and tear osmolarity measurements, together with an overall severity score. Function and morphology of the corneal innervation were evaluated by corneal esthesiometry and subbasal nerve imaging using in vivo confocal microscopy (IVCM). High incidence of mild to moderate dry eye disease was observed in both groups 1 month postoperatively, which remained significantly higher in the LASIK group than in the SMILE group 6 months after surgery (overall severity score [0–4]: 1.2 ± 1.1 vs. 0.2 ± 0.4 , respectively, $P < 0.01$), leading to more frequent use of tear substitutes over the long term. Corneal sensitivity was better in SMILE than in LASIK eyes 1 month postoperatively (3.5 ± 1.79 vs. 2.45 ± 2.48 , respectively, $P < 0.01$) and then recovered to statistically similar values at 6 months. Corneal nerve density, number of long fibers, and branchings as assessed by IVCM were significantly higher in the SMILE group compared with the LASIK group 1 and 6 months after surgery. Corneal sensitivity was negatively correlated with dry eye-related corneal damage ($R^2 = 0.48$, $P < 0.01$), and the long fiber nerve density was independently correlated with the OSDI score ($R^2 = 0.50$, $P < 0.01$) and the Schirmer test ($R^2 = 0.21$, $P < 0.01$) 6 months postoperatively.

Copyright © 2019 Muwafaq Mustafa Abdul Razzaq et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Citation: Dr. Muwafaq Mustafa Abdul Razzaq, Dr. Abdulkarim Hamdoun Ahmed Hassan Al-Tai and Dr. Bassil Saleh Abdul Qader Ashour. 2019. "Dry Eye Disease after Refractive Surgery", *International Journal of Current Research*, 11, (01), 755-759.

INTRODUCTION

The SMILE procedure has a less pronounced impact on the ocular surface and corneal innervation compared with LASIK, further reducing the incidence of dry eye disease and subsequent degradation in quality of life after refractive surgery. For the past 2 decades, LASIK has become the most popular corneal refractive surgery with approximately 1 million procedures per year in the United States (Ambrósio, 2008). Although a high satisfaction rate is reported, dry eye is still the most common adverse effect of LASIK. Many patients experienced mild-severity dry eye symptoms for a few months after LASIK, which are sufficiently eased using conventional tear substitutes, but patients still reported dry eye over the long term, with an occurrence of chronic dry eye disease ranging from 20% to 40% at least 6 months after surgery (Calvillo et al., 2004).

Dry eye causes damage to the ocular surface and symptoms of ocular discomfort associated with visual disturbance, which degrades not only the visual outcomes but also the quality of everyday life (Chao et al., 2014). Thus, it could be assumed that hundreds of thousands of patients are likely to develop chronic dry eye disease after LASIK every year, further affecting the health status of this young and active population. Total disruption of corneal nerves due to flap making combined with excimer photoablation is a likely cause of post-LASIK dry eye. A 90% decrease in central nerve fiber density has been reported in the first few months after LASIK, lasting for years until it recovers preoperative values or does not (Denoyer et al., 2012). As a result, LASIK induces a decrease in tear film quality, tear secretion, blinking rates, and epithelial wound healing, all factors known to be involved in the pathogenesis of dry eye disease. Femtosecond laser was developed for LASIK to improve flap making and allows customization. However, the control and optimization of flap features brought few improvements in post-LASIK dry eye (Deschamps et al., 2013), thus the need to develop new

*Corresponding author: Dr. Muwafaq Mustafa Abdul Razzaq,
Mousl Health Directorate, Iraq.

procedures to better protect the ocular surface after refractive surgery. Small incision lenticule extraction (SMILE) is a recent procedure using femtosecond laser to create an intrastromal lenticule that is then removed through a small corneal incision (<http://www.aao.org/newsroom/upload/Eye-Health-Statistics-April-2011.pdf>. Updated April 2011. Accessed November 4, 2014). Contrary to LASIK, this all-in-one femtosecond refractive surgery no longer needs excimer laser photoablation or a full flap cut. As a result, SMILE could constitute a minimally invasive approach to corneal refractive surgery because it only requires a small tunnel, which may have less impact on corneal innervation, thus further protecting patients against iatrogenic dry eye disease. Although clinical studies have reported refractive outcomes, corneal sensitivity, and clinical dryness after SMILE, nothing has been done to evaluate the overall severity of the disease, which requires a combination of objective tests and subjective symptom assessment as recommended by Delphi (Kanellopoulos, 1997), and its precise relationship with morphologic and functional changes in corneal innervation.

Thus, uncertainty remains about long-term ocular surface recovery and subsequent patient health status after SMILE, which could become the new gold standard for corneal refractive surgery, provided its theoretic benefits are demonstrated. This nonrandomized study was designed to prospectively compare SMILE with LASIK for surgically induced corneal changes and dry eye disease in accurately matched populations in terms of age, gender, and refraction. Clinical evaluation, a vision-related quality of life questionnaire, tear osmolarity assessment, corneal esthesiometry, anterior segment optical coherence tomography (OCT), and in vivo confocal microscope (IVCM) imaging were performed 1 and 6 months postoperatively to determine whether the SMILE procedure preserves the ocular surface and put an end to the common but sometimes deleterious post-refractive dry eye disease.

MATERIALS AND METHODS

Thirty Iraqi subjects scheduled for bilateral SMILE (J.F.F.) and 30 Iraqi age-, sex-, and spherical equivalent-matched subjects scheduled for bilateral LASIK (F.A.) were prospectively included. Inclusion criteria were planned myopic SMILE or LASIK (spherical correction range, -1 to -8 diopters; cylinder range, 0 to -1.5 diopters), willingness to participate in the study, and the ability to give informed consent. Exclusion criteria were any ocular pathology but myopia, any clinical sign or symptom of dry eye disease (Schirmer I test >10 mm/5 minutes, tear film breakup time [TBUT] >10 seconds, no corneal/conjunctival staining, no Meibomian gland dysfunction, and Oxford score = 0), previous ocular/eye lid medical or surgical treatment, systemic disorder, and pregnancy. All the examinations were performed 1 month and 6 months after the surgery, except OCT, which was performed at 6 months only. Detailed patient data are shown in Table 1. Data are reported as mean \pm standard deviation. The severity of dry eye disease was scored according to an overall index (range, $0-4$) including signs and symptoms (Chao *et al.*, 2014), in small incision lenticule extraction (SMILE) and LASIK cases 1 month (A) and 6 months (B) after the surgery. The mean score was significantly higher in the LASIK than in the SMILE group at 6 months postoperatively ($P < 0.01$) (Table 2). Six months after the surgery, patient-reported vision-related quality of life (OSDI) together with tear film

quality (TBUT) and osmolarity were significantly impaired in the LASIK group compared with the SMILE group, leading to a worse severity score of dry eye disease in the LASIK group (Table 2, Fig 1B). At this point, 80% of patients in the SMILE group did not use any eye drops at 6 months postoperatively versus 57% in the LASIK group, with 20% of the LASIK group needing daily and frequent use of tear substitutes or even gels versus none of the patients in the SMILE group (Fig 2). Corneal Sensitivity and Innervation:- Corneal sensitivity, as assessed by the Cochet-Bonnet esthesiometer, was hampered in both groups 1 month after the surgery, but was slightly higher in the SMILE group than in the LASIK group (Fig 3A). Both groups recovered to normal and did not have statistically different values at 6 months post-surgery. A, Corneal sensitivity as measured by the Cochet-Bonnet esthesiometer (Luneau, Prunay-Le-Gillon, France). LASIK eyes showed lower sensitivity than SMILE eyes at 1 month postoperatively ($*P < 0.05$). B, Corneal innervation as assessed using in vivo confocal microscopy. Nerve density, number of long fibers, and secondary branchings were higher in SMILE than in LASIK eyes ($*P < 0.05$; $**P < 0.01$). Control group is presented for illustrative purposes, which is taken from a previous study conducted by our team ($n = 15$). The subbasal nerve plexus of the cornea was evaluated using IVCM. The nerve density, number of long nerve fibers, and nerve branchings in the SMILE group were statistically superior to those in the LASIK group 1 month and 6 months after the surgery (Fig. 3B).

In addition, the density of dendritic cells at the corneal surface was greater in the LASIK group compared with the SMILE group at 1 month and 6 months postoperatively (156.4 ± 63.2 cells/mm² vs. 75.9 ± 26 cells/mm² at 1 month and 107 ± 34.5 cells/mm² vs. 52 ± 18.6 cell/mm² at 6 months, $P < 0.01$ for both), whereas the density of activated keratocytes was lower in the LASIK group 1 month postoperatively (252.9 ± 62.9 vs. 331 ± 71.5 , $P = 0.01$) and not statistically different from that of the SMILE eyes 6 months. Correlations of Dry Eye Disease Severity with Surgically Induced Changes in Corneal Innervation. The correlation matrix revealed a statistical association of corneal sensitivity with corneal staining and the overall severity score of dry eye disease (Table 2). In regard to IVCM innervation data, nerve density was negatively correlated with the OSDI score and corneal staining; the number of long fibers was negatively correlated with the OSDI score, corneal staining, overall severity score, and corneal sensitivity (Table 2). Because clinical data were highly interlinked, a stepwise regression routine was performed to determine independent correlations. Corneal sensitivity appeared to correlate with corneal staining only (R^2 increment = 0.48, $P < 0.01$). In addition, nerve density was found to independently correlate with the OSDI score and the Schirmer test (R^2 increment = 0.35, $P < 0.01$; and R^2 increment = 0.16, $P = 0.02$, respectively), as was the number of long nerve fibers (R^2 increment = 0.50, $P < 0.01$; and R^2 increment = 0.21, $P < 0.01$, respectively).

DISCUSSION

Dry eye is still the most frequent complication of refractive surgery (Lee *et al.*, 2000). Post-refractive dry eye disease is an immediate issue because the patients' visual comfort and quality of life dictate their overall satisfaction (Lee *et al.*, 2000). On a more global scale, ocular dryness after refractive surgery may lead to permanent pain, visual fluctuations, and

Table 1. Patient Features, Visual Outcomes, and Corneal Morphology as Assessed by Anterior Segment Optical Coherence Tomography

	SMILE Group (n=30)	LASIK Group (n=30)	t Test (P)
Preoperative data			
Age (yrs)	31.1±4.7	32.2±7.5	NS
Gender (M/F)	0.47	0.47	NS
Mean keratometry (D)	42.9±1.6	43.7±1.5	NS
Spherical equivalent (D)	-4.65±2.38	-4.42±1.78	NS
6-mo outcomes			
Mean keratometry (D)	40.9±1.4	39.9±2.5	NS
Spherical equivalent (D)	-0.03±0.41	0.13±0.4	NS
Distant best-uncorrected visual acuity (logMAR)	0.07±0.10	0.08±0.10	NS
Epithelial thickness (µm)	39.9±14.1	39.6±13.6	NS
Total corneal thickness (µm)	496.3±39.3	506.7±39.5	NS
Depth of the interface (µm)	117.2±4.6	117±4.5	NS

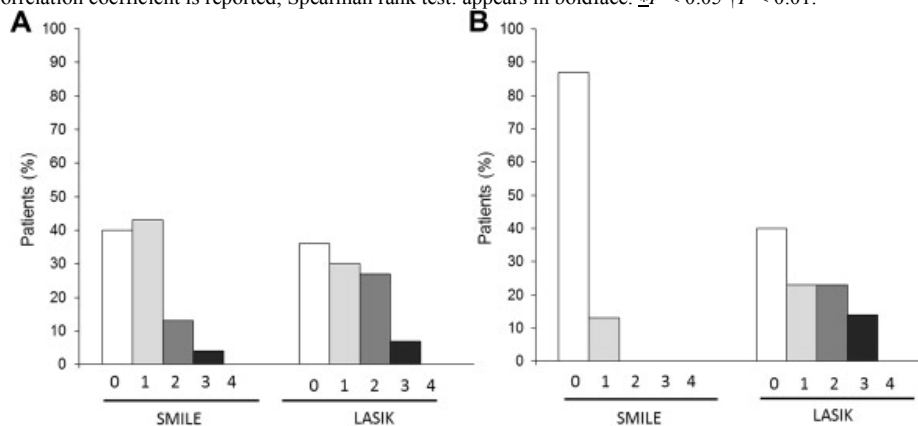
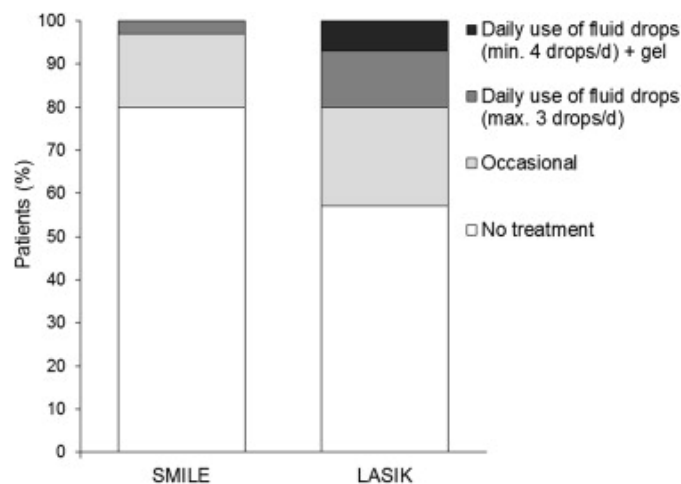
View Table in HTML Data are reported as mean ± standard deviation. D = diopters; logMAR = logarithm of the minimum angle of resolution; NS = not significant; SMILE = small incision lenticule extraction.

Table 2. Correlations of Signs and Symptoms of Dry Eye with Corneal Sensitivity and Innervation

	Esthesiometry		In Vivo Confocal Microscopy	
	Corneal Sensitivity	Nerve Density	No. of Long Fibers	Branchings
Age	0.28	-0.05	0.02	-0.22
Preoperative spherical equivalent	-0.31	0.1	-0.32	0.20
OSDI	-0.65††	-0.46*	-0.55††	-0.34
TBUT	0.01	0.12	-0.06	0.33
Schirmer	-0.15	0.11	-0.29	0.17
Corneal staining	-0.69††	-0.41*	-0.40*	-0.36
Overall dry eye severity score	-0.60††	-0.32	-0.44*	-0.20
Tear osmolarity	0.01	0.02	0.13	-0.02
Corneal sensitivity		0.36	0.45*	0.13

View Table in HTML OSDI = Ocular Surface Disease Index; TBUT = tear film breakup time.

R correlation coefficient is reported; Spearman rank test: appears in boldface. * $P < 0.05$ † $P < 0.01$.

**Figure 1. Distribution of post-refractive dry eye disease****Figure 2. The use of tear substitute eye drops 6 months after small incision lenticule extraction (SMILE) versus LASIK.**

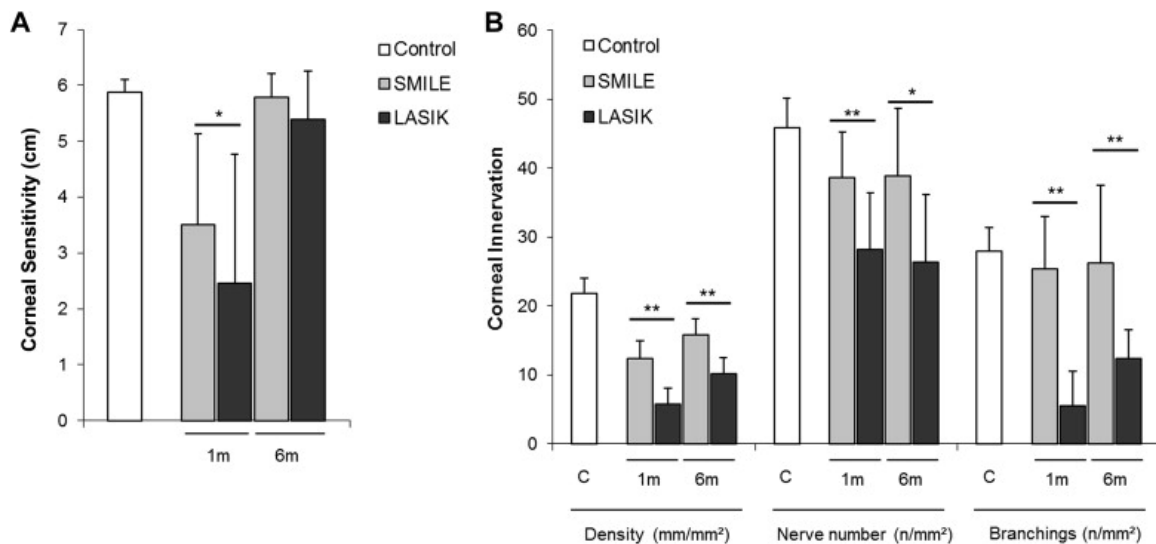


Figure 3. Morphologic and functional assessment of corneal innervation 1 month and 6 months after small incision lenticule extraction (SMILE) versus LASIK

the need for daily treatment, which affects health status, quality of life, and vision when it lasts for months or even years. New corneal procedures, such as SMILE, could both reduce the risk for iatrogenic dry eye disease and improve the overall outcome, and make indications for refractive surgery evolve by reducing limitations related to preoperative ocular dryness. According to the definition of the Dry Eye WorkShop, dry eye disease is a multifactorial pathology at the ocular surface, which includes tear film changes with or without corneal damage, ocular symptoms, visual degradation, and increased tear osmolarity, together leading to degradation of quality of life (Chao, 2014).

As a result, a full appropriate evaluation is required to accurately diagnose and evaluate the disease, especially because no specific marker reflecting its overall severity has been identified. The 2 main strengths of the present study are the matching of SMILE with LASIK cases in terms of age, gender, and refraction, the main recognized risk factors for dry eye, to optimize the relevance of the results; and the complete evaluation of the disease combined with a morphologic and functional analysis of innervation and corneal changes. Although post-LASIK dry eye is a well-documented complication, a few studies have analyzed both objective and subjective symptoms after LASIK, one including the OSDI-validated questionnaire for dry eye disease⁹. As recommended by Delphi, and only one has analyzed them for SMILE. The present study was designed within a complete, original, and comprehensive approach to dry eye disease after refractive surgery, and it demonstrated an increase in symptoms (OSDI score), signs (TBUT), and tear osmolarity 6 months after LASIK compared with SMILE. Accordingly, some authors have reported decreased values on these scales in patients receiving LASIK up to years after surgery (Li, 2013), although clinical signs are often found to be highly variable, as pointed out by Feng *et al.* (Kanellopoulos *et al.*, 1997). As for SMILE, Shah *et al.* found that approximately 40% of the patients thought that their eyes were dryer than before the surgery using a self-reported symptom questionnaire. Li *et al.* recently compared LASIK and SMILE for dry eye disease and reported a better OSDI and TBUT in SMILE eyes compared with LASIK eyes than reported in this article. We also report that the higher incidence of dry eye disease after

LASIK was associated with more frequent use of eye drops over the long term, which may also degrade the quality of life and raises the question of the cost of treatments in this young population. LASIK-induced dry eye relies mainly, but not exclusively, on the dramatic breakdown of subbasal nerves as a result of making the flap. In contrast, the SMILE procedure protects corneal innervation because it creates a 40°- to 60°-wide penetrating tunnel only, compared with the approximately 300°-wide penetrating tunnel for LASIK. From the early beginnings of refractive surgery, studies have reported a significant decrease in corneal sensitivity after LASIK, which likely lasts for months or even years despite the use of a femtosecond laser for flap making.¹⁰ As for SMILE, 3 recent studies clinically reported that SMILE maintained corneal sensitivity compared with LASIK. The present study has confirmed a significant decrease in corneal sensitivity at 1 month postoperatively after LASIK, with similar values recorded between groups at 6 months, according to the findings by Demirok *et al.* In both groups, the corneal sensitivity at 6 months appeared not to be different than that obtained in healthy controls in a previous study conducted by our team, suggesting a progressive recovery of the normal values in both procedures.

More interestingly, we originally combined clinical assessment of corneal innervation (i.e., sensitivity measurement) with IVCN imaging of the nerves to determine the relationship between morphology and function. Basically, LASIK was objectively found to reduce the corneal nerve density over the long term, whereas SMILE preserved nerve density as previously reported. Objective features of the corneal innervation 6 months after SMILE were found to be normal and not differ from those previously obtained by our team after the same image analysis in healthy patients. More precisely, we investigated specific parameters of corneal innervation (e.g., total nerve density, number of long fibers, and secondary branchings) and analyzed their relationship with the overall clinical data. We demonstrate (1) a positive correlation between corneal sensitivity and the number of long nerve fibers and (2) significant associations of corneal innervation parameters with clinical signs of dryness and patient-reported symptoms, further improving our clinical understanding of what occurs at the ocular surface after SMILE compared with

LASIK surgery. Vestergaard *et al* recently conducted a prospective controlled study to compare SMILE with femtosecond lenticule extraction (FLEX) using the same analysis methods as in the present study. Accordingly, TBUT, corneal sensitivity, and corneal nerve morphology at 6 months were found to be significantly better after SMILE than after FLEX. No statistical association between the nerve density and the other variables was reported except a moderate correlation for the Schirmer test ($P = 0.05$) in the FLEX group, consistent with what we found. Even if FLEX is not the same procedure as LASIK, it could be assumed that it also causes a dramatic breakdown of corneal subbasal nerves, further confirming the benefits of SMILE. The pathophysiology of post-refractive dry eye is a wide open field of basic and clinical research. Surgically induced changes in corneal innervation play a pivotal role in the pathogenesis of tear dysfunction and dryness, considered as neurogenic/neuropathic dry eye disease, as recently reported by Chao *et al.* (2004) We have reported significant hypoesthesia in the LASIK group versus the SMILE group 1 month postoperatively but not at 6 months, which correlated with tear secretion, but we could have improved the outcomes of the study by optimizing the assessment of corneal sensitivity, for example, using a noncontact esthesiometer, and by measuring the blink rate and tear clearance, which was not possible because of the lack of appropriate tools and standardized procedures. Surgical factors for corneal denervation (e.g., preoperative refraction, flap diameter and depth, and hinge position) and related dry eye have been studied, but their true impact has not been fully elucidated (Kanellopoulos *et al.*, 1997).

The aim of the present study was not to investigate risk factors for dry eye disease, but it would have been valuable to make a lateral hinge flap to specify this point. It should also be noted that high variability of post-surgery corneal reinnervation, whose duration ranges from 3 months to 5 years depending on the studies, could be another limitation in this study because the end point was 6 months after surgery. This study reports a pathologic increase in tear osmolarity 6 months after LASIK, thus including this mechanism within the pathogenesis of post-LASIK dry eye, contrary to SMILE. In fact, the neurogenic origin of post-refractive dry eye is undoubtedly associated with inflammatory mechanisms. This study originally reported a high density of dendritic cells at the ocular surface 6 months after LASIK, further confirming the role of inflammatory processes in the disease, which could be better analyzed by measuring other inflammatory mediators, such as cytokine in tears.

Central epithelial thickness as assessed by OCT did not differ between SMILE and LASIK at 6 months after surgery. Repeated mapping of the epithelial thickness in the entire cornea could better detail the impact of post-SMILE dry eye and inflammation on epithelial changes. Last, we revealed transient changes in keratocyte activation, for which a long-term follow-up could be valuable.

REFERENCES

- Ambrósio, R. Jr., Tervo, T. and Wilson, S.E. 2008. LASIK-associated dry eye and neurotrophic epitheliopathy: pathophysiology and strategies for prevention and treatment. *J Refract Surg.*, 24: 396–407
- Calvillo, M.P., McLaren, J.W., Hodge, D.O. and Bourne, W.M. 2004. Corneal reinnervation after LASIK: prospective 3-year longitudinal study. *Invest Ophthalmol Vis Sci.*, 45: 3991–3996
- Chao, C., Golebiowski, B. and Stapleton, F. 2014. The role of corneal innervation in LASIK-induced neuropathic dry eye. *Ocul Surf.*, 12: 32–45
- Denoyer, A., Rabut, G. and Baudouin, C. 2012. Tear film aberration dynamics and vision-related quality of life in patients with dry eye disease. *Ophthalmology.* 119: 1811–1818
- Deschamps, N., Ricaud, X., Rabut, G. *et al.* The impact of dry eye disease on visual performance while driving. *Am J Ophthalmol.* 2013; 156: 184–189
- Eye health statistics at a glance. Compiled by American Academy of Ophthalmology. Available at: <http://www.aaopt.org/newsroom/upload/Eye-Health-Statistics-April-2011.pdf>. Updated April 2011. Accessed November 4, 2014.
- Kanellopoulos, A.J., Pallikaris, I.G., Donnenfeld, E.D. *et al.*, 1997. Comparison of corneal sensation following photorefractive keratectomy and laser in situ keratomileusis. *J Cataract Refract Surg.*, 23: 34–38
- Lee, J.B., Ryu, C.H., Kim, J. *et al.*, 2000. Comparison of tear secretion and tear film instability after photorefractive keratectomy and laser in situ keratomileusis. *J Cataract Refract Surg.*, 26: 1326–1331
- Li, M., Zhao, J., Shen, Y. *et al.*, 2013. Comparison of dry eye and corneal sensitivity between small incision lenticule extraction and femtosecond LASIK for myopia. *PLoS One.* 8: e77797
- Yu, E.Y., Leung, A., Rao, S. and Lam, D.S. 2000. Effect of laser in situ keratomileusis on tear stability. *Ophthalmology.* 107: 2131–2135
