Impact of Dry Eye Disease on Visual Function and Quality after Femtosecond Laser-Assisted In-Situ Keratomileusis

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Abstract
Purpose: The purpose of this study was to determine how objective and subjective parameters of dry eye disease correlate with objective vision quality changes following femtosecond laser in-situ keratomileusis (FS-LASIK) surgery in low and high myopes.

Methods and Materials: This prospective, observational case series recruited patients undergoing bilateral FS-LASIK. Patients were divided into low/moderate and high myopia groups based on pre-operative assessment. Objective and subjective measurements of dry eye, as well as measurements of vision quality were obtained pre-operatively, 1-week, 1 month, and 3 months post-operatively. Thirty patients were included. The low/moderate and high myopia groups each contained 15 patients.

Results: Non-invasive keratography tear break up time (NIKBUT) decreased after FS-LASIK in both groups. Objective scatter index (OSI) improved in the L/M myopia group but worsened in the H myopia group post-operatively. Modulation transfer function (MTF) cutoff improved in both groups post-operatively. A negative correlation was identified between the NIKBUT and both the OSI and MTF results. Changes in ocular surface disease index (OSDI) scores support these objective findings.

Conclusion: The results of our study provide evidence that ocular surface changes associated with dry eye contribute to reduced subjective vision quality after FS-LASIK. Refractive surgeons should address dry eye pre-operatively and manage its sequelae post-operatively.

Keywords: Dry eye disease, Femtosecond laser in-situ keratomileusis, Myopia, Modulation transfer function, Objective scatter index, Ocular Surface Disease Index

Introduction
Myopic femtosecond laser in-situ keratomileusis (FS-LASIK) surgery is the most frequently performed corneal procedure for reducing refractive error and eliminating the need for distance spectacle or contact lens correction [1]. It is well tolerated overall and highly successful, with patient satisfaction rates in the range of 82-98% [2]. Despite having numerous advantages, adverse events can arise from this elective surgery. Dry eye disease (DED) is one of the most common reasons for patient dissatisfaction with the surgical outcome [3]. The pathophysiology of FS-LASIK-induced DED is multifactorial. Severing corneal nerves causes disruption of their trophic effects on the corneal epithelium. This alters the afferent nervous system feedback loop, leading to reduced lacrimal gland stimulation, aqueous tear deficiency (ATD), and reduced tear film breakup time (TFBUT) [4]. These all contribute to an unstable ocular surface [1,5-8]. Tear film instability has been shown to not only cause symptomatic ocular irritation but also reduced vision quality and function [9]. Dry eye symptoms commonly peak 1-3 weeks postoperatively but can persist for months after surgery.
While degraded vision quality after LASIK has been well established in existing literature, linking this phenomenon to subjective and objective measures of post-LASIK dry eye and objective measures of vision quality has not yet been established.

Normal visual function is dependent upon a normal tear film and a regular ocular surface [11-13]. Many different methods have been used to quantify tear film quality. They include a variety of diagnostic tests and imaging devices [14,15]. Tear film break-up time (TFBUT), lipid layer thickness (LLT), tear osmolarity, tear film matrix metalloproteinase-9 (MMP-9), Schirmer’s test, and vital dye staining are all objective measures of tear film function and ocular surface disease. Current imaging devices used to assess the contribution of ocular surface irregularity to visual function include corneal topography and tear film analysis. Aberrations in the overall optical system can be measured by wavefront analysis and double-pass technology [16-19].

In spite of these factors, evaluating the success of FS-LASIK surgery is heavily dependent on final Snellen visual acuity (VA) measurements. While important, this is an incomplete representation of visual function and overall patient satisfaction. It has been shown that LASIK can introduce visual disturbances in the form of higher order aberrations (HOAs), intraocular scatter, and impaired contrast sensitivity. These commonly lead to patient dissatisfaction with surgical outcome [1,16,20]. While the effect of these have been mitigated with the introduction of wavefront aberrometry guided ablative treatments, the wavefront imaging system can overestimate the vision quality of the eye by neglecting intraocular scatter of the visual apparatus [10,18,21-23]. The double-pass imaging system, utilized in this study, addresses many of wavefront imaging’s shortcomings in FS-LASIK patients [18,24].

The primary aim of our study was to determine if the degree of post-LASIK dry eye correlated with the degree of vision quality degradation as measured by double-pass imaging technology. A secondary aim of this study was to evaluate whether the changes in dry eye symptoms and objective vision quality correlated with the amount of pre-operative myopia treated by LASIK. Finally, we sought to determine whether subjective dry eye symptoms correlated with objective dry eye measurements.

Materials and Methods

Patients

This prospective, observational case series was approved by the institutional review board (IRB) of the Tianjin Medical University (approved 2017KY(L)-17). The methods adhered to the tenets of the Declaration of Helsinki, and all patients signed an informed consent form prior to participation. This study enrolled myopic patients undergoing FS-LASIK to correct their RE. Patients were recruited from the Tianjin Medical University Eye Hospital from June 2017 to December 2017. Patients underwent FS-LASIK by a single operator. Sixty eyes from 30 patients (13 male, 17 female) between 18 and 35 years of age (mean age 24.4 ± 4.92 years) were included. All patients were targeted for plano. Patients had a stable refractive error and did not have changes in ocular or systemic medications for three months prior to inclusion. Patients were prescribed fluorometholone 0.1% ophthalmic solution for 1 month and sodium hyaluronate artificial tears for 3 months postoperatively. Exclusion criteria included pregnancy; use of DED-inducing medications (gabapentin, pregabalin, antiepileptics, duloxetine, venlafaxine, or tri-cyclic antidepressants); recent (within 3 months prior to recruitment) use of corticosteroids; history of corneal disease or incisional surgery; use of ocular topical medications other than for DED; and the presence of systemic diseases known to cause DED (human immunodeficiency virus, sarcoidosis, graft-versus-host disease, or collagen vascular disease).

Methods

Pre-Operative Examination

Slit lamp biomicroscopy of the anterior segment, best corrected VA, intraocular pressure (IOP), Schirmer I testing, TFBUT, ocular surface disease index (OSDI) questionnaire, pupillary diameter, corneal diameter, and corneal thickness were recorded preoperatively as well as 1 week, 1 month, and 3 months postoperatively. Patients also underwent a thorough posterior segment examination. At each of these visits, the patient’s vision quality as it relates to ocular surface integrity was measured with the double pass optical quality analysis system (OQAS2) and Keratograph 5M (K5M) advanced corneal topographer. The average of three separate measurements for each device was recorded at each visit.

Ocular Surface Disease Index (OSDI)

The OSDI is a standardized and validated questionnaire used to determine subjective complaints related to DED. Patients are given a score out of 100 based on their responses, higher scores indicating more severe symptoms. This was administered to all patients at each peri-operative visit [25].

Keratograph 5M (K5M) Advanced Corneal Topography

The K5M device is based on the Placido ring principle and provides a high-definition camera with a multi-wavelength light source for data analysis. The device records images of the non-invasive keratography first tear breakup time (NIKBUTf) and non-invasive keratography average tear breakup time (NIKBUTav). These measurements were then used to assign dry eye severity into the following grades: grade 0 (normal) NIKBUTf ≥ 10 sec and NIKBUTav ≥ 14 sec; grade 1 (suspicious dry eye) NIKBUTf 6-9 sec and NIKBUTav 8-13 sec; grade 2 (dry eye) NIKBUTf ≤ 5 sec and NIKBUTav ≤ 7 sec. The K5M allows the clinician to objectively grade TFBUT in a noninvasive manner. The K5M user interface is demonstrated in Figure 1.
Optical Quality Analysis System (OQAS2)

Snellen VA provides a subjective evaluation of visual performance and measures lower order aberrations. The OQAS2 provides an objective measurement of the optical quality of the human eye by using double pass imaging technology, which determines the detrimental changes of retinal image degradation and intraocular scatter. In a dark room, the system directs a single, near-infrared point source through the cornea and into the ocular media. It then collects the images of what has reflected off of the retina back to the sensor, thus traveling twice through the optical media [18]. The device produces both an objective scattering index (OSI) and a modulation transfer function (MTF).

The OSI is the ratio of peripheral (12-20 arc/min) to central (1 arc/min) light energy collected by the double pass instrument [1]. It reflects the scattering of light that has passed through an intraocular refractive medium and is an important contributor to retinal image degradation. The OSI value of the normal eye is generally less than 0.5, between 1.5 and 4.0 in eyes developing a cataract and higher than 4 in eyes with a measure cataract [26].

The MTF is the ratio between the contrast of an image after it has passed through the human eye and a previously defined contrast value assigned to that image at different spatial frequencies. In this way, it defines the loss of contrast introduced by the eye’s optics [27]. MTF cutoff values represent the limit of the resolution of the human eye as it reaches the corresponding spatial frequency of the MTF at 0.01. The MTF cutoff can be described as an objective visual quality measurement of the human eye as it pertains to the ocular system’s ability to distinguish contrast [28]. The MTF cutoff for a healthy human eye is greater than 30 cycles/deg, which correlates with a decimal visual acuity of 1.0 [29]. The larger the value, the better the retinal imaging quality and the better the visual quality [30].

The OQAS2 user interface is pictured in Figure 2.
Surgical Methods
The femtosecond laser assisted flap creation was carried out using Intralase FS60 (Intralase, USA). Flap diameter was 8.5 mm and flap thickness was 110 um. A 6.0-6.5 mm optical zone was used depending on patient pupil size. The Amaris excimer laser (Schwind, Germany) was used to treat the stromal bed. Wavefront guided treatment was used for each patient. The surgical procedure was performed by the same operator for all patients presented in this study.

Statistical Analysis
All data were analyzed using SPSS for Windows software (version 19.0, SPSS Inc.). The student’s t-test was used for comparison between measurements obtained at the preoperative and 3-month post-operative visit. Normality test was used before analysis. The analysis of variance (ANOVA) was used for comparison between myopia groups. The comparison of repeated measurement data was analyzed by ANOVA of repeated measurement data, the independent variable factors were time and refractive state preoperatively. The sphericity of the repeat data was tested by Mauchly’s Test for Sphericity. The Pearson correlation analysis between the two groups of data was performed using the correlation coefficient. The significance level of $\alpha=0.05$ was set, corresponding to a statistical significance of $P<0.05$.

Results
The participants of this study were divided into two groups: a low-moderate (L/M) myopia group ($<-6.00$ D, $n = 30$ eyes) and a high (H) myopia group ($> -6.00$ D, $n = 30$ eyes). Changes in refractive error are outlined in table 1. The spherical equivalent (SE) was significantly reduced in all patients after LASIK surgery ($P < 0.05$). There was no statistically significant difference in final spherical equivalent between these groups (Table 1).

Table 1: Average pre-operative and post-operative SE in diopters

<table>
<thead>
<tr>
<th></th>
<th>Pre</th>
<th>1 w post</th>
<th>1 m post</th>
<th>3 m post</th>
</tr>
</thead>
<tbody>
<tr>
<td>L/M</td>
<td>-3.75±1.26</td>
<td>+0.23±0.25*</td>
<td>+0.15±0.27*</td>
<td>+0.10±0.32*</td>
</tr>
<tr>
<td>H</td>
<td>-7.24±1.17</td>
<td>+0.51±0.27*</td>
<td>+0.30±0.29*</td>
<td>-0.16±0.39*</td>
</tr>
</tbody>
</table>

OSDI outcomes at preoperative and postoperative visits are outlined in Table 2. By convention, a score of 0-12 represents no DED, 13-22 represents mild DED, 23-32 represents moderate DED, and over 32 represents severe DED. There was a statistically significant increase in OSDI scores at the 3 month postoperative visit compared to the preoperative score.
Table 2: OSDI Preoperative and postoperative values

<table>
<thead>
<tr>
<th>Group</th>
<th>Pre</th>
<th>1 w post</th>
<th>1m post</th>
<th>3 m post</th>
<th>F value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>L/M</td>
<td>7.57±6.69</td>
<td>16.11±11.48</td>
<td>11.80±8.27</td>
<td>11.83±8.67</td>
<td>10.417</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>H</td>
<td>9.83±9.09</td>
<td>18.26±10.97</td>
<td>15.21±7.47</td>
<td>16.82±12.40</td>
<td>3.338</td>
<td>0.027</td>
</tr>
</tbody>
</table>

These are also compared against the objectively measured tear break-up time (NIKBUTf), recorded by the K5M device (Table 3). There was a statistically significant increase in subjective dry eye symptoms and decrease in NIKBUTf 3 months postoperatively relative to pre-operative observations in both groups. The negative correlation coefficient was statistically significant in both groups.

Table 3: Relationship between NIKBUTf and OSDI scores

<table>
<thead>
<tr>
<th>L/M</th>
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</tr>
</thead>
<tbody>
<tr>
<td>r value</td>
<td>-0.702</td>
<td>0.003</td>
<td>-0.789</td>
<td>&lt; 0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H</td>
<td></td>
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</tr>
</tbody>
</table>

Changes in vision quality parameters were recorded at each visit with the OQAS2. Table 4 demonstrates the changes in OSI and MTF cutoff. While there was a statistically significant increase in post-operative OSI in the high myopia group, the OSI in the L/M myopia group showed a statistically significant decrease at 3 months. Additionally, there was a statically significant increase in MTF cutoff values for both groups (Tables 4).

Table 4: Changes in intraocular scatter post-operatively (OSI, MTF cutoff)

<table>
<thead>
<tr>
<th>Group</th>
<th>Pre</th>
<th>1 w post</th>
<th>1 m post</th>
<th>3 m post</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>L/M</td>
<td>0.80±0.40</td>
<td>1.20±0.50</td>
<td>0.78±0.32</td>
<td>0.72±0.26</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>H</td>
<td>0.93±0.55</td>
<td>1.20±0.61</td>
<td>1.02±0.59</td>
<td>1.03±0.60</td>
<td>0.045</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group</th>
<th>Pre</th>
<th>1 w post</th>
<th>1 m post</th>
<th>3 m post</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>L/M</td>
<td>25.00±13.78</td>
<td>27.86±7.78</td>
<td>25.26±9.35</td>
<td>32.65±8.66</td>
<td>0.036</td>
</tr>
<tr>
<td>H</td>
<td>0.93±0.55</td>
<td>1.20±0.61</td>
<td>1.02±0.59</td>
<td>1.03±0.60</td>
<td>0.045</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group</th>
<th>Pre</th>
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<th>1 m post</th>
<th>3 m post</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>L/M</td>
<td>23.95±10.35</td>
<td>29.98±9.31</td>
<td>29.58±9.14</td>
<td>28.61±8.83</td>
<td>0.002</td>
</tr>
<tr>
<td>H</td>
<td>0.93±0.55</td>
<td>1.20±0.61</td>
<td>1.02±0.59</td>
<td>1.03±0.60</td>
<td>0.045</td>
</tr>
</tbody>
</table>

L/M: low/moderate myopia group; H: high myopia group; OSI: objective scatter index; MTF: modulation transfer function; all values are average measurements.

Finally, the findings of both subjective and objective dry eye were compared against the OSI and MTF cutoff values observed in this study. These findings are outlined in Table 5. As mentioned in the methods section, dry eye grades were assigned based on K5M measurements. A statistically significant increase in OSI values was seen with increasing dry eye grades in both the L/M and H myopia groups (P < 0.001, P = 0.007 respectively). MTF cut-off values showed a statistically significant decrease with increasing grades of dry eye in both myopia groups (P < 0.001, both groups) (Table 5).

Table 5: Correlation between dry eye and intraocular scatter measurements at 3-month post-operative visit

<table>
<thead>
<tr>
<th>Group</th>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>L/M</td>
<td>0.41±0.20</td>
<td>0.72±0.14*</td>
<td>0.91±0.21*△</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>MTF cut-off</td>
<td>37.13±5.93</td>
<td>30.11±4.63*</td>
<td>19.94±6.32*△</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group</th>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>0.57±0.06</td>
<td>0.50±0.24</td>
<td>1.62±0.99*△</td>
<td>0.007</td>
</tr>
<tr>
<td>MTF cut-off</td>
<td>36.10±5.68</td>
<td>28.72±3.63*</td>
<td>20.75±5.39*△</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

* = statistically significant difference when compared with Grade 0 (P<0.05)
△ = statistically significant difference when compared with Grade 1 (P<0.05)
**Discussion**

FS-LASIK, while an effective refractive surgery procedure, can introduce ocular surface changes that result in both symptomatic dry eye and reduced quality of vision. This study explored these changes using objective measurements. Changes in the ocular surface following FS-LASIK were documented using the K5M non-invasive tear break-up time analyzer. Prior research has demonstrated that DED is exacerbated by LASIK surgery and that DED patients experience reduced vision quality [1-4,8,12,15,20]. This is the first study to bring these elements together and demonstrate that reduced vision quality after LASIK is caused, at least in part, by the induced DED. Not only have we demonstrated these changes, but we also established that subjective dry eye complaints are correlated with an accurate, reproducible, noninvasive objective means of dry eye measurement.

There was a dramatic increase in dry eye complaints in the weeks and months following surgery as evidenced by a sustained increase in average OSDI scores post-operatively. Subjective visual complaints as determined by OSDI scores were also negatively correlated with the objective K5M measurements, showing that K5M is a useful tool to objectively quantify dry eye. We conclude that the instability of the tear film introduced by FS-LASIK are manifested by a rapid TFBUT and symptomatic DED.

Surface changes introduced into the ocular system following LASIK surgery were measured using double-pass imaging with the OQAS2 system, an effective instrument in analyzing vision quality [31]. We found a statistically significant decrease in the OSI in the L/M myopia but a statistically significant increase in the H myopia group. This indicating in OSI scores between L/M and H myopia can be explained due to the fact that high myopes require deeper ablation depths to achieve similar levels of emmetropia compared to lower myopes. Because of this, micro-wrinkles are necessarily introduced into the flap-stroma interface with increasing ablation depths, resulting in increased light scatter. Both L/M and H myopia groups saw a dramatic improvement in their MTF cutoff frequency after surgery with a statistically significant, sustained improvement 3 months after surgery. Our results using double-pass imaging parameters from FS-LASIK surgery differ somewhat with other published work. A study by Onategui et al. showed a decrease in the MTF cutoff frequency by a factor of 1.06 and an increase in OSI by a factor of 1.57, three months after FS-LASIK surgery [1]. Vilaseca et al. found an improvement in optical quality parameters (MTF cutoff frequency, strehl ratio) in patients with low pre-operative optical quality but not in those with high pre-operative optical quality [23]. Finally, Chiche et al. found that average OSI improved throughout the postoperative period in their 23 patients [32]. While reduced vision quality is common after LASIK, these changes have never been linked to the DED frequently observed after LASIK.

To investigate the impact that dry eye measurements have on vision quality changes, the L/M and H groups were further divided based on dry eye grades assigned by K5M measurements. This revealed a dramatic increase in intraocular scatter and decrease in objective visual quality with increasing dry eye grades (Table 5). Unlike the OSI changes observed after FS-LASIK in the two groups, the impact of dry eye on vision quality did not depend upon on level of pre-operative myopia. These vision quality changes based on objective dry eye severity measurements provide evidence that ocular surface integrity plays a vital role in the success FS-LASIK surgery, independent of higher order aberrations or ablative depth differences. While the role of a healthy tear film in vision quality has been well established, this is the first study to objectively measure these changes in this population of patients with particularly high expectations for vision quality [9,11]. Refractive surgeons must be aware of and prepared to treat the potential introduction of DED caused by FS-LASIK and the reduced vision quality that may result.

**Authors Contribution:** All authors meet the criteria for authorship.

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**Conflicts of Interest:** The authors declare no conflict of interest.

**References**


