Journal of the Optical Society of America A
OPTICS, IMAGE SCIENCE, AND VISION

Tear-film dynamics by combining double-pass images, pupil retro-illumination, and contrast sensitivity

Antonio Benito,* Juan M. Bueno, Guillermo M. Pérez, and Pablo Artal

Laboratorio de Óptica, Instituto Universitario de Investigación en Óptica y Nanofísica, Universidad de Murcia, Campus de Espinardo (Ed. 34), 30100 Murcia, Spain
**Corresponding author: abenito@um.es*

Received 14 November 2018; revised 12 March 2019; accepted 19 March 2019; posted 22 March 2019 (Doc. ID 351922); published 1 April 2019

Tear-film dynamics were analyzed by a synchronizing recording of double-pass (DP) and pupil retro-illumination (RI) images with contrast sensitivity (CS) measurements. Simultaneous DP and RI images were acquired in three subjects wearing contact lenses while keeping the eye open. Changes in contrast sensitivity for an 18 c/deg green grating were also estimated. From the DP retinal images, the effect of the tear film is described through the objective scattering index (OSI). This presented a negative correlation with the increase in CS during tear-film deterioration (as observed by RI imaging). These results show a relationship between visual outcome degradation due to tear-film breakup and the increase in intraocular scattering. This work shows a combined methodology for the evaluation of tear-film dynamics.

https://doi.org/10.1364/JOSAA.36.00B138

1. INTRODUCTION

The tear film is a liquid layer mainly composed of water that is indispensable to ocular surface health. It supplies nutrients and flushes away waste products, helps to protect the eye against environmental challenges, and provides a smooth optical interface to the anterior corneal surface [1]. During the inter-blink time, the tear film tends to naturally deteriorate over time, although with a variable behavior due to differences in the initial composition induced by changes in gland secretion, rate of evacuation/evaporation, etc. [2]. Dysfunction of the tear film may result in dry eye [3]. Tear-film abnormalities have their origin in a tear deficit (insufficient supply), an excessive loss, or an anomalous composition [4].

The clinical diagnosis of dry eye disease is commonly performed by means of tests able to demonstrate a reduced tear volume or a decreased flow. The Schirmer and the tear-film breakup time (BUT) tests are easy to perform and provide useful information on tear-film volume and quality. However, they are invasive techniques, and the results may depend on managing skills [5,6]. Other objective tests include imaging the tear meniscus over the inferior eye lid [7,8] or the anterior segment through OCT [9–12]. Osmolarity assessment has also been reported as an alternative and useful procedure [13,14]. Objective studies of the tear-film dynamics are based on fluorescence patterns [15,16], retro-illumination [17], and interferometric [18–21] imaging techniques. Other procedures include the analysis of the temporal changes of the first Purkinje image (as a noninvasive version of the BUT named NIBUT) [22], measurements of the temporal deterioration of the Placido disks images [23,24], and comparisons of temporal changes in corneal and ocular aberrations [25–27]. Subjective methods to assess tear-film quality (or alternatively the ocular surface disease index) are based on studying the impact of a degraded tear film on daily activities and ocular comfort by means of questionnaires [28] or through dynamic measurements of the visual quality [29,30]. However, a standard, objective, and quantitative method to assess the tear-film dynamical behavior remains a challenge due to its own nature and to the lack of agreement among the different existing techniques [31]. In this sense, a widely used approach to better score tear-film degradation is the combination of results obtained from different techniques [32–34].

A decrease in the homogeneity of the optical interface at the anterior corneal surface reduces the retinal image quality that can be measured by analyzing the intensity profile of the double-pass (DP) retinal image [35]. A degraded tear film would increase the intraocular light scattering, which can be objectively estimated through the DP image. This method is based on recording images of a point-source object after reflection on the retina and passing twice through the ocular media [36]. The objective scattering index (OSI) measures the contribution of intraocular scattering and is defined as the ratio of energy contained in an annular area around the peak of the DP image and that of the peak. The OSI value was originally proposed as a metric to objectively determine cataract grading [37,38].

In a previous work [39], we modified a commercially available DP instrument to include an additional channel for acquisition of retro-illumination (RI) images and another for visual contrast sensitivity (CS) testing. Results confirmed the relationship between image quality parameters obtained from DP images and visual function outcomes under different scattering scenarios. In that sense, the main objective of the present study has been to use that modified instrument to check the possible relationship between tear-film degradation, OSI increase, and visual quality decrease.

2. METHODS

The setup used in this study was a modified version of the Optical Quality Vision Analyzer-II (OQAS-II, Visiometrics SL, Tarrasa, Spain) previously described. The instrument is able to simultaneously record DP and RI images. In addition, CS measurements can also be performed during image recording. From the DP images, the corresponding OSI values were computed. CS was estimated for a sinusoidal green grating of 18 c/deg (equivalent to visual acuity 0.22 LogMAR). Further details on the operation can be found elsewhere [39]. The experiment was carried out in one eye of three well-trained healthy members of our laboratory that were familiar with the procedure: #1 (male, 37 y/o), #2 (female, 33 y/o), and #3 (male, 35 y/o). After being informed on the goal of the study, they gave an informed consent following the tenets of the Declaration of Helsinki. The spherical refractive error of each subject was corrected by means of the OQAS-II internal optometer. Astigmatism was compensated for with external trial lenses.

Series of images, both DP and RI, were simultaneously recorded at 2 Hz. Both series can easily be matched, having the last blink as a reference. At this point, the tear film is considered to have the best quality. At the time image acquisition started, a custom software allowed the projection of the grating with a defined spatial frequency, whose contrast was changed by the subject using a wireless keyboard. At the beginning of each series, subjects were asked to blink and then keep the eye under test open for as long as they could, while keeping the grating visible at threshold by modifying its contrast. Data of the contrast were automatically saved for posterior processing.

Data were obtained as the difference between the actual value (at a certain time point) and the initial baseline value right after the blink (time = 0 s). The initial idea was to measure the changes in OSI (δOSI) and contrast (δCS) as well as to record RI images under natural viewing conditions (i.e., naked eye). Most of the series showed negligible changes of δOSI with time. Accordingly, the contrast was also quite stable, even for series longer than 20 s. For longer periods of time, the tear film started to show signs of degradation as well as δOSI and δCS increase, but subjects reported ocular discomfort and finally blinked. This involuntary blink led to a sudden finishing of the measurement before being able to register the optical or visual effect of tear-film degradation. In view of this, and in order to increase subject's comfort and enlarge the tear-breaking image acquisition series, a plano daily disposable soft contact lens (CL; Alcon Laboratories Inc., Ft. Worth, Texas) was used [17]. To facilitate the analysis and comparison between series, data were averaged every 2 s. Statistical analysis and regression models were performed by using SPSS (v. 24.0, IBM Inc., Armonk, New York).

3. RESULTS

Figure 1 presents the results of δOSI for the three subjects for natural viewing conditions (Fig. 1, left) and when wearing the CL (Fig. 1, right). Measurements with the CL lasted longer, since all the subjects could keep the eye open for at least 35 s. A simple visualization reveals that when using the CL, just after blinking, little variations in OSI over time took place for several seconds, but then δOSI started to increase. In addition, intra-individual differences among series were found as shown by the error bars. This variation is associated with the degradation of the tear film as shown in the series of RI images. The use of a CL leads to a faster change in the behavior of the tear film that facilitates the experiment described herein.

When the subjects wore the CL, two different types of tear-film break-up series were observed. Some examples of this are depicted in Fig. 2, together with the RI images recorded in parallel that show the large distortion (or not) of the tear-film surface with time. In the so-called *smooth sequences* (Fig. 2(B)) the changes in OSI were small, remaining close to the baseline value for relatively long periods of time as under natural viewing conditions. However, there were also *fast break-up sequences*. In these, at some point δOSI started to grow rapidly (Fig. 2(A)). Degradation of the first Purkinje image as well as tear-film features can be observed.

Average results for percent of grating contrast obtained from each series are presented in Fig. 3. As time went on, subjects needed to increase the grating contrast to keep it visible, although certain intra-subject variability is also present.

Since both OSI (Fig. 1, right) and contrast (Fig. 3) change with time, it was interesting to explore their relationship. The CS was calculated from the grating contrast, and its relative change (δCS) from the baseline value was computed in a similar manner as done with δOSI. Figure 4 depicts the relationship between δOSI and δCS for the three subjects. Regression models showed that δOSI and δCS were significantly related ($p < 0.001$; ANOVA). A reduction in CS was closely associated with an increase in OSI (r2 was 0.985, 0.972, and

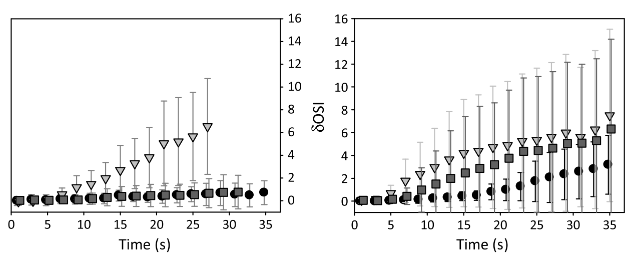

Fig. 1. Average δOSI as a function of time for all the subjects involved in the present experiment (#1, circles; #2, triangles; #3, squares). Left: data corresponding to the mean of six series registered under natural viewing conditions. Right: data corresponding to the mean of twelve series recorded with the CL on. Error bars represent one standard deviation.

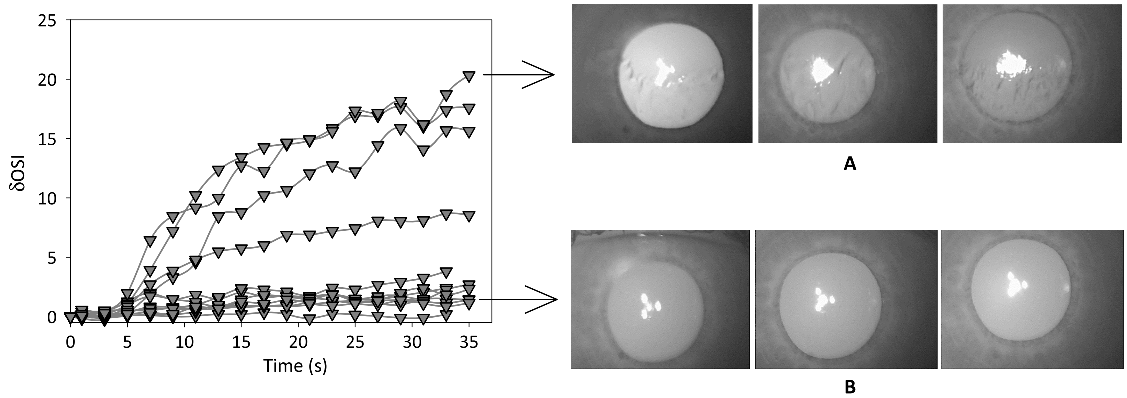

Fig. 2. Individual series of δOSI for different series recorded in subject #2 while wearing the CL. On the right, some representative RI images show a fast breakup (A, upper panels) and a smooth series (B, lower panels).

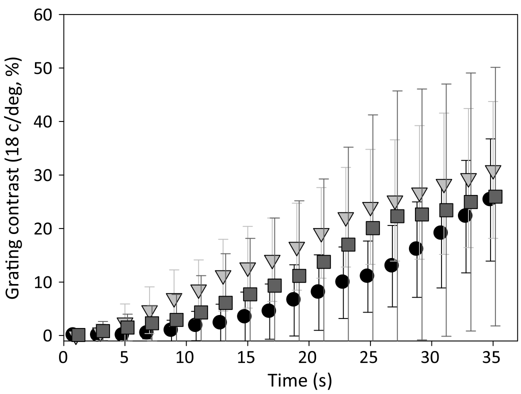

Fig. 3. Change in grating contrast directly for subject #1 (circles), subject #2 (triangles), and subject #3 (squares) while wearing a CL. Each value is the averages across twelve series. Error bars represent one standard deviation.

0.977 for subjects #1, #2, and #3, respectively). However, the actual relationship of OSI/CS strongly depends on the subject. In this study, whereas subjects #2 and #3 present similar behavior (slope for the linear fit), in subject #1 the increase in δOSI was related to a larger decrease of δCS (quadratic fitting). This relationship between the OSI increase and the CS decrease was previously reported for both 12 c/deg and 18 c/deg frequencies for different scattering-induced levels [39].

4. DISCUSSION

Unlike wavefront sensors that only measure lower-order aberrations (such as defocus, astigmatism, coma, or spherical aberration), the DP retinal image contains information on the overall optical performance of the human eye, including the contribution of aberrations and intraocular scattering. Nowadays, there are other methods to estimate the amount of intraocular straylight, but their acquisition time is relatively large, which make them unsuitable to study tear-film dynamics [40,41]. OSI can be recorded at 2 Hz, and an increase in OSI during the inter-blink period cannot be explained in terms of a large increase of low-order aberrations but by an increase in scattering due to a deteriorating precorneal tear film [42–45]. This relatively fast image acquisition might benefit the development of dry-eye diagnosis and therefore treatments [46].

Along this work, a modified version of a DP clinical instrument was used to analyze the retinal image quality, the tear break, and the CS during the inter-blink period. The procedure combined retinal DP and RI images as well as CS measurements. The degradation of the tear (as observed in the RI images) induced changes in the visual outcomes computed through δOSI and δCS.

Three normal healthy subjects were included in the present work. Only subject #2 reported some ocular allergic symptoms that could explain the different results obtained under natural viewing conditions (Fig. 1, left; triangles). For the other two subjects, the measured OSI values were quite stable over relatively long periods of time (Fig. 1, left; circles and squares). This is coherent with RI image stability and with little or no changes in contrast. Since under natural viewing conditions it was not possible to routinely record series with a significant tear-film degradation, we decided to use a CL. This method is widely used in this type of study as it accelerates tear-film degradation while the comfort of the subjects increases. As a drawback, the CL leads to a larger variability in the results due to the artificial alteration of the tear-film stability, especially in subjects with good tear-film stability. When subjects wore the CL, the tear film deteriorated faster, and so did the visual quality (Fig. 3). Optical and visual effects associated with tear-film deterioration under natural conditions are like those obtained with a soft CL. Then, the results found herein can be assumed valid since the CL was only used to accelerate the tear-break time.

Even using only three subjects, the results were highly variable. However, this was not an effect of considering a small sample but to the nature of the tear-film dynamics. In a previous work we measured the OSI parameter in 20 symptomatic dry eyes and 18 young controls [42]. In the control group we found that a good tear film caused little variation of OSI over time, and then a stable tear-film surface and a fairly good visual quality are expected. When measuring eyes with diagnosed dry-eye syndrome, the behaviors of the OSI series were also

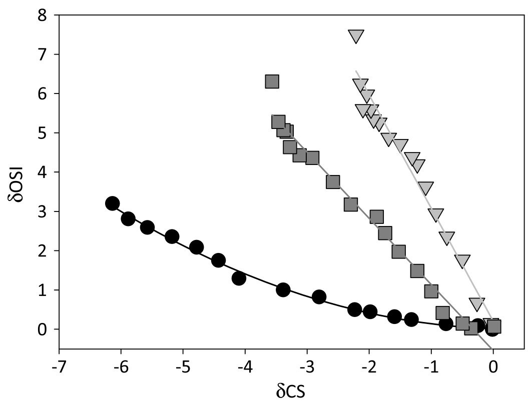

Fig. 4. Relationship between δOSI and δCS. Lines represent the best fitting for subject #1 (circles; quadratic), subject #2 (triangles; linear), and subject #3 (squares; linear).

highly variable. In the present study, a dual nature of tear-film dynamics was described: in the so-called smooth sequences, OSI values are stable over relatively long periods of time, as occurred for subjects #1 and #3 under natural viewing conditions. In that case, there is no change in the visual outcomes and no disruption areas appear over the tear-film surface during the inter-blink period. But within the break-up sequences there are abrupt increases of OSI at different moments and with different amplitude. Moreover, these are related to a decrease in visual outcomes and the appearance of disrupted areas over the tear-film surface. This may mean that those patients who have eye conditions that induce a degraded tear film may be continuously suffering unstable visual sensation.

In conclusion, a modified version of a DP image clinical device that includes a path for RI imaging and another for psychophysical measurements was used to characterize the behavior of the tear-film dynamics in normal healthy eyes without symptoms of a tear-film deficiency. A negative correlation between intraocular scattering and contrast sensitivity was found. This means that beyond ocular discomfort, a degraded tear film is associated with a reduction in visual performance. This study showed the potential benefit of using a combination of methods to study the dynamics of the tear film. In addition, these results validate the correlation between OSI and visual quality.

Funding. H2020 European Research Council (ERC) (ERC-2013-AdG-339228); Secretaría de Estado de Investigación, Desarrollo e Innovación (SEIDI) (FIS2016-76163-R); Fundación Séneca (f SéNeCa) (19897/GERM/15).

REFERENCES

1. G. Rieger, "The importance of the precorneal tear film for the quality of optical imaging," Br. J. Ophthalmol. **76**, 157–158 (1992).
2. M. Elliott, H. Fandrich, T. Simpson, and D. Fonn, "Analysis of the repeatability of tear break-up time measurement techniques on asymptomatic subjects before, during and after contact lens wear," Contact Lens Anterior Eye **21**, 98–103 (1998).
3. S. C. Pflugfelder, A. Solomon, and M. Stern, "The diagnosis and management of dry eye: a twenty-five-year review," Cornea **19**, 644–649 (2000).
4. M. E. Johnson and P. J. Murphy, "Changes in the tear film and ocular surface from dry eye syndrome," Prog. Retinal Eye Res. **23**, 449–474 (2004).
5. A. J. Bron, M. B. Abelson, G. Ousler, E. Pearce, A. Tomlinson, N. Yokoi, J. A. Smith, C. Begley, B. Caffery, K. Nichols, D. Schaumberg, O. D. Schein, M. Calonge, C. Baudouin, E. Goto, F. Grus, and J. Paugh, "Methodologies to diagnose and monitor dry eye disease: report of the diagnostic methodology subcommittee of the international dry eye workshop (2007)," Ocul. Surf. **5**, 108–152 (2007).
6. M. D. P. Willcox, P. Argüeso, G. A. Georgiev, J. M. Holopainen, G. W. Laurie, T. J. Millar, E. B. Papas, J. P. Rolland, T. A. Schmidt, U. Stahl, T. Suarez, L. N. Subbaraman, O. Ö. Uçakhan, and L. Jones, "TFOS DEWS II tear film report," Ocul. Surf. **15**, 366–403 (2017).
7. N. Yokoi, A. Bron, J. Tiffany, N. Brown, J. Hsuan, and C. Fowler, "Reflective meniscometry: a non-invasive method to measure tear meniscus curvature," Br. J. Ophthalmol. **83**, 92–97 (1999).
8. M. Dogru, K. Ishida, Y. Matsumoto, E. Goto, M. Ishioka, T. Kojima, T. Goto, M. Saeki, and K. Tsubota, "Strip meniscometry: a new and simple method of tear meniscus evaluation," Invest. Ophthalmol. **47**, 1895–1901 (2006).
9. O. M. Ibrahim, M. Dogru, Y. Takano, Y. Satake, T. H. Wakamatsu, K. Fukagawa, K. Tsubota, and H. Fujishima, "Application of visante optical coherence tomography tear meniscus height measurement in the diagnosis of dry eye disease," Ophthalmology **117**, 1923–1929 (2010).
10. T. Schmoll, A. Unterhuber, C. Kolbitsch, T. Le, A. Stingl, and R. Leitgeb, "Precise thickness measurements of Bowman's layer, epithelium, and tear film," Optom. Vis. Sci. **89**, E795–E802 (2012).
11. J. Huang, Q. Yuan, B. Zhang, K. Xu, P. Tankam, E. Clarkson, M. A. Kupinski, H. B. Hindman, J. V. Aquavella, T. J. Suleski, and J. P. Rolland, "Measurement of a multi-layered tear film phantom using optical coherence tomography and statistical decision theory," Biomed. Opt. Express **5**, 4374–4386 (2014).
12. D. Schmidl, K. J. Witkowska, S. Kaya, C. Baar, H. Faatz, J. Nepp, A. Unterhuber, R. M. Werkmeister, G. Garhofer, and L. Schmetterer, "The association between subjective and objective parameters for the assessment of dry-eye syndrome," Invest. Ophthalmol. **56**, 1467–1472 (2015).
13. A. Tomlinson, S. Khanal, K. Ramaesh, C. Diaper, and A. McFadyen, "Tear film osmolarity: determination of a referent for dry eye diagnosis," Invest. Ophthalmol. **47**, 4309–4315 (2006).
14. M. A. Lemp, A. J. Bron, C. Baudouin, J. M. Benítez Del Castillo, D. Geffen, J. Tauber, G. N. Foulks, J. S. Pepose, and B. D. Sullivan, "Tear osmolarity in the diagnosis and management of dry eye disease," Am. J. Ophthalmol. **151**, 792–798 (2011).
15. H. Zhuang, X. Zhou, and J. Xu, "A novel method for pachymetry mapping of human precorneal tear film using Pentacam with fluorescein," Invest. Ophthalmol. **51**, 156–159 (2010).
16. C. Begley, T. Simpson, H. Liu, E. Salvo, Z. Wu, A. Bradley, and P. Situ, "Quantitative analysis of tear film fluorescence and discomfort during tear film instability and thinning," Invest. Ophthalmol. **54**, 2645–2653 (2013).
17. N. L. Himebaugh, A. R. Wright, A. Bradley, C. G. Begley, and L. N. Thibos, "Use of retroillumination to visualize optical aberrations caused by tear film break-up," Optom. Vis. Sci. **80**, 69–78 (2003).
18. A. Dubra, C. Paterson, and C. Dainty, "Double lateral shearing interferometer for the quantitative measurement of tear film topography," Appl. Opt. **44**, 1191–1199 (2005).
19. P. E. King-Smith, B. A. Fink, J. J. Nichols, K. K. Nichols, and R. M. Hill, "Interferometric imaging of the full thickness of the precorneal tear film," J. Opt. Soc. Am. A **23**, 2097–2104 (2006).
20. D. Siedlecki, H. Kasprzak, and B. K. Pierscionek, "Dynamic changes in corneal topography and its influence on the point-spread function of the eye," Appl. Opt. **46**, 1361–1366 (2007).
21. D. H. Szczesna, D. Alonso-Caneiro, D. R. Iskander, S. A. Read, and M. J. Collins, "Lateral shearing interferometry, dynamic wavefront sensing, and high-speed videokeratoscopy for noninvasive assessment of tear film surface characteristics: a comparative study," J. Biomed. Opt. **15**, 037005 (2010).

22. L. S. Mengher, K. S. Pandher, and A. J. Bron, "Non-invasive tear film break-up time: sensitivity and specificity," Acta Ophthalmol. **64**, 441–444 (1986).
23. J. Németh, B. Erdélyi, B. Csákány, P. Gáspár, A. Soumelidis, F. Kahlesz, and Z. Lang, "High-speed videotopographic measurement of tear film build-up time," Invest. Ophthalmol. **43**, 1783–1790 (2002).
24. D. Alonso-Caneiro, J. Turuwhenua, D. R. Iskander, and M. J. Collins, "Diagnosing dry eye with dynamic-area high-speed videokeratoscopy," J. Biomed. Opt. **16**, 076012 (2011).
25. S. Koh, N. Maeda, T. Kuroda, Y. Hori, H. Watanabe, T. Fujikado, Y. Tano, Y. Hirohara, and T. Mihashi, "Effect of tear film break-up on higher-order aberrations measured with wavefront sensor," Am. J. Ophthalmol. **134**, 115–117 (2002).
26. R. Montés-Micó, J. L. Alió, and W. N. Charman, "Dynamic changes in the tear film in dry eyes," Invest. Ophthalmol. **46**, 1615–1619 (2005).
27. J. Xu, J. Bao, J. Deng, F. Lu, and J. C. He, "Dynamic changes in ocular Zernike aberrations and tear menisci measured with a wavefront sensor and an anterior segment OCT," Invest. Ophthalmol. **52**, 6050–6056 (2011).
28. R. M. Schiffman, M. D. Christianson, G. Jacobsen, J. D. Hirsch, and B. L. Reis, "Reliability and validity of the ocular surface disease index," Arch. Ophthalmol. **118**, 615–621 (2000).
29. E. Goto, Y. Yagi, Y. Matsumoto, and K. Tsubota, "Impaired functional visual acuity of dry eye patients," Am. J. Ophthalmol. **133**, 181–186 (2002).
30. R. Ishida, T. Kojima, M. Dogru, M. Kaido, Y. Matsumoto, M. Tanaka, E. Goto, and K. Tsubota, "The application of a new continuous functional visual acuity measurement system in dry eye syndromes," Am. J. Ophthalmol. **139**, 253–258 (2005).
31. P. Cho and W. Douthwaite, "The relation between invasive and non-invasive tear break-up time," Optom. Vis. Sci. **72**, 17–22 (1995).
32. B. D. Sullivan, D. Whitmer, K. K. Nichols, A. Tomlinson, G. N. Foulks, G. Geerling, J. S. Pepose, V. Kosheleff, A. Porreco, and M. A. Lemp, "An objective approach to dry eye disease severity," Invest. Opthalmol. **51**, 6125–6130 (2010).
33. S. Koh, C. Tung, J. Aquavella, R. Yadav, J. Zavislan, and G. Yoon, "Simultaneous measurement of tear film dynamics using wavefront sensor and optical coherence tomography," Invest. Ophthalmol. **51**, 3441–3448 (2010).
34. M. Kaido, M. Uchino, N. Yokoi, Y. Uchino, M. Dogru, M. Kawashima, A. Komuro, Y. Sonomura, H. Kato, S. Kinoshita, and K. Tsubota, "Dry-eye screening by using a functional visual acuity measurement system: the Osaka study," Invest. Ophthalmol. **55**, 3275–3281 (2014).
35. J. I. Prydal, P. Arral, H. Woon, and F. W. Campbell, "Study of human precorneal tear film thickness and structure using laser interferometry," Invest. Ophthalmol. **33**, 2006–2011 (1992).
36. J. Santamaría, P. Artal, and J. Bescós, "Determination of the point-spread function of human eyes using a hybrid optical-digital method," J. Opt. Soc. Am. A **4**, 1109–1114 (1987).
37. F. Díaz-Doutón, A. Benito, J. Pujol, M. Arjona, J. L. Güell, and P. Artal, "Comparison of the retinal image quality with a Hartmann-Shack wavefront sensor and a double-pass instrument," Invest. Ophthalmol. **47**, 1710–1716 (2006).
38. P. Artal, A. Benito, G. M. Pérez, E. Alcón, A. De Casas, J. Pujol, and J. M. Marín, "An objective scatter index based on double-pass retinal images of a point source to classify cataracts," PLoS One **6**, e16823 (2011).
39. J. M. Bueno, G. Pérez, A. Benito, and P. Artal, "Impact of scatter on double-pass image quality and contrast sensitivity measured with a single instrument," Biomed. Opt. Express **6**, 4841–4849 (2015).
40. H. Ginis, O. Sahin, A. Pennos, and P. Artal, "Compact optical integration instrument to measure intraocular straylight," Biomed. Opt. Express **5**, 3036–3041 (2014).
41. L. Franssen, J. E. Coppens, and T. J. T. P. Van Den Berg, "Compensation comparison method for assessment of retinal straylight," Invest. Ophthalmol. **47**, 768–776 (2006).
42. A. Benito, G. M. Pérez, S. Mirabet, M. Vilaseca, J. Pujol, J. M. Marín, and P. Artal, "Objective optical assessment of tear-film quality dynamics in normal and mildly symptomatic dry eyes," J. Cataract Refract. Surg. **37**, 1481–1487 (2011).
43. C. H. Tan, A. Labbé, Q. Liang, L. Qiao, C. Baudouin, X. Wan, and N. Wang, "Dynamic change of optical quality in patients with dry eye disease," Invest. Opthalmology **56**, 2848–2854 (2015).
44. A. Y. Yu, T. Lu, A. P. Pan, D. R. Lin, C. C. Xu, J. H. Huang, and F. J. Bao, "Assessment of tear film optical quality dynamics," Invest. Opthalmology **57**, 3821–3827 (2016).
45. A. Herbaut, H. Liang, G. Rabut, L. Trinh, K. Kessal, C. Baudouin, and A. Labbé, "Impact of dry eye disease on vision quality: an optical quality analysis system study," Trans. Vis. Sci. Technol. **7**, 5–10 (2018).
46. A. Igarashi, K. Kamiya, H. Kobashi, and K. Shimizu, "Effect of rebamipide ophthalmic suspension on intraocular light scattering for dry eye after corneal refractive surgery," Cornea **34**, 895–900 (2015).