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Comparison of non-invasive and fluorescein tear film break-up time in a 65-year-old Norwegian population: a cross-sectional study

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ABSTRACT

Objectives Measurement of tear film stability is central in dry eye disease (DED) diagnosis. In this study, we aimed to compare the performance of two methods of tear film stability measurement: non-invasive tear break-up time (NIBUT) and fluorescein tear film break-up time (FTBUT).

Design Cross-sectional study.

Setting and participants The study involved 132 subjects of 65-year-old inhabitants of the Oslo region who were not seeking ophthalmic care.

Interventions The participants underwent a battery of DED tests, including NIBUT measured on Oculus Keratograph 5M and a traditional method using fluorescein drops (FTBUT). Oculus Keratograph 5M measures two types of NIBUT:; appearance time of the first dry spot ($NIBUT_{First}$) and average $NIBUT_{Avg}$.

Results 74 participants (56%) were female and 58 were male (44%). Subjects presented with varying degrees of DED signs and symptoms. Mean values of $NIBUT_{First}$ and FTBUT from all the participants were significantly different (6.2±4.9 s vs 8.6±6.2 s, p<0.0001). There was also a significant difference between $NIBUT_{First}$ and $NIBUT_{Avg}$ values (6.2±4.9 s vs 8.3±5.5 s, p<0.0001). In contrast, no difference was observed between FTBUT and $NIBUT_{Avg}$ values (8.6±6.2 s vs 8.3±5.5 s, p=0.655). The receiver operating characteristic curve analysis was performed to compare NIBUT and FTBUT in regards to other clinical tests (Ocular Surface Disease Index, ocular surface staining, blink interval, eye redness, corneal sensitivity, lid debris, Schirmer I test, tear osmolarity, meibum quality, meibum expressibility, lid hyperemia, tear meniscus height,. irregular lid margin, conjunctival hyperaemia, margin telangiectasia, lipid layer and meibomian gland drop-out). While FTBUT demonstrated results with area under the curve>0.6, neither $NIBUT_{First}$ nor $NIBUT_{Avg}$ showed significant results.

Conclusion $NIBUT_{First}$ was shorter than FTBUT. Low correlation between NIBUT and FTBUT indicates that these diagnostic tests are not interchangeable. Other DED tests had correlation, though low, while NIBUT did not demonstrate correlation.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Homogenous group of patients in terms of age.
⇒ Small variations in the examination time of the day, thus, potentially reducing variations in obtained examination result.
⇒ Examinations took place over three seasons—summer, autumn and winter—which may have impacted tear break-up time (TBUT) in subjects and air the humidity at the clinic.
⇒ An average value of three non-invasive BUT measurements would be better.

INTRODUCTION

The Tear Film and Ocular Surface Society (TFOS) Dry Eye Workshop (DEWS) II report defines dry eye disease (DED) as "… *a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles*".[1] The symptoms of DED can vary, and a feeling of dryness, soreness, irritation, foreign body sensation, stinging and photophobia as well as ocular pain are frequent symptoms.[1] DED can range from mild discomfort to severe negative impact on daily quality of life.[2–4] The disease has a significant socio-economic burden.[5]

DED is classified into two major groups:; aqueous deficiency and evaporative DED. In the former, aqueous tear- producing glands are affected, while in the latter oil-producing glands are often disturbed, leading to reduced stability of the precorneal tear film.[1] A battery of tests is required to diagnose DED accurately.[6] One of the most important diagnostic tests is the tear film break-up time (TBUT).[6–8]

There are two major methods of measurement of TBUT. A commonly performed and widely adapted method is using fluorescein sodium solution, known as fluorescein tear film break-up time (FTBUT). In this method, a solution of fluorescein sodium is instilled into the lower fornix. The test is performed on a slit-lamp using a blue filter. The patient is asked to blink three times and afterwards not to blink until the first dry spot appears. The FTBUT is recorded as the number of seconds that elapses between the last blink and the appearance of the first dry spot in the tear film. A commonly accepted cut-off value is 10 s, and a shorter FTBUT is indicative of a less stable tear film.[9 10] To carry out the FTBUT, because of the ease of use and accessibility, many clinicians prefer to apply paper strips impregnated with fluorescein sodium. Instillation of fluorescein is done by wetting the paper strip with two drops of sterile saline and gently and briefly touching the strip onto the inferior bulbar conjunctiva.[11] This method is easy to perform, but it is impossible to control the volume of fluorescein sodium. Hence, dosing the fluorescein sodium with a pipette gives better control. Thus, instilling 10 µL of 2% solution of fluorescein sodium is the recommended method.[10]

Non-invasive break-up time (NIBUT) measurements have become popular in recent years due to advancements in diagnostic methods and renewed recommendations in clinical guidelines. It has been reported that fluorescein affects tear film stability and therefore NIBUT is the preferred method.[6] Due to both the non-invasive nature and the objectivity, using NIBUT is recommended.[6] There are different techniques of measuring NIBUT.[10 12–18] One of the most popular techniques is detecting TBUT by observing distortion in the contours of reflected Placido disc mires.[19] Some devices, such as the Oculus Keratograph (Oculus, Wetzlar, Germany), have integrated scan software that detects tear break-up time automatically. To prevent photophobia, infrared illumination is employed.[20 21]

To our knowledge, the current available literature lacks strong evidence supporting the diagnostic accuracy of NIBUT in DED. Moreover, the TFOS DEWS II guidelines advocate more studies involving normal populations. Therefore, in this study our objective was to compare diagnostic ability of NIBUT and FTBUT to determine their utility in DED diagnosis in a population of 65-year-old subjects who did not seek ophthalmic care.

METHODS

Subjects

This cross-sectional study is a part of a larger study on oral and ocular health in the young elderly and was performed at the University of Oslo and the Norwegian Dry Eye Clinic.[22–27] A cohort of 458 65-year-old individuals were randomly selected for the oral part of the study, and 150 also accepted to participate in the ocular study before inclusion stopped due to the COVID-19 pandemic. The list of the participants was obtained from the Norwegian National Population Registry. Thus, the study participants were not patients seeking ophthalmic care at the clinic. Written informed consent was obtained from all subjects prior to participation in the study that was performed between July 2019 and March 2020. The study included an extensive dry eye examination. A total of 150 subjects participated in the study. 18 participants were excluded in the analyses due to missing values of NIBUT, presence of dermatochalasis or pterygium.

Diagnostic tests

All subjects underwent the tests in the following order: McMonnies Dry Eye Questionnaire[28] and Ocular Surface Disease Index (OSDI) questionnaire,[29] blink interval,[30] NIBUT,[20 21] tear meniscus height,[31] tear osmolarity,[6] FTBUT,[32] presence of conjunctival hyperaemia,[33] irregular lid margin,[34] lid debris,[6] conjunctival papillae,[33] ocular surface staining (OSS, The Oxford grading scale, range: 0–15),[35] corneal sensitivity,[36] Schirmer test (without anaesthesia), meibum expressibility,[37] meibum quality and meibography.[38]

Non-invasive break-up time

Oculus Keraograph 5M with integrated software was used to perform the test. The subjects were instructed to blink naturally and hold the eyes open until instructed to blink again. If subjects could not refrain from blinking before the tear film broke up, that time was considered the final value. The integrated software produces two values of NIBUT: the first break-up time ($NIBUT_{First}$) and the average break-up time ($NIBUT_{Avg}$). $NIBUT_{First}$ is the time when the first break in the tear film occurs, while $NIBUT_{Avg}$ is the average time of all the break-ups that occurred during the measurement.[39]

Fluorescein tear film break-up time

In performing FTBUT, 5 uL 2% solution of fluorescein sodium was used. The subjects were asked to look up, and the fluorescein solution was instilled into the temporal lower fornix. The participants were asked to blink three times before the measurement was taken. After the third blink, subjects were asked not to blink until the first break appeared. Three readings in seconds were recorded with a stopwatch, and the average of the three was recorded as a final variable.

Statistical analyses

The statistical analyses were performed with the commercial software SPSS, V.26 (IBM, Chicago, Illinois, USA). Data from the right eye were used. The normality of the data was verified by the Shapiro-Wilk test. The means of all data for ocular measurements in male and female participants were compared. Independent t-test was used in comparison of parameters with normal distribution, while the Mann-Whitney test was used for parameters with non-normal distribution. Wilcoxon signed-rank test was used to compare FTBUT and NIBUT values. Receiver operator characteristics (ROC) curve was used to identify

Table 1 Demographic characteristics of participants

	Male (n=58)	Female (n=74)
Education completed		
Basic education (8 years)	2 (3%)	4 (5%)
High school/vocational education	14 (24%)	25 (34%)
Higher education (<4 years)	10 (17%)	19 (26%)
Higher education (>4 years)	32 (56%)	26 (35%)
Occupation		
Working	43 (74%)	52 (70%)
Retired	11 (19%	17 (23%)
Disabled/not working	4 (7%)	5 (7%)
Marital status		
Married/co-habiting	50 (86%)	64 (87%)
Single/separated/ widow(er)	8 (14%)	10 (13%)

the diagnostic ability of NIBUT and FTBUT in the discrimination of pathological values of dry eye tests (tables 1 and 2). Correlations between variables were checked using the Pearson correlation or Spearman rank analyses. The results are presented as the mean ± SD. A p value of <0.05 was considered significant throughout the analyses.

Patient and public involvement

None.

RESULTS

The majority of the participants were occupationally active and non-smoking. Detailed demographic characteristics are given in table 1.

An overview of the examination results as well as comparison between males and females is presented in Table 4. As evident from online supplemental figure 1, there was a large variability of dry eye symptoms, and signs showed overlapping results. Subjectively, at least 70% of participants did not experience dry eye symptoms (based on OSDI score results) even though they had abnormal dry eye signs (ie, abnormal Schirmer test, OSS, NIBUT or FTBUT).

When the cut-off value for FTBUT was chosen as 10 s, 64% subjects had FTBUT<10 s, while this number was lower when the cut-off value of 5 s was chosen (39%). These numbers were higher for $NIBUT_{First;}$ 84% and 63%, respectively. For $NIBUT_{Avg}$, 71% of subjects had a value of under 10 s and 41% of subjects had a value of under 5 s.

The mean values of $NIBUT_{First}$ (range: 0.45–23.13) and FTBUT (range: 0.91–36.00) from all the participants were significantly different (6.2±4.9 vs 8.6±6.2, p<0.0001). There was also a significant difference between $NIBUT_{First}$ and $NIBUT_{Avg}$ (range: 1.27–26.78) values (6.2±4.9 vs 8.6±6.2, p<0.0001). In contrast, no difference was observed between FTBUT and $NIBUT_{Avg}$ values (8.6±6.2 vs 8.3±5.5, p=0.655).

While there was a strong correlation between $NIBUT_{First}$ and $NIBUT_{Avg}$ (r=0.877, p<0.001), there was a weak correlation between FTBUT and $NIBUT_{Avg}$ (r=0.184, p=0.038) and no significant correlation between $NIBUT_{First}$ and FTBUT.

Table 2 Overview of the clinical data obtained from subjects

	Total (n=132)	Male (n=58)	Female (n=74)	
Diagnostic test	Mean±SD	Mean±SD	Mean±SD	P value*
McMonnies	6.3±4.1	5.8±3.8	6.7±4.3	0.227
OSDI	8.7±11.7	7.1±9.4	10.0±13.3	0.155
Blink interval	12.3±8.3	12.7±9.8	12.0±8.3	0.636
$NIBUT_{First}$	6.2±4.9	6.9±5.8	5.7±4.1	0.428
$NIBUT_{Avg}$	8.3±5.6	9.2±6.4	7.6±4.7	0.3
Tear meniscus height	0.27±0.08	0.29±0.07	0.25±0.08	0.01
Osmolarity	315.2±19.8	314.1±25.5	315.8±15.6	0.982
FTBUT	8.6±6.2	10.0±6.8	7.6±5.5	0.048
Ocular surface staining	0.7±1.1	0.5±0.9	0.9±1.2	0.021
Schirmer test	14.5±9.5	13.1±8.8	15.7±10.0	0.188
Corneal sensitivity	59.8±1.6	60.0±0.0	59.6±2.0	0.444
Meibomian gland expressibility	3.7±1.1	3.9±0.9	3.6±1.2	0.273
Meibum quality	4.0±3.0	4.1±3.1	4.0±2.9	0.902

*Comparison between males and females
FTBUT, fluorescein tear film break-up time; $NIBUT_{Avg}$, non-invasive tear break-up time average; $NIBUT_{First}$, non-invasive tear break-up time first; OSDI, Ocular Surface Disease Index.

Table 3 AUC for $NIBUT_{First}$, $NIBUT_{Avg}$ and FTBUT in regards to other DED tests

Test variables	Cut-off pathological value	$NIBUT_{First}$		$NIBUT_{Avg}$		FTBUT	
		AUC	P value	AUC	P value	AUC	P value
OSDI	>12	0.522	0.695	0.492	0.888	0.580	0.176
OSS	>1	0.5965	0.059	0.577	0.13	0.662	0.002
OSS	>3	0.667	0.067	0.653	0.095	0.807	0.002
Schirmer I	<5 mm/5 min	0.582	0.280	0.558	0.441	0.675	0.021
Schirmer 1	<10 mm/5 min	0.509	0.853	0.519	0.713	0.625	0.018
Conjunctival papillae	>0	0.618	0.694	0.137	0.217	0.769	0.36
Conjunctival hyperaemia	>0	0.576	0.234	0.556	0.379	0.622	0.06
Meibum quality	>1	0.539	0.527	0.505	0.939	0.629	0.039
Tear meniscus height	<0.2 mm	0.214	0.331	0.511	0.979	0.603	0.73
Tear osmolarity	>308 mOsm/L	0.438	0.467	0.413	0.304	0.594	0.275
Lid debris	>0	0.552	0.499	0.527	0.732	0.682	0.03
Lid thickening	>0	0.486	0.806	0.469	0.584	0.601	0.08
Irregular lid margin	>0	0.526	0.662	0.493	0.906	0.587	0.15
Lid hyperaemia	>0	0.573	0.148	0.528	0.581	0.451	0.35
Margin telangiectasia	>0	0.565	0.265	0.506	0.918	0.688	0.002
$NIBUT_{First}$	<5	1.000	<0.0001	0.907	<0.0001	0.626	0.017
$NIBUT_{First}$	<10	1.000	<0.0001	0.974	<0.0001	0.637	0.065
$NIBUT_{Avg}$	<5	0.918	<0.0001	1.000	<0.0001	0.617	0.029
$NIBUT_{Avg}$	<10	0.866	<0.0001	1.000	<0.0001	0.610	0.058
FTBUT	<5	0.564	0.223	0.592	0.079	1.000	0.001
FTBUT	<10	0.549	0.373	0.548	0.375	1.000	0.001

AUC, area under the curve; DED, dry eye disease; FTBUT, fluorescein tear film break-up time; $NIBUT_{Avg}$, non-invasive tear break-up time average; $NIBUT_{First}$, non-invasive tear break-up time first; OSDI, Ocular Surface Disease Index; OSS, ocular surface staining.

In our population, the ROC curve analyses revealed that neither $NIBUT_{First}$ nor $NIBUT_{Avg}$ had significant values of the area under the curve (AUC) in regard to other DED tests. Detailed results are shown in table 3. FTBUT, however, showed some significant results with (AUC) over 0.6 (tables 1 and 2).

Even though FTBUT had AUC over 0.6 in regard to other DED tests, sensitivity and specificity levels were rather low.

ROC curve analyses of the subjects based on sex were also performed. Although this grouping gave even more homogenous samples representing samples with the same age and sex, the obtained outcome resembled the results in table 4 (data not shown).

As shown in table 5, there was a weak negative correlation between $NIBUT_{First}$ and OSS (r=−0.176, p<0.04). No significant correlations between $NIBUT_{Avg}$ and other clinical variables were observed. There were significant but rather weak correlations between FTBUT and several other clinical parameters; blink interval (r=0.186, p=0.04), OSS (r=−0.392, p<0.0001), Schirmer test (r=0.210, p=0.019), lid debris (r=−0.195, p=0.029), conjunctival hyperaemia (r=−0.207, p=0.02), lid margin thickening (r=−0.197, p=0.027), margin telangiectasia (r=−0.335, p<0.0001), meibomian gland expressibility (r=−0.188, p=0.034) and lipid layer thickness (r=−0.325, p<0.0001).

DISCUSSION

The present study compared NIBUT and TFUBT and investigated their correlations with other DED tests. The majority of the study population of 65-year-old subjects did not report a subjective feeling of ocular dryness. Nevertheless, as a group they presented with varying degrees of dry eye signs. $NIBUT_{First}$ was significantly shorter than FTBUT, while no difference was detected between $NIBUT_{Avg}$ and FTBUT. However, the correlation between $NIBUT_{Avg}$ and FTBUT was weak. Using the ROC curve analyses, $NIBUT_{First}$ and $NIBUT_{Avg}$ values did not show significant AUC results, while FTBUT produced several significant results with AUC>0.6. However, FTBUT had relatively low sensitivity and specificity in detecting abnormal signs of DED.

TFOS DEWS II report mentions that fluorescein may reduce tear film stability.[6 11 40] Mengher *et al* concluded that fluorescein may shorten TBUT.[40] The study from 1984 compared FTBUT and NIBUT in nine healthy subjects. In order to detect NIBUT, the authors used a

Table 4 Results from the ROC analyses of FTBUT in regard to other DED tests

		FTBUT		Sensitivity	Specificity
Test variables	Cut-off pathological value	AUC	P value		
OSS	>1	0.713	0.001	0.66	0.64
OSS	>3	0.765	0.005	0.70	0.62
Schirmer 1	<5 mm/5 min	0.675	0.021	0.82	0.57
Schirmer 1	<10 mm/5 min	0.602	0.05	0.74	0.42
Conjunctival hyperemia	>0	0.648	0.02	0.62	0.46
Meibum quality	>1	0.788	0.02	0.83	0.75
Lid debris	>0	0.668	0.03	0.62	0.55
Lid thickening	>0	0.625	0.02	0.62	0.56
Margin telangiectasia	>0	0.718	0.001	0.71	0.68
$NIBUT_{First}$	<5	0.611	0.03	0.59	0.52
$NIBUT_{Avg}$	<5	0.617	0.029	0.52	0.70

AUC, area under the curve; DED, dry eye disease; FTBUT, fluorescein tear film break-up time; $NIBUT_{Avg}$, non-invasive tear break-up time average; $NIBUT_{First}$, non-invasive tear break-up time first ; OSS, ocular surface staining; ROC, receiver operating characteristic.

non-automated optical instrument consisting of a hemispherical steel bowl, mounted at the apex onto a binocular slit-lamp biomicroscope. The examiner would look through the slit-lamp microscope and evaluate loss of tear film integrity. Mooi and colleagues evaluated the impact of fluorescein volume on TBUT using Tearscope-Plus.[11] 41 subjects underwent three measurements; NIBUT, FTBUT with 1 µL followed by 15–30 µL of fluorescein fluid via a conventional fluorescein strip. The tests were performed with 15 min intervals. The results of the study revealed that measurement of tear film stability with 1 µL was comparable to the non-invasive method, while measurement with 30 µL showed reduced tear film stability.

In our analyses, we found that mean FTBUT (8.6±6.2) was higher than $NIBUT_{First}$ (6.2±4.9 s, p<0.0001) but did not differ significantly from $NIBUT_{Avg}$ (8.3±5.6 s,

Table 5 Correlation between $NIBUT_{First}$, $NIBUT_{Avg}$, FTBUT and other clinical parameters

	$NIBUT_{First}$		$NIBUT_{Avg}$		FTBUT	
Test variables	Spearman (r)	P value	Spearman (r)	P value	Spearman (r)	P value
McMonnies	–0.094	0.284	0.020	0.818	–0.047	0.598
OSDI	–0.149	0.089	–0.066	0.451	–0.087	0.331
OSS	–0.176	0.043	–0.137	0.118	–0.392	<0.001
Blink interval	–0.094	0.292	–0.039	0.660	0.186	0.04
Eye redness	–0.070	0.438	0.033	0.716	0.076	0.410
Tear osmolarity	–0.012	0.930	–0.007	0.958	0.121	0.369
Schirmer test	0.022	0.805	0.006	0.942	0.210	0.019
Conjunctival papillae	–0.036	0.686	0.109	0.214	–0.086	0.334
Conjunctival hyperaemia	–0.105	0.235	–0.077	0.379	–0.207	0.020
Meibum quality	–0.026	0.768	0.030	0.732	–0.064	0.472
Meibum expressibility	0.047	0.591	0.125	0.155	–0.188	0.034
Tear meniscus height	0.003	0.970	0.048	0.585	0.096	0.281
Lid debris	–0.060	0.499	–0.031	0.730	–0.195	0.029
Lid thickening	0.022	0.805	0.048	0.585	–0.197	0.027
Irregular lid margin	–0.038	0.662	0.011	0.904	–0.128	0.151
Lid hyperaemia	–0.127	0.148	–0.049	0.581	0.051	0.569
Margin telangiectasia	–0.100	0.255	–0.012	0.891	–0.335	<0.001

FTBUT, fluorescein tear film break-up time; $NIBUT_{Avg}$, non-invasive tear break-up time average; $NIBUT_{First}$, non-invasive tear break-up time first ; OSDI, Ocular Surface Disease Index; OSS, ocular surface staining.

p=0.443). The discrepancy between our findings and those of Mengher *et al* can be explained by a difference in sample size (132 vs 9), use of different tools (automated vs non-automated) and fluorescein volume (10 µL vs a drop (about 50 µL)). A similar argument can be made when comparing our results to those of Mooi and colleagues. While Tearscope-Plus requires an examiner to identify TBUT, Oculus 5M detects it automatically. Markoulli *et al* compared NIBUT measured with Tearscope-Plus and Oculus 5M.[41] In their study with 24 subjects, the results obtained from the two devices were not significantly different. In another study with 20 relatively younger subjects (mean age: 38.6 years±8.1), NIBUT obtained with Oculus keratograph was shorter than Tearscope values (5.8 s vs 7.5 s, p=0.002).[42] Comparable findings with Oculus 5M generating shorter TBUT values were reported by both Best *et al*[20] and Hong *et al*.[21] The latter compared FTBUT and NIBUT in patients with dry eye as well as healthy controls. Our findings with relatively shorter $NIBUT_{First}$ values are in line with the abovementioned studies. However, a study including 296 eyes by Abdelfattah *et al* observed longer $NIBUT_{Avg}$ than FTBUT.[43] Similar findings were reported by Lan and colleagues who studied healthy volunteers.[44] This disagreement can be explained by the complexity of DED diagnostics and known variability of DED test results.

Automatic detection of tear film break-up spots may have advantages in being objective and having acceptable repeatability and reproducibility.[41 45] Fluorescein dye is widely used in ophthalmology due to its practicality and non-toxicity. It is also worth mentioning the disadvantages of each of the two approaches, for instance, NIBUT is dependent on the measurement area, while FTBUT could be variable as the determination of tear film break-up can vary between examiners.

The study has several strengths. First, the study subjects in the current study are homogenous in terms of age. Second, the study follows TFOS DEWS II recommendations and included a homogenous population not seeking ophthalmic care. Also, these subjects will be followed over several years, enabling researchers to observe longitudinal changes of many variables, including tear film stability. A slight variation in the time of the day (±3 hours; as examinations took place between 17:00 and 20:00) of examination may have contributed to less variations in the obtained examination results. Moreover, the vast majority of the study participants were examined by one examiner in the current study, which means the findings, that is, comparison between NIBUT and FTBUT, and correlations between FTBUT and other clinical dry eye tests, represented only the results from that one examiner. There are limitations to the study. The examinations took place between July 2019 and March 2020, over three seasons: summer, autumn and winter. This may have impacted the TBUT in subjects as well as the air humidity at the clinic. Another limitation of the study is taking one measurement of NIBUT. An average value of three measurements might have generated a different value. Moreover, the participants that had eye conditions may have been over-represented in the eye examination study since these participants could benefit from having an eye examination at a specialty clinic. This could have led to a skewed participant attendance.

CONCLUSION

$NIBUT_{First}$ was shorter than FTBUT. The latter had better, but rather low, correlations with other DED tests compared with NIBUT. Low correlation between NIBUT and FTBUT indicates that these diagnostic tests are not interchangeable.

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Patient consent for publication Consent obtained directly from patient(s)

Ethics approval This study involves human participants and was approved by the Norwegian Regional Committee for Medical and Health Research Ethics (REK 2018/1383). The study was performed in compliance with the tenets of the Declaration of Helsinki. Participants gave informed consent to participate in the study before taking part.

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Data availability statement Data are available upon reasonable request. Raw data were generated at the University of Oslo and the Norwegian Dry Eye Clinic. Derived data supporting the findings of this study are available from the corresponding author [BT] on request.

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