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Diagnostic value of three simple and rapid dry eye tests: lid parallel conjunctival folds, tear meniscus height and tear ferning

Дијагностичка вредност три брза теста за суво око: набори коњунктиве паралелни ивици капка, висина менискуса суза и тест гранања суза

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SUMMARY

Introduction/Objective The objective of this paper was to assess the diagnostic value of three simple dry eye (DE) tests: lid parallel conjunctival folds (LIPCOF), tear meniscus height (TMH), and tear ferning (TF).

Methods Diagnostic DE tests LIPCOF, TMH and TF tests were performed in 100 patients. Eighty of them were referred to us by rheumatologists and general practitioners either during evaluation for Sjögren's syndrome, or because of DE symptoms. Control group was made of 20 patients, with no DE relating symptoms. Ocular Surface Disease Index (OSDI) questionnaire was used for DE symptoms' evaluation. Results of LIPCOF, TMH and TF tests were compared with results of Copenhagen criteria (CC) DE tests i.e., tear fluorescein break up time, Schirmer I and Rose Bengal tests. Ability of tests to recognize DE in various grades according to Dry Eye Work Shop (DEWS) report score system was assessed.

Results Compared to CC, sensitivity of LIPCOF and TMH was high: 92.8% and 83.5%, while specificity was low: 34.4% and 49.2%, respectively. TF had low sensitivity of 59.1% but high specificity of 82.7%. Mean values of both LIPCOF and TMH differed significantly (F = 7.222, p < 0.001 and F = 11.802, p < 0.001) between control group and all DEWS DE grades, but not among different grades of DE.

Conclusions Diagnostic tests TMH and LIPCOF showed high sensitivity which makes them excellent screening DE tests. Low sensitivity of TF suggests that it is not truly a good screening test on its own, but its high specificity is of definite value.

Keywords: Dry eye disease; Lid Parallel Conjunctival Folds; Tear Meniscus Height; Tear Ferning

САЖЕТАК

Увод/Циљ Циљ овог рада је да се процени дијагностичка вредност три једноставна теста за суво око: набори коњунктиве паралелни ивици капка (*LIPCOF*), висина менискуса суза (*TMH*) и тест гранања сузе (*TF*).

Методе Дијагностички тестови *LIPCOF*, *TMH* и *TF* су изведени код 100 пацијената. 80 пацијената нам је упућено на преглед од стране реуматолога и надлежних офталмолога, током испитивања на Сјогренов синдром или због симптома сувог ока. Контролну групу чинило је 20 пацијената без симптома сувог ока. Симптоми су евалуирани применом упитника индекса болести површине ока (*OSDI*). Резултати тестова *LIPCOF*, *TMH* и *TF* су упоређени са вредностима резултата тестова за суво око по Копенхаген критеријумима (*CC*), а то су: време прекида сузног филма обојеног флуоресценином (*FTBUT*), мерење секреције суза без анестезије током пет минута *Schirmer I* траком и бојење површине ока виталном бојом *Rose bengal*. Такође је процењена способност тестова да препознају различите стадијуме по *Dry Eye Work Shop* (*DEWS*) систему градирања болести.

Резултати Поређењем са *CC* групом тестова, *LIPCOF* и *TMH* су показали високу сензитивност (92,8% и 83,5%), док им је специфичност била ниска (34,4% и 49,2%). *TF* је имао ниску сензитивност (59,1%), али високу специфичност (82,7%). Просечне вредности *LIPCOF* и *TMH* теста се статистички значајно разликују између контролне групе и свих стадијума болести по *DEWS* градацији, али не и између различитих стадијума болести сувог ока.

Закључак Тестови *TMH* и *LIPCOF* су показали високу сензитивност што их чини одличним тестовима за скрининг болести сувог ока. Ниска сензитивност *TF* теста га не сврстава у добре скриниг тестове, али његова висока специфичност му даје дијагностичку вредност.

Кључне речи: болест сувог ока, набори коњунктиве паралелни ивици капка, висина менискуса суза, тест гранања сузе

INTRODUCTION

Out of the pool of diagnostic tests for dry eye (DE), no test is found to be sensitive or specific enough on its own [1]. For reaching DE diagnosis in practice, there is a tendency to use a group of clinical tests, chosen at examiners discretion, to complement overall clinical judgment. To state it otherwise, although there is a consensus of a group of experts on DE definition (DEWS) [2], there is no consensus on a definite set of tests (nor their outcomes) for DE. Also, symptoms often do not correlate with signs of DE nor do they correlate well with the stage of DE [3,4]. New report of DEWS group from 2017. suggest evaluating symptoms with Ocular Surface Disease Index (OSDI) or 5 Item Dry Eye (DEQ-5) questioner. Clinical tests for reaching DE diagnosis in their opinion are non invasive break up time or fluorescein tear break up time (FTBUT), tear osmolarity, or ocular surface staining. But for grading of disease and assessing the type of DE they recommend other tests, like non- invasive tear volume measurement, assessing meibomian gland disfunction (MGD) and lipid thickness/dynamics [1].

While searching for any well-defined set of clinical DE tests, commonly used as a whole, rather than as an ex-tempore formed group of tests, Copenhagen criteria (CC) tests stand out as a very well defined and time-honored set. These tests combine acceptable levels of both sensitivity and specificity for non Sjögren Syndrome (SS) DE though they were initially devised for SS related DE [5]. They were, accordingly, used in our study as criteria for DE diagnosis and a reference clinical standard for comparison with single tests that we were interested in: Lid Parallel Conjunctival Folds (LIPCOF), Tear Meniscus Height (TMH) and Tear Ferning (TF).

There is a rising number of people suffering from DE symptoms, seeking help from their eye doctors, who do not always have time or resources to apply sophisticated diagnostic tests. Epidemiological studies have demonstrated that DE has a prevalence of 5–45%,

depending on the criteria and location [6–10]. In a study with over 20.000 glaucoma patients, Erb et al., report TMH and LIPCOF as simple and noninvasive tests for dry eye [11]. TF was suggested by DEWS group as a potentially good screening test [1].

Our aim was to compare LIPCOF, TMH and TF tests with CC DE tests and to analyze their ability to recognize dry eye disease (DED) in it its various stages.

METHODS

Out of 100 subjects we examined for DE (200 eyes) at Clinic for eye diseases, Clinical centre of Serbia, during 2013 and 2014, 88 were woman. Mean age ±SD was 50.17±16.74. Thirty of them were referred to us by rheumatologists during evaluation for SS, and 50 were referred by general practitioners because of DE symptoms. Control group was made of 20 patients, with no DE relating symptoms, examined during evaluation for cataract surgery. The two groups were matched for age (no statistically significant difference between groups p = 0.21) and gender (p = 0.45). Exclusion criteria in our study were any ocular surgery that was performed within one year, contact lens wear, topical eye therapy (if only tear substitutes, they had to be suspended at least 8 hours before the examination), entropion, ectropion or other lid closure problems, ocular allergies or presence of anterior blepharitis. The study was approved by the Ethical committee of University of Belgrade, Faculty of Medicine. All patients signed an informed consent form.

We performed the following clinical tests: Shirmer without anesthesia (Shirmer I), fluorescein tear break-up time (FTBUT), Rose Bengal (RB), LIPCOF, TMH and TF. Eyelids were inspected for meibomian gland disfunction (MGD). Symptoms were evaluated based on Ocular Surface Disease Index (OSDI). Only the patients with OSDI score under then 13 were enrolled in control group.

To confirm DED in our study, we considered results from a group of three clinical tests. These three tests: Schirmer I, FTBUT and RB represent the ophthalmological part of testing for SS according to Copenhagen criteria but proved useful in diagnosing DE out of SS context, also [5]. In order to be diagnosed with DE, patient should be positive on 2 out of 3 CC tests in one or both eyes. According to CC positive result for Schirmer I test is value less than 10 mm, for FTBUT test value less than 10 seconds, and for RB test score equal or greater than 4 according to Van Bijsterveld grading system [12]. Eighty of them had DED, since one or both eyes were positive in 2 out of 3 clinical tests. Twenty among this symptomatic group of patients had some form of MGD. In control group no eye met these criteria. One patient from control group had MGD, without signs or symptoms of DED. Baring in mind that we separately analyzed both eyes we found that 139 eyes were positive for DED. We also graded dry eye severity from 1 to 4, according to DEWS report score system, where grade 1 is mild DE and 4 is the most severe [13].

Tests were performed during one examination, in the morning by two examiners. Patients' TMH and presence of folds for LIPCOF test were examined by slit-lamp. We performed these tests at the beginning of examination to avoid blinking induced by prolonged gaze and also to avoid induced reflex tearing. For TMH, we registered values as 0.3mm, 0.2mm, 0.1mm, and less than 0.1mm. Tear meniscus height was compare with variable slit – lamp beam height, which was regulated with mechanical cylinder attached to slit lamp. Ones we adjust beam height, we read the value from the measuring scale connected to cylinder. The lowest value on measuring scale at our disposal, was 0,2, then 0,3. When tear meniscus height was half of 0.2 mm beam height, we registered value as 0.1, and if TMH was lower than half of 0,2 mm beam height, it was registered as lower than 0,1 mm. Measuring of TMH was done at 6 o'clock, where lower limbus was in closest contact with lid, in order to avoid influence of conjunctival folds on measurement. For LIPCOF test, we registered values only

in temporal zone as no folds, ½ of fold (if horizontal fold wasn't present completely throughout temporal zone), one fold less that 0.2mm height, two folds 0.2mm height, 3 folds or more over 0.2mm. These stages although similar, are not completely analogous to those most commonly used, described by Höh et al. [14]. Instead of using term normal meniscus tear height, we used the value of 0.2 mm as a cut-off value between stages. This value was considered as normal height for tear meniscus by other authors as well [15, 16]. In order to form four grades as DEWS dry eye severity score system has, we divided stage 1 by Höh in two stages. Then we performed Shirmer I, BUT and RB test. The Schirmer I test was performed by hooking the folded end of Schirmer paper over the temporal one-third of the lower lid margin. After a period of 5 minutes, we measured the length of wetting from the notch. For FTBUT, the dye was applied on ocular surface with impregnated strips. Looking through cobalt blue filter, we measured the time for dyed tear film to break. After applying tetracaine eye drops, we instilled RB dye and scored result with Van Bijsterveld grading system. Collecting tear sample from the inferior tear meniscus, for performing TF test was done by Eppendof automatic micropipette with a single use 1-10 μl Eppendof Tips. Tear sample was pipetted onto a clean microscope slide and allowed to air-dry for 10 minutes. Then it was observed by phase contrast light microscope at magnification level of 20X and 40X, and quantified according to Rolando grading scale, based on level of arborization, where grade 1 is characterized with uniformed large arborization, while in grade 4 there is no ferning [17].

We analyzed sensitivity (ability to recognize disease), specificity (ability to rule out disease), positive and negative predictive value (PPV and NPV) of all clinical tests used in the study. By using One way ANOVA and Post-hoc test, we tested their ability to grade severity of DE according to the severity score system from DEWS report. Data were

statistically evaluated by using SPSS version 20 (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0 Armonk, NY: IBM Corp).

RESULTS

Most of eyes (37.5%) diagnosed as dry in our study belong to grade 2 according to severity score system from DEWS report. Fifty-four (27.0%) eyes belong to grade 1, 23 (11.5%) to grade 3 and only 11 eyes (5.5%) to grade 4.

All of the clinical tests that we used in this study were able to distinguish normal from dry eyes. Mean value of parameters measured by these tests and significance of difference between test values for non-dry eye and dry eye groups are presented in Table 1.

When tested against group of DE tests form Copenhagen criteria, FTBUT had the highest sensitivity (95.0%), followed by LIPCOF and TMH (92.8% and 83.5%). RB and Shirmer I had a 100% specificity, but TF had high specificity as well (82.7%). Sensitivity and specificity of all tests as well as PPV and NPV are presented in the Table 2.

We analyzed mean FTBUT values between different grades of severity according to DEWS (Table 3). By using ANOVA we found that the average FTBUT value differs between groups (F = 62.474, p < 0.001). Post Hoc test allowed us to establish that this difference was statistically significant for every group compared to all the other groups (Figure 1).

When we analyzed mean values between different dry eye DEWS grades with ANOVA (Table 4), we found that there is a statistically significant difference for TF test (F = 18.192, p < 0.001). Analyzed with Post Hoc test, we found a significant difference between all groups, except between second and third and third and fourth grade.

LIPCOF and TMH tests mean values also differed significantly (Table 5 and Table 6) between groups (respectively F = 7.222, p < 0.001; F = 11.802, p < 0.001). With Post hoc test we established that this was due to the significant difference between control group and all

other severity grade groups, including mild dry eye grade, for both tests (cut off value was 0.19 for TMH and 0.97 for LIPCOF). The difference was not significant among different grades of dry eye.

We analyzed separately patients with DE who in the course of this study were diagnosed with SS according to revised international criteria [18]. Comparing average values of Shirmer I test between dry eyes of the patients with SS (11.79mm), and patients without SS (18.23mm), we found that the first group, expectedly, had significantly lower values (t = -4.25, p < 0.001). Average FTBUT value of 4.15 seconds in SS patients was also significantly lower than 5.64 in non Sjögren dry eyes (t = -3.13, p = 0.002), and the RB in average was significantly higher (4.06 in SS group versus 2.98 in non-SS group, t = 2.64, p = 0.009). Eyes of the patients with SS had in average more folds in LIPCOF test (1.52 in SS group versus 1,33 in non-SS group, t = 1.57, p = 0.06), but there was no difference between the groups when it comes to TF test and TMH (respectively, t = 0.27, p = 0.39; t = -0.39, p = 0.35). Eyes of the patients with SS were statistically more in higher grades of severity (t=4.02, p<0.0001).

DISCUSSION

According to DEWS Diagnostic Methodology Subcommittee we should be aware of difference between DE tests we use for screening, where high sensitivity is preferable and group of diagnostic tests for DED with high overall accuracy along with good sensitivity [1]. Screening tests that DEWS group suggested are TMH and TF, especially the first one, being rapid and simple, and also with good sensitivity, as confirmed in other studies [11]. In our study, both LIPCOF and TMH had good sensitivity, comparing to Copenhagen criteria DED clinical tests group (92.8%, 83.5%). Their ability to distinguish normal from mild dry eyes makes them especially convenient for screening. Garsia-Resua et al. found that there is a good correlation between osmolarity and subjective grading of TMH as well as measuring of

TMH using open-source software (NIH ImageJ) [19]. Both tear osmolarity and tear meniscus OCT measurements comply with the DEWS grading system as previously reported by Tukenmez-Dikmen et al. [20] Mean values of TMH and LIPCOF between different grades of DE didn't show statistically significant difference, so according to our result they are not convenient for grading DE. In our study mean value of TMH in group without DE was 0.17 mm. It is a bit lower than the one published by Immamura et al. measured on slit-lamp with graticule for 3 different age groups of patients without DE (from younger to older: group 1, 206 µm, group 2, 209 µm, group 3, 226 µm) [15]. One would expect that average value in older group would be lower as in their study, but they assume that obstruction of lacrimal drainage that occurs with age may influence the results in their study. When comparing average value of TMH measured with slit-lamp and with OCT in normal subjects, Immamura et al. find no statistical differences. Since variability in measurement was less shown with slit-lamp method, they suggest slit–lamp measuring of TMH may still be one of the most useful clinical methods to evaluate tear meniscus. With cut off value 0.19 mm, sensitivity of TMH in our study was 83.5%. With cut off value of 205 µm, Singh et al. found that sensitivity of TMH measured with OCT was 98.3% [21]. As reported in the study by Erb C et al. [11], we also found that LIPCOF has a high sensitivity with cut off value of 0.97, but its ability to rule out diagnosis where dry eye was not recognized by other clinical tests was low (33.9%). Specificity of TMH compared to CC DE tests was also low (49.2%). TF was reported before as a valuable test by Rolando and the grading scale he devised, as the most popular one, was used by other authors [17,22]. Tear ferning test shows strong correlation with osmolarity as reported by Versura et al. [23], statistically significant for each DE subgroup. In our study, TF didn't have high sensitivity and couldn't distinguish between all DE subgroups, but had a good specificity.

Values of Schirmer I and FTBUT tests of patients with SS were significantly lower, then in group of patients with no SS. Average value of RB was higher for eyes of the patients with SS, as reported in other studies as well [24]. One would expect that average value of TMH would be lower in SS group, but that wasn't a case in our study. On the other hand, there were more conjunctival folds in LIPCOF test in eyes of patients with SS. TF showed no difference between two groups.

New methods of meniscometry have been developed to facilitate simple and dynamic visualization of the tear meniscus. Optical coherence tomography (OCT) assessment of the tear meniscus and conjunctival folds has been extensively studied in the last decade [25,26]. Spectral-domain OCT meniscometry has shown high reproducibility, but can be biased by conjunctivochalasis and LIPCOF in the same way as with slit-lamp measurements of tear meniscus [1]. Measuring TMH at 6 o'clock is optimal when using slit-lamp in our opinion, but the same position is suggested as preferred when using Swept source OCT by other authors [15]. Whether we observe tear meniscus or presence of conjunctival folds, analysis of the image acquired with OCT may be complex, time consuming and operator-dependent. Therefore, we think that slit-lamp measurements of TMH and LIPCOF are preferred as screening test available in every day ophthalmology practice.

CONCLUSION

Diagnostic tests TMH and LIPCOF are rapid and simple dry eye tests, whose high sensitivity and ability to recognize even mild cases, in spite of lacking the strength to rule out disease where other tests are negative, makes them excellent screening DE tests. Due to low sensitivity in our study TF seems not to be such a good screening test. In our study, FTBUT, showed a remarkably high sensitivity and ability to correctly distinguish between all DED

severity groups, which makes him a good screening test, but also a good test for grading and monitoring the effect of therapy for dry eye disease.

NOTE

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Conflict of interest: None declare.

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Table 1. Results of clinical tests from dry eye group and group of normal eyes

Clinical test	Mean value dry eyes	CI 0.95	Mean value normal eyes	CI 0.95	t	P
Schirmer I	15.61	±1.469	25.125	±1.989	-7.74	<0.0001
FTBUT	5.08	±0.457	10.6	±0.573	-11.47	<0.0001
RB	3.38	±0.385	0.35	±0.212	13.82	<0.0001
TMH	0.11	±0.008	0.165	±0.019	-5.34	<0.0001
LIPCOF	1.41	±0.117	0.625	±0.222	6.26	<0.0001
TF	2.52	±0.137	1.5789	±0.212	7.52	<0.0001

CI – confidence interval; t – value of Student's t test; Schirmer I – Schirmer test without anesthesia; FTBUT – fluorescein tear break-up time; RB – Rose Bengal; TMH – tear meniscus height; LIPCOF – lid parallel conjunctival folds; TF – tear ferning; p is highly significant at level < 0,01

Table 2. Sensitivity, specificity PPV and NPV of clinical tests, each against DE tests from Copenhagen criteria

Parameters	FTBUT	RB	Sch I	LIPCOF	TMH	TF
Se (%)	95	48.9	33.1	92.8	83.5	59.1
Sp (%)	80.3	100	100	34.4	49.2	82.7
PPV	0.92	1	1	0.76	0.79	0.89
NPV	0.85	0.46	0.44	0.68	0.57	0.47

Se – sensitivity; Sp – specificity; PPV – positive predictive value; NPV – negative predictive value; DE – dry eye; FTBUT – fluorescein tear break-up time; RB – Rose Bengal; Sch I – Schirmer I; LIPCOF – lid parallel conjunctival folds; TMH – tear meniscus height; TF – tear ferning

Table 3. Mean FTBUT values in different dry eye severity groups

Groups	N	Mean	SD	SE	95% Confidence Interval for Mean		Min	Max
					Lower Bound	Upper Bound		
.00	37	10.59	1.94	.32	9.95	11.24	4.00	15.00
1.00	54	6.96	2.72	.37	6.22	7.71	3.00	11.00
2.00	75	5.08	2.30	.27	4.55	5.61	2.00	10.00
3.00	23	3.48	2.48	.52	2.40	4.55	.00	10.00
4.00	11	.55	.93	.28	-.08	1.17	.00	2.00
Total	200	6.18	3.49	.25	5.69	6.66	.00	15.00

FTBUT – fluorescein tear break-up time; N – number of eyes; Mean – average parameter

value of tested eyes of different grades; SD – standard deviation; SE – standard error

Table 4. Mean TF values in different dry eye severity groups

Groups	N	Mean	SD	SE	95% Confidence Interval for Mean		Min	Max
					Lower Bound	Upper Bound		
0	34	1.59	.701	.120	1.34	1.83	1	3
1	53	2.11	.847	.116	1.88	2.35	1	4
2	72	2.54	.786	.093	2.36	2.73	1	4
3	21	2.81	.680	.148	2.50	3.12	1	4
4	10	3.50	.527	.167	3.12	3.88	3	4
Total	190	2.33	.897	.065	2.20	2.46	1	4

TF – tear ferning; N – number of eyes; Mean – average value of tested eyes of different

grades; SD – standard deviation; SE – standard error

Table 5. Mean values for TMH in different dry eye severity groups

Groups	N	Mean	SD	SE	95% Confidence Interval for Mean		Min	Max
					Lower Bound	Upper Bound		
.00	37	.17	.06	.01	.15	.19	.10	.30
1.00	54	.12	.06	.01	.10	.14	.05	.30
2.00	75	.11	.05	.01	.10	.13	.05	.30
3.00	23	.09	.03	.01	.07	.10	.05	.20
4.00	11	.09	.07	.02	.05	.14	.00	.20
Total	200	.12	.06	.00	.11	.13	.00	.30

TMH – tear meniscus height; N – number of eyes; Mean – average parameter value of tested

eyes of different grades; SD – standard deviation; SE – standard error

Table 6. Mean values for LIPCOF in different dry eye severity groups

Groups	N	Mean	SD	SE	95% Confidence Interval for Mean		Min	Max
					Lower Bound	Upper Bound		
0	37	.73	.72	.12	.49	.97	.00	2.00
1	54	1.19	.82	.11	.96	1.41	.00	3.00
2	75	1.39	.75	.09	1.21	1.56	.00	3.00
3	23	1.65	.65	.13	1.37	1.93	1.00	3.00
4	11	1.55	.69	.21	1.08	2.01	1.00	3.00
Total	200	1.25	.80	.06	1.14	1.36	.00	3.00

LIPCOF – lid parallel conjunctival folds; N – number of eyes; Mean – average parameter

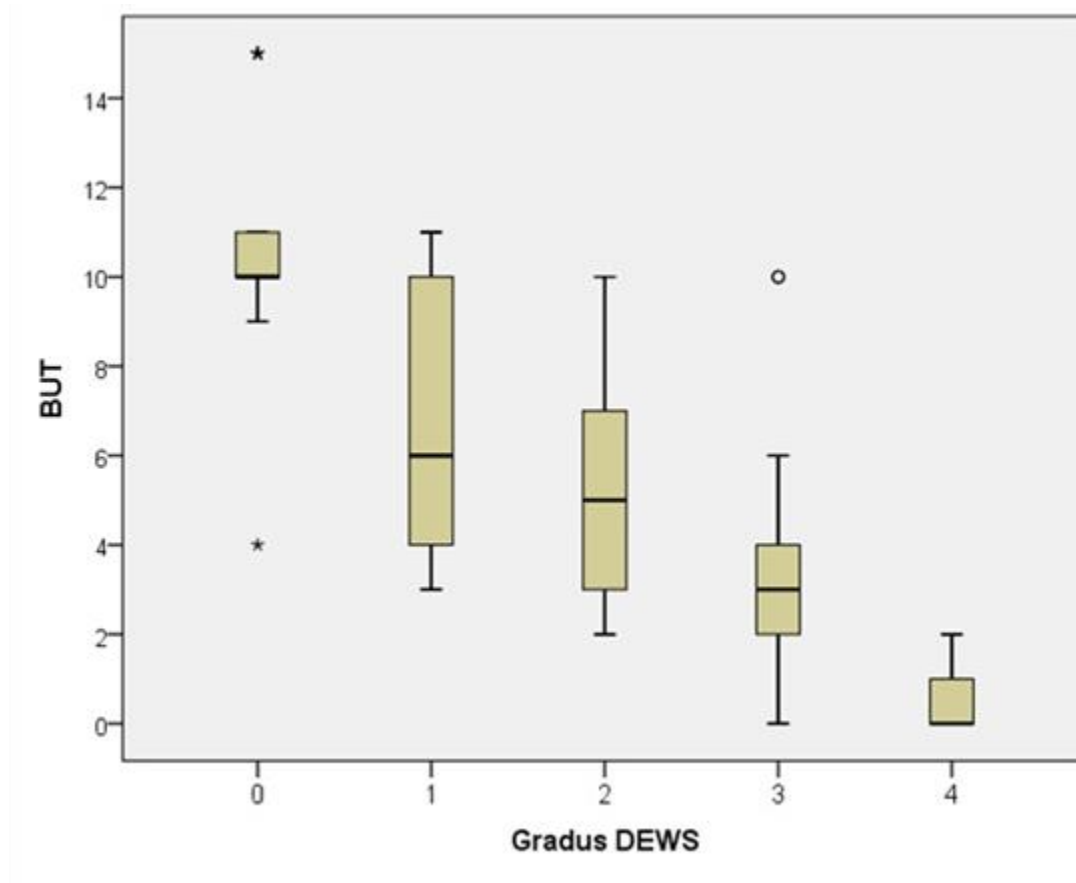value of tested eyes of different grades; SD – standard deviation; SE – standard error

Figure 1. Mean fluorescein tear break-up time values in different DE severity groups;

Average fluorescein tear break-up time value differs between the groups tested with ANOVA

($F = 62,474$, $p < 0,001$); difference is statistically significant for every group compared to all

the other groups analyzed with Post Hoc test; the mean difference is significant at the 0.05

level; BUT – fluorescein tear break-up time; Gradus DEWS – grades by the Dry Eye Work

Shop report score system [2]