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☏ +381 11 4092 776, Fax: +381 11 3348 653
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Tanja Kalezić[1,2,♣], Ivana Vuković[1,3], Vedrana Pejin[2], Svetlana Stanojlović[1,2], Nemanja Karamarković[4], Dijana Risimić[1,2], Marija Božić[1,2], Aleksandra Radosavljević[1,2]

Dry eye examination – benefits of Ocular Surface Disease Index (OSDI) questionnaire with clinical testing

Испитивање сувог ока – предности упитника за индекс предње површине ока (*OSDI*) са клиничким тестовима

[1]University of Belgrade, Faculty of Medicine, Belgrade, Serbia;
[2]University Clinical Centre of Serbia, Clinic for Eye Diseases, Belgrade, Serbia;
[3]University Clinical Centre of Serbia, Clinic for Gynecology and Obstetrics, Belgrade, Serbia;
[4]University Clinical Centre of Serbia, Clinic for Cardiac Surgery, Belgrade, Serbia

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♣**Correspondence to:**
Tanja KALEZIĆ
Ibarska 9, 11000 Belgrade, Serbia
E mail: **tanjakalezic@gmail.com**

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SUMMARY

Introduction/Objective Dry eye is a multifactorial disease with up to 50% in population. It is characterized by a loss of homeostasis of the tear film and accompanied by ocular symptoms. Ocular Surface Disease Index (OSDI) questionnaire is designed to provide a rapid assessment of the symptoms. The aim of this study was to evaluate diagnostic capacity of OSDI.

Methods A prospective, randomized and observational study was conducted at the Clinic for Eye Disease, Clinical Center of Serbia, between December 2018 and February 2019. The OSDI questionnaire was used to rate the severity of dry eye disease. Schirmer I test, tear break-up time test (TBUT), Rose Bengal test and lid-parallel conjunctival folds (LIPCOF) test were performed as a clinical proof of the symptoms.

Results A total of 27 patients, 15 male (55.4%) and 12 female (44.6%), with mean age of 60 ± 15 years were included in the study. The average value of OSDI score was 26.37 ± 23.98 (0-80). Schirmer I test and Rose Bengal test for right and left eye, as well as BUT test for left eye were positively correlated with OSDI score (Spearman correlation coefficient).

Conclusion OSDI questionnaire is fast, reliable, and cheap test. In our study we have found correlation between OSDI score and other clinical tests, except with LIPCOF test. At this moment, the questionnaire that could be the gold standard for dry eye disease diagnosis doesn't exist, therefore further studies concerning this topic are needed.

Keywords: dry eye; OSDI questionnaire; LIPCOF; Schirmer test; TBUT test; Rose Bengal test

САЖЕТАК

Увод/Циљ Суво око је болест са инциденцом и до 50% у популацији. То је мултифакторијална болест површине ока где губитак хомеостазе сузног филма прати очне симптоме. *Occular Surface Disease Index* (*OSDI*) је упитник који омогућава брзо постављање дијагнозе. Циљ овог рада је процена дијагностичке вредности теста *OSDI* у болести сувог ока и градацији тежине у односу на налаз релевантних клиничких тестова.

Методе Проспективна, рандомизована и опсервациона студија обављена је на Клиници за очне болести Универзитетског Клиничког центра Србије, у периоду од децембра 2018. до фебруара 2019. године. Упитник *OSDI* је коришћен ради евалуације симптома и корелације са клиничким тестовима. Клинички тестови примењени у овој студији су Ширмеров тест I, *tear break-up time test* (*TBUT*), тест *Rose Bengal* и *lid-parallel conjunctival folds* (*LIPCOF*).

Резултати Укупно је било 27 болесника – 15 мушкараца (55.4%) и 12 жена (44.6%), просечне старости од 60 ± 15 година. Просечна вредност *OSDI* скора у студији је била 26.37 ± 23.98 (0–80). Пронађена је позитивна корелација са *OSDI* скором између Ширмера I и теста *Rose Bengal* за десно и лево око, као и *TBUT* теста за лево око (Спирманов коефицијент корелације).

Закључак Упитник *OSDI* је брз, поуздан и јефтин тест који добро процењује постојање и тежину сувог ока. У нашој студији пронађена је корелација *OSDI* упитника са свим клиничким тестовима у дијагностици сувог ока, изузев теста *LIPCOF*. Тренутно не постоји упитник који би представљао златни стандард у дијагностици сувог ока, те су даља истраживања у овом смеру неопходна.

Кључне речи: суво око; упитник *OSDI*; *LIPCOF*; Ширмеров тест; *TBUT*; тест *Rose Bengal*

INTRODUCTION

Dry eye is multifactorial eye surface disease, characterized by loss of tear film homeostasis and eye symptoms [1]. It is one of the most frequent reasons for visiting ophthalmologist, so it represents significant outlay for health care system [2]. Most of the patients have mild symptoms, but sometimes very complex interventions are necessary to avoid further progression to corneal ulcer and conjunctival scaring [3]. Contact lens wear and

refractive surgery can cause a dry eye [4]. In etiology of dry eye main factors are tear film instability, hyperosmolarity, inflammation, eye surface damage and neurosensory abnormalities [1]. Sjogren syndrome, transplantation (graft versus host reaction) and aging can also cause dry eye [5].

Following nowadays knowledge, ocular and lacrimal inflammation take main role because they are making defects of corneal and conjunctival cells and causing symptoms [1]. What is happening is proved on molecular and biochemical level, where is also shown that lower levels of androgen and higher levels of pro inflammatory cytokines followed by loss of immunologic homeostasis of lacrimal gland and eye surface lead to pathological changes [6]. Neurogenic mechanisms- loss of innervation and lower sensitivity can also cause a dry eye [4]. Dry eye disease (DED) is one of the most prevalent ophthalmic disorders in general population, and it can go up to 50% in different studies [2].

In classification of dry eye disease, we have two big categories: aqueous tear-deficient dry eye (Sjogren syndrome dry eye) and evaporative dry eye (Non Sjogren syndrome dry eye) [7]. Aqueous tear-deficient dry eye implies that dry eye is due to a failure of lacrimal tear secretion, and it represents about 10% of all cases. Evaporative dry eye is due to deficiency in lipid part of tear film, which is manifested with higher evaporation. The main cause is Meibomian gland disfunction, and it represents 85% of all cases [8]. Blepharitis, eyelid margin inflammation is a cause, and also a consequence of Meibomian gland disfunction, but in differential diagnosis we also need to think of rosacea, atopy, seborrheic dermatitis and staphylococcal infection [1].

Etiological important factors in dry eye disease are female gender and ageing (low levels of androgen play main role in Meibomian gland disfunction) [8]. Except those, important factors also are lagophthalmos, decreased blinking, systemic autoimmune diseases, atopy, vitamin A deficiency and external conditions with low air humidity [9]. A number of questionnaires have been developed, and they are in use in combination to help to make a dry eye diagnosis, but none of them, separately, has required sensitivity and specificity to be a gold standard [10]. The clinical presentation of dry eye disease is very variable, what makes a diagnosis even more difficult. Patients frequently have unspecific symptoms such as visual disturbance, ocular discomfort, photophobia, itching, and irritation. Sometimes patients can experience excessive tearing because of discomfort. Symptoms doesn't have strong correlation

with clinical findings, especially if there is low pain tolerance [11]. For the purpose of making diagnosis, checking severity of disease, starting the management and follow up, many questionnaires have been made, and one of them is Dry Eye questionnaire (DEQ-5) [12] and OSDI [13].

OSDI questionnaire has been made by Outcomes Research Group at Allergan Inc, in order to provide fast evaluation of ocular irritation symptoms in connection with dry eye disease and their impact on vision [13]. Therefore, the aim of this study was to evaluate diagnostic capacity OSDI questionnaire in assessment of the dry eye disease and the severity of disease relative to clinical diagnostic procedures.

METHODS

This study was a prospective, randomized and observational study,conducted at the Clinic for Eye Disease, University Clinical Center of Serbia at the Department of Cornea and External Eye Disease, between December 2018 and February 2019. Patients were randomized upon the arrival for a clinical examination such as cataract or blepharitis, and had no previous history of dry eye treatment. Anamnestic characteristics were collected at the beginng of the study. Participation was voluntary and informed consent was obtained from each participant. Ethical approval was obtained from the Institutional Review Board (IRB).

The 12-item Ocular Surface Disease Index (OSDI) questionnaire is a self-administered questionnaire used to rate the severity of dry eye disease. Responses to each item were scored on a 5-point Likert scale, where 0 indicates "none of the time “; 1 indicates "some of the time“; 2 indicates "half of the time “; 3 indicates "most of the time “ and 4 indicates "all of the time“. The OSDI score calculates on the basis of the given formula: OSDI = ((sum of scores for all questions answered) x 100) / ((total number of questions answered) x 4)). The OSDI is assessed on a scale of 0 to 100, with higher scores representing greater disability [14].

For the purpose of this study, additional clinical measures were performed.

Schirmer I test

The Schirmer I test was used to determine flow of the tears produced by the tear glands and measures the basal and reflex secretions of the main and accessory glands. It is performed using calibrated, bended strips of a non-toxic filter paper. On the lateral and middle-third of the lower eyelid, a shorter folded end is attached, in order to avoid irritation of the cornea. This test is performed without previously applied anesthesia, and on both eyes at the same time. The test length is 5 minutes, and after removing strips from lower eyelids, we measure the amount of wetting of the paper strips. The limit values of Schirmer I tests for dry eye disease are ≤10mm/5min [15].

Tear break-up time test (TBUT)

Tear breakup time (TBUT) is a clinical test used to assess the stability of tear film. It is performed by instilling a small amount of fluorescein on the ocular surface of the lower eyelid, after which the respondent was asked to blink, in order to spread fluorescein evenly across the surface of the eye. Then, patient is instructed to keep their eyes opened, without blinking. Using cobalt blue illumination, the TBUT is recorded as the number of seconds elapsed between the patients last blink of an eye and presence of the first defect in the tear film. The normal values of the TBUT test are over 10 seconds, and the results below this value indicate that there is a disruption in the quality of the tear film [15].

Rose Bengal test

The Rose Bengal test is used to indirectly measure the presence of reduced tear volume, detecting damaged and devitalized epithelial cells that have lost the role of creating tears. The results of this test can be read immediately. On the surface of the eye, we observe three zones: cornea, nasal and temporal part of conjunctival staining. Points from 0 to 3 are assigned to each of these zones, depending on whether there is no coloring, if there are few colored dots, lots of colored dots or if confused zones are present. The positive result of this test are four or more points for all three zones combined, with a maximum of nine points [16].

LIPCOF test

A small folds, parallel to the lower lid margin, in infero-nasal and infero-temporal quadrants of the bulbar conjunctiva are defined as Lid-parallel conjunctival folds (LIPCOF), and they were first described by Höh et al. [17]. LIPCOF correlates with reduced mucin production and with epitheliopathy of the eyelid edge. Using the method described by Höh et al., the LIPCOF test graded from 0 to 3, by the slit lamp examination [17]. According to the comparison of the number of conjunctival folds with the height of the normal tear meniscus height there is a scale of grading. In grade 0, no fold appears; in 1, a single small fold appears smaller than the normal tear film meniscus; in grade 2, multiple folds up to the height of normal tear meniscus appear; and in grade 3, multiple folds higher than the normal tear meniscus appear.

Statistical analysis

Numerical data were presented as arithmetic mean and median with corresponding measures of variability (standard deviation, minimal and maximal value, range). Categorical data were presented as absolute numbers with frequencies. Differences of OSDI questionnaire results according to gender were analyzed by Mann Whitney U test. Spearman correlation coefficients were calculated to explore the relationship between LIPCOF test grade and patient's age. $P < 0.05$ was considered statistically significant. Statistical analysis was done using IPSS 1.3 program.

RESULTS

A total of 27 patients, 15 male (55.4%) and 12 female (44.6%), with mean age of 60 ± 15 years (ranging from od 22 to 82 years) were included in the study (Table 1).

The average value of OSDI score in our study population was 26.37 ± 23.98, ranging from 0 to 80. The median value of Schirmer I test was 6 for right eye (ranging from 0 to12),

and 3 for left eye (ranging from 0 to 10). Median values of LIPCOF test, Rose Bengal test and BUT test are presented in Table 2.

The correlations between OSDI score and age, as well as Schirmer I, LIPCOF, Rose Bengal and BUT test results are presented in Table 3. As is shown in the table 3, Schirmer I test for right and left eye were positively correlated with OSDI score: rho = 0.639; $p < 0.001$ and rho = 0.540, $p = 0.004$, respectively. Rose Bengal test (OD rho = 0.458, $p = 0.016$; OS rho = 0.193, $p = 0.334$), and BUT test for left eye (rho = 0.439, $p = 0.022$) were also positively correlated with OSDI score (Table 3).

No statistically significant difference was found between OSDI score and gender ($p = 0.136$) (Figure 1). Also, no correlation between age of the respondents and OSDI score was found (rho = 0.099, $p = 0.623$).

DISCUSSION

The results of this study showed that OSDI score was positively correlated with age, as well as Schirmer I, Rose Bengal and BUT test results. Also, no statistically significant difference was found between OSDI score and gender and no correlation between age of the respondents and OSDI score. This study is limited by small group of patients but some further testing within bigger groups would be suggested for better validation of the findings.

The core pathophysiological mechanisms of dry eye are lower tear production, higher evaporation, or their combination, with tear film hyperosmolarity and eye surface inflammation [1]. In clinical observation it was found patients usually do not meet the criteria of making the diagnosis of disease by all tests, so more classifications were made, of which is most popular one from Copenhagen. This phenomenon is probably consequence of multifactorial ethiology of dry eye. Copenhagen criteria are including three main factors-changes in aqueous layer (Schirmer), higher level of evaporation (TBUT) and eye surface defects (Rose Bengal Staining) [3]. By using more tests, the chance of making correct diagnosis is rising, but the consensus which combination, besides best specificity and sensitivity, would cover other aspects such as severity, quality of life, and follow up, doesn't exist [3]. To overcome this problem,

questionnaires like DEQ-5, McMonnies and OSDI are added to battery of clinical examinations [10].

In this study in which 27 patients took part the values of OSDI score matches with OSDI scores in other studies in this field. Mean age of patients in our study is slightly higher than in other studies [18]. In literature overview, we found that the significant correlations between OSDI questionnaire and clinical examinations are common [19]. In general, positive correlation is most common between OSDI score and BUT test [19, 20, 21]. The potential explanation for this correlation can be complex etiologic mechanisms in dry eye disease, which implicit on symptoms, and individuality of clinical status which OSDI evaluates in regard to other aspects that every other test is evaluating.

When we analyzed LIPCOF clinical test results, we have found that almost 50% of patients have negative results, and just 20% of patients were positive to this test and similar findings are found by other studies. It is not in correlation to positive findings between OSDI score and LIPCOF grade in our study [21]. Further study of etiopathogenic mechanisms, symptoms and different aspects that every single test evaluates, as well as more patients included would help in clarification of these differences.

CONCLUSION

OSDI questionnaire is fast, reliable and cheap test and it is great tool in evaluation of first symptoms of dry eye disease. In our study we have found the correlation between OSDI score and most common clinical diagnostic tests, whereas only LIPCOF test had not been with statistical significance. The gold standard questionnaire that could be for dry eye disease does not still be found therefore further studies with greater number of participants concerning this topic are needed.

Conflict of interest: None declared.

REFERENCES

1. Hantera M.M. Trends in Dry Eye Disease Management Worldwide. Clinical Ophthalmology (Auckland, NZ), 2021: 15: 165. DOI https://doi.org/10.2147/OPTH.S281666
2. Minjeong, K., Chun Y.S., Kim. K.W. Different perception of dry eye symptoms between patients with and without primary Sjogren's syndrome.Scientific Reports 2022: 1-9. DOI https://doi.org/10.1038/s41598-022-06191-x
3. Sabeti Saama et al. Management of meibomian gland dysfunction: a review. Survey of ophthalmology 2020; 205-217. PMID: 31494111 DOI: 10.1016/j.survophthal.2019.08.007
4. Ourania F. et al. Preoperative dry eyes disease in cataract patients with deficient tear break up time: evaluation of OSDI questionnaire, its subcategories and Keratograph 5M device results.International Ophthalmology 2022 : 1-9. PMID: 35394587 DOI: 10.1007/s10792-022-02287-5
5. Ogawa, Yoko. "Sjögren's syndrome, non-sjögren's syndrome, and graft-versus-host disease related dry eye." Investigative Ophthalmology & Visual Science 2018: DES71-DES79. doi:https://doi.org/10.1167/iovs.17-23750
6. Vehof J, Hysi PG, Hammond CJ. A metabolome-wide study of dry eye disease reveals serum androgens as biomarkers. Ophthalmology. 2017;124: 505-11. https://doi.org/10.1016/j.ophtha.2016.12.011
7. Fu, Jiayao, et al. LncRNA PVT1 links Myc to glycolytic metabolism upon CD4+ T cell activation and Sjögren's syndrome-like autoimmune response. Journal of autoimmunity 2020: 102358. PMID: 31757716 DOI: 10.1016/j.jaut.2019.102358
8. Chan, Tommy CY, et al. "Update on the association between dry eye disease and meibomian gland dysfunction." Hong Kong Medical Journal 2019: 38. PMID: 30713149 DOI: 10.12809/hkmj187331
9. Sullivan DA, Rocha EM, Aragona P, Clayton JA, Ding J, Golebiowski B, et al. TFOS DEWS II Sex, Gender, and Hormones Report. Ocul Surf. 2017;15(3):284- 333. https://doi.org/10.1016/j.jtos.2017.04.001
10. Ji, Yong Woo, et al. "The correction of conjunctivochalasis using high-frequency radiowave electrosurgery improves dry eye disease." Scientific reports 2021: 1-10. DOI https://doi.org/10.1038/s41598-021-82088-5
11. Kojima T, Dogru M, Kawashima Met al. Advances in the diagnosis and treatment of dry eye. Progress in retinal and eye research, 2020: 100842. PMID: 32004729 DOI: 10.1016/j.preteyeres.2020.100842
12. Guo Y, Peng R, Feng K et al. Diagnostic performance of McMonnies questionnaire as a screening survey for dry eye: a multicenter analysis. Journal of ophthalmology, 2016; 2016: 6210853. PMCID: PMC488459 PMID: 27293876
13. Midorikawa-Inomata A, Inomata T, Nojiri S et al. Reliability and validity of the Japanese version of the Ocular Surface Disease Index for dry eye disease. BMJ open, 2019; 9(11): e033940. PMCID: PMC6886996. PMID: 3177211
14. Guarnieri, Adriano, et al. "Relationship between OSDI questionnaire and ocular surface changes in glaucomatous patients." International Ophthalmology 2020: 741-751. PMID: 31813109 DOI: 10.1007/s10792-019-01236-z
15. Almutairi A. H, Alalawi B. S, Badr G. H et al. Prevalence of dry eye syndrome in association with the use of contact lenses in Saudi Arabia. BMC ophthalmology, 2021;21(1): 1-7. DOI https://doi.org/10.1186/s12886-021-01912-8
16. Mejía, L. F., J. C. Gil, and M. Jaramillo. "Intense pulsed light therapy: A promising complementary treatment for dry eye disease." Archivos de la Sociedad Española de Oftalmología (English Edition) 2019: 331-336. PMID: 31079987 DOI: 10.1016/j.oftal.2019.03.009
17. Pult H, Bandlitz S. Lid-parallel conjunctival folds and their ability to predict dry eye. Eye & contact lens 2018 (44): S113-S119. PMID: 29023310 DOI:10.1097/ICL.0000000000000435
18. Ayyildiz, Taha, and Fikriye Milletli Sezgin. "The effect of ocular demodex colonization on schirmer test and OSDI scores in newly diagnosed dry eye patients." Eye & contact lens 2020(46): S39-S41.
19. Bandlitz S, Purslow C, Murphy P. J et al. Lid-parallel conjunctival fold (LIPCOF) morphology imaged by optical coherence tomography and its relationship to LIPCOF grade. Contact Lens and Anterior Eye, 2019; 42(3): 299-303. PMID: 30442513 DOI: 10.1016/j.clae.2018.10.025
20. Raghuwanshi S, Agarwal R, Raghuwansh SK, Shidhaye PR Correlation between ocular-surface disease index questionnaire, tear film break-up time and schirmer tests for evaluation of the tear film in patients of dry eye syndrome. Int J Med Res Rev 2016; 4(3):309-313. DOI: https://doi.org/10.17511/ijmrr.2016.i03.04
21. Tsubota K, Yokoi N, Shimazaki J et al. New perspectives on dry eye definition and diagnosis: a consensus report by the Asia Dry Eye Society. The ocular surface, 2017: 65-76. PMID: 27725302 DOI: 10.1016/j.jtos.2016.09.003

Table 1. Demographic characteristics of the patients

Sex, n (%)	
Male	15 (55.4)
Female	12 (44.6)
Age, mean ± SD	60 ± 15

Table 2. Median test values for Schirmer I, lid-parallel conjunctival folds (LIPCOF), Rose Bengal, and tear break-up time (TBUT) tests

Test	n	mean	SD	median	minimum	maximum
Schirmer OD	27	5.57	3.03	6.0	0	12
Schirmer OS	27	4.09	2.95	3.00	0	10
LIPCOF OD	27	0.7	0.77	1.00	0	2
LIPCOF OS	27	0.59	0.64	1.00	0	2
Rose Bengal OD	27	1.89	2.21	1.00	0	8
Rose Bengal OS	27	1.30	1.2	1.00	0	4
BUT OD	27	4.81	3.17	5.00	1	10
BUT OS	27	4.7	3.66	3.00	1	14

OD – right eye; OS – left eye

Table 3. Correlation between Ocular Surface Disease Index (OSDI) score and age, Schirmer I, lid-parallel conjunctival folds (LIPCOF), Rose Bengal, and tear break-up time (TBUT) tests

Variable	OSDI score	
	ρ	**p**
Age	0.099	0.623
Schirmer OD	0.639	**0.001**
Schirmer OS	0.540	**0.004**
LIPCOF OD	0.114	0.572
LIPCOF OS	-0.130	0.517
Rose Bengal OD	0.458	**0.016**
Rose Bengal OS	0.193	0.334
BUT OD	-0.064	0.749
BUT OS	0.439	**0.022**

OD – right eye; OS – left eye

Figure 1. Ocular Surface Disease Index (OSDI) score according to sex