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Correlation between conjunctival scraping cytology and other clinical dry eye metrics in determination of dry eye related inflammation

Korelacija između citološkog nalaza epitela konjunktive dobijenog skrajpingom i drugih kliničkih testova pri utvrđivanju inflamacije suvog oka

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Abstract

Background/Aim. New and improved definition of dry eye disease (DED) emphasized that hiperosmolarity and inflammation with initial tear film instability play etiological role. The aim of this study was to explore relation of some commonly used clinical tests to dry eye disease (DED) related inflammation measured by conjunctival scraping cytology. **Methods.** We examined 100 subjects, 80 of them having DED. We performed Schirmer without anesthesia (Schirmer I), Fluorescein Tear Break Up Time (FTBUT), Rose Bengal (RB), Lid Parallel Conjunctival Folds (LIPCOF), Tear Meniscus Height (TMH) and Tear Ferning (TF) and compared the values to scraping scores of tarsal conjunctiva. **Results.** FTBUT had the best sensitivity (93.6%). The highest specificity was found with RB (93.2%), but it was also high with Schirmer I, TF and FTBUT (respectively 89.8%, 84.5%, 78.0%). RB and FTBUT had the highest correlation with conjunctival scraping score ($r = 0.707$, $p < 0.001$; $r = -0.507$, $p < 0.001$). **Conclusion.** In our study, FTBUT, though often used in many combinations of the DED tests, showed a remarkably high sensitivity and specificity on its own, as well as good correlation with DED related inflammation detected with conjunctival scraping cytology.

Key words:
dry eye syndromes; conjunctiva; cytological techniques; sensitivity and specificity; diagnostic tests, routine; diagnosis, differential.

Apstrakt

Uvod/Cilj. Nova unapređena definicija bolesti suvog oka ističe hiperosmolarnost i upalu sa inicijalnom nestabilnošću suznog omotača kao najčešće etiološke faktore. Cilj rada bio je da se ispita korelacija između nekih često korišćenih kliničkih testova za suvo oko i citološkog nalaza epitela konjuktive dobijenog skrejpingom pri utvrđivanju inflamacije suvog oka. **Metode.** Od ispitanih 100 bolesnika, dijagnozu suvog oka smo postavili kod 80. Učinjeno je merenje sekrecije suza bez anestezije u 5 minuta Schirmer trakom (Schirmer I), vreme prekida suznog filma obojenog fluoresceinom (*Fluorescein Tear Break Up Time* – FTBUT), bojenje površine oka vitalnom bojom Rose Bengal (RB). Ispitano je prisustvo nabora konjunktive paralelnih ivica donjeg kapka (*Lid-Parallel Conjunctival Folds* – LIPCOF), izmerena visina meniskusa suza (*Tear Meniscus Height* – TMH) i urađen test granja suze (*Tear Ferning* – TF). **Rezultati.** FTBUT je pokazao najvišu senzitivnost (93,6%). Najvišu specifičnost je pokazao RB test (93,2%), ali je visoka specifičnost utvrđena i kod Shirmer I, TF i FTBUT testa (89,8%, 84,5%, 78,0%). Najbolju korelaciju sa citološkim nalazom konjunktivnog skrejpinga imali su RB i FTBUT ($r = 0,707$, $p < 0,001$; $r = -0.507$, $p < 0,001$). **Zaključak.** FTBUT iako često korišćen u kombinaciji sa drugim testovima, samostalno je pokazao značajno visoku senzitivnost i specifičnost, kao i dobru korelaciji sa inflamacijom u sklopu bolesti suvog oka citološki detektovanoj skrejpingom konjunktive.

Ključne reči:
oko, suvo, sindromi; konjunktiva; citologija; osetljivost i specifičnost; dijagnostički testovi; rutinski; dijagnoza, diferencijalna.

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Introduction

While investigation on complex mechanism of dry eye disease (DED) has still been ongoing, hiperosmolarity and inflammation that are underlined since the first Dry Eye Workshop (DEWS) report [1] as well as by the OCEAN group [2] are something that all of us are focused on. Advance in the diagnostic tools, but also in therapy are based on these two crucial steps in that vicious circle [3, 4]. New and improved definition of DED, published within the Tear Film and Ocular Surface Society (TFOS) DEWS II Definition and Classification Report [5], emphasizes that hiperosmolarity and inflammation, together with the initial tear film instability and neurosensory abnormalities play etiological roles.

Measuring osmolarity, especially after the introduction of portable *in situ* osmometer (TearLab™, OcuSence, TearLab Corp, San Diego, CA, USA) into clinical practice, seems to be a good way to recognize DED in its early stage [2, 6]. However, there is a question of overlapping of normal subjects and mild form of dry eye (DE) [2]. The rapid point-of-care diagnostic, 9-level test (InflammaDry; Rapid Pathogen Screening, Inc, Sarasota, FL) to detect elevated matrix metalloproteinase, was reported by Sambursky et al. [7] as a diagnostic tool with high sensitivity and specificity when detecting DE related inflammation. Messmer et al. [8] identified the presence of ocular surface inflammation in 40% of confirmed DE patients with this diagnostic test. Although the time-consuming laboratory test, the conjunctival scraping was introduced by Versura et al. [9] as a reliable method to diagnose and score ocular surface inflammation in DE.

We were interested in exploring relation of some commonly used clinical tests available to ophthalmologists in our country with DED- related inflammation measured by conjunctival scraping cytology, in order to make the decision easier as to start an anti-inflammatory treatment.

Methods

We examined 100 subjects (200 eyes), 88 woman and 12 men. Mean age ± standard deviaton (SD) was 50.17 ± 16.74 years. Eighty of them were referred to us by rheumatologists and general practitioners either during evaluation for the Sjögren syndrome (SS – 30 patients), or because of dry eye symptoms (50 patients). The control group was made of 20 patients in evaluation for cataract surgery, with no DE related symptoms. The exclusion criteria were any ocular surgery that was performed in the period of 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 as well as ocular allergies, or presence of anterior blepharitis. The patients suspected to have the SS were not yet under any kind of systemic anti-inflammatory therapy. The study was approved by the Ethics Committee, of the Faculty of Medicine, Belgrade University. All patients signed an informed consent form.

We performed the following clinical tests: Schirmer without anesthesia (Schirmer I), fluorescein tear break up time (FTBUT), Rose Bengal (RB), Lid Parallel Conjuctival Folds (LIPCOF), Tear Meniscus Height (TMH) and Tear Ferning (TF). Eyelids were inspected for meibomian gland dysfunction (MGD). We also performed scraping of tarsal conjunctiva in order to evaluate ocular surface inflammation. Symptoms were evaluated on the basis of the Ocular Surface Disease Index (OSDI) and McMonnies questionnaires.

To confirm the DE diagnosis in our study, we considered results from a group of three clinical tests. These three tests, the Schirmer I, FTBUT and RB, represented the ophthalmological part of testing for SS according to the Copenhagen criteria, but proved useful in diagnosing DE out of SS context, also [10]. Eighty patients, as we expected, had the dry eye disease, since one, or both eyes were positive in 2 of 3 clinical tests. Twenty patients from this symptomatic group had some form of MGD. In the control group, no eye met these criteria. One patient from the control group had MGD, without the signs, or symptoms of DED. Bearing in mind that we analyzed separately both eyes, we found that 139 eyes were positive and 61 negative for DED. We also graded the DE severity from 0 to 4 according to the DEWS report score system [1]. Numbers of eyes within different grades are presented in Table 1.

Table 1
Distribution of eyes according to dry eye severity with the 0–4 score system from the DEWS report

Dry eye severity	Number of eyes	%	Cumulative %
0	37	18.5	18.5
1	54	27.0	45.5
2	75	37.5	83.0
3	23	11.5	94.5
4	11	5.5	100.0
Total	200	100.0	

DEWS – Dry Eye Workshop Severity.

All tests were performed during one examination in the morning by two examiners. First, we examined the patients' TMH and LIPCOF. TMH was measured by slit-lamp. We registered the values as 0.3 mm, 0.2 mm, 0.1 mm, less than 0.1 mm, using the slit –lamp microscope with objective lens graticule in 0.1 units. For the LIPCOF test, we registered in the temporal zone the values as no folds, ½ of fold in the temporal zone, one fold less that 0.2 mm height, two folds 0.2 mm height, 3 folds or more over 0.2 mm. Although similar, these stages, are not completely analogous to those most commonly used, described by Höh et al.[11] Instead of using a term normal meniscus tear height, we used the value of 0.2 mm as a cut-off value between the stages. Other authors also used this value as a normal one [12], and considered pathological if below [13]. We also divided the Stage 1 by Hö h into two stages with present folds, in order to form four grades as the DEWS dry eye severity score system has. Then we performed the Schirmer I, FTBUT and RB test as outlined in the DEWS report [14]. After folding the Schirmer paper strip at the notch, we placed the shorter part under the temporal one-third of the lower lid of both eyes. The patients were asked to close their eyes. We measured the length of wetting from the

notch after 5 minutes, and the cut-off value was ≤ 10 mm/5 min. For FTBUT we applied sodium fluorescein with the impregnated strips and used the average value of three times measured the elapsed time from blink till appearance of the first break in the tear film. The cut-off value was ≤ 10 mm. Punctate staining of the ocular surface, after applying topical anesthesia and Rose Bengal dye was graded with the van Bijsterveld system, with the cut-off value ≥ 4. The TF test was performed by collecting the tear sample from the inferior tear meniscus by using an Eppendof automatic micropipette with a single use 1–10 μL Eppendof Tips. The collected tear sample was pipetted onto a clean microscope slide and allowed to air-dry for 10 minutes. Ferning of the tear was observed by phase contrast light microscope at the magnification level of ×20 and ×40 and quantified according to the Rolando grading scale [15]. Scraping of both upper and lower conjunctiva was performed with a hockey knife at the end of the clinical (slit lamp) examination, in topical anesthesia. The samples were air-dried at room temperature, fixed in methanol and then stained with May-Grunwald–Giemsa. We counted the number of neutrophils, lymphocytes and monocytes under the phase contrast light microscopes in 50 microscopic fields at ×40 as described by Versura et al. [9], and graded inflammation by the Conjuctival Scraping Cytology Scoring System.

We compared each clinical test with the scraping scores and calculated the sensitivity, specificity, positive and negative predictive value (PPV and NPV). To determine the relationship between all the tests we used the Pearson's correlation coefficient r, since all of the tests were parametric. The results of both questionnaires were compared with the conjunctival scrapings of worse eye and we made the comparison between the different age groups (younger, or equal to 60 versus older than 60).

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

Results

The average value of scraping scores for the group of eyes diagnosed as dry according to the Copenhagen criteria was 5.33 ± 1.99 (95% CI 5.00–5.66), while the average value for the group of non-dry eyes was 2.75 ± 2.04 (95% CI 2.23–3.28). The difference in the average scraping score between the two groups was found to be highly statistically significant by the Student's *t*-test ($t = 8.368$; $p < 0.001$).

The average scraping scores for the different groups of eyes were graded according to the DEWS report and presented in Figure 1. Most overlapping occurs between normal eyes and eyes with a mild form of a dry eye. The difference between all other DEWS groups was statistically significant ($F = 43.197$; $p < 0.001$).

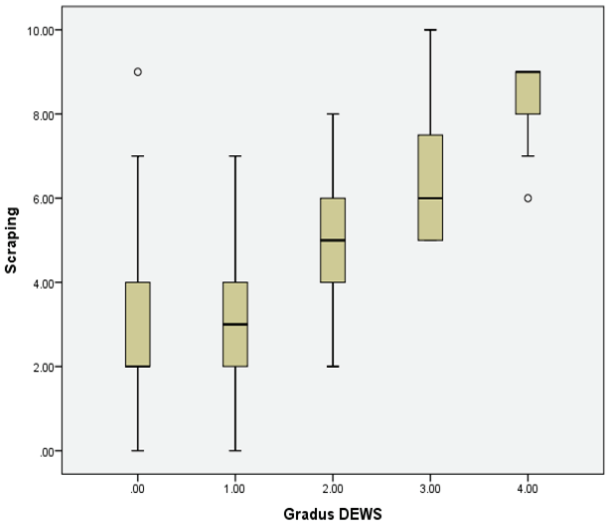

Fig. 1 – The mean scraping scores in different dry eye severity groups.
The average scraping scores for the different groups of eyes graded as in the DEWS report show that the most of the overlapping we have between normal eyes and the ones that have a mild form of dry eye. The difference among all the other DEWS groups is statistically significant ($F = 43.197$, $p < 0.001$).
DEWS – Dry Eye Workshop Severity.

Of all clinical tests that we used, as compared to the conjunctival scraping, the FTBUT as a single test had the best sensitivity (93.6%). The LIPCOF and TMH also had a high sensitivity (92.2% and 80.9%, respectively). The highest specificity was found with RB (93.2%), but it was also high with Schirmer I, TF and FTBUT (89.8%, 84.5%, 78.0%, respectively) (Table 2).

All the tests were in a statistically significant correlation with the conjunctival scraping and among themselves. RB and FTBUT had the highest correlation factor with conjunctival scraping ($r = 0.707$, $p < 0.001$; $r = -0.507$, $p < 0.001$). Among the clinical tests, the best correlation was found between FTBUT and RB ($r = -0.620$, $p < 0.001$), and FTBUT and TF ($r = -0.535$, $p < 0.001$) (Table 3).

Table 2
Sensitivity (Se), specificity (Sp), PPV and NPV of clinical tests compared to the conjunctival scraping cytology

Parameters	FTBUT	RB	Sch I	LIPCOF	TMH	TF
Se (%)	93.6	45.4	41.1	92.2	80.9	59.9
Sp (%)	77.9	93.2	89.8	33.9	44.1	84.5
PPV	0.91	0.94	0.91	0.77	0.78	0.89
NPV	0.85	0.42	0.39	0.65	0.49	0.48

PPV – positive predictive value; NPV – negative predictive value; 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

Correlation of all tests

Test		FTBUT	Scraping	Sch I	RB	TF	TMH	LIPCOF
FTBUT	r	1	-0.507**	0.504**	-0.620**	-0.535**	0.422**	-0.292**
	p		0.000	0.000	0.000	0.000	0.000	0.000
	n	200	200	200	200	190	200	200
Scraping	r	-0.507**	1	-0.383**	0.707**	0.486**	-0.352**	0.328**
	p	0.000		0.000	0.000	0.000	0.000	0.000
	n	200	200	200	200	190	200	200
Sch I	r	0.504**	-0.383**	1	-0.373**	-0.342**	0.237**	-0.233**
	p	0.000	0.000		0.000	0.000	0.001	0.001
	n	200	200	200	200	190	200	200
RB	r	-0.620**	0.707**	-0.373**	1	0.433**	-0.380**	0.300**
	p	0.000	0.000	0.000		0.000	0.000	0.000
	n	200	200	200	200	190	200	200
TF	r	-0.535**	0.486**	-0.342**	0.433**	1	-0.385**	0.318**
	p	0.000	0.000	0.000	0.000		0.000	0.000
	n	190	190	189	190	190	190	190
TMH	r	0.422**	-0.352**	0.237**	-0.380**	-0.385**	1	-0.377**
	p	0.000	0.000	0.001	0.000	0.000		0.000
	n	200	200	200	200	190	200	200
LIPCOF	r	-0.292**	0.328**	-0.233**	0.300**	0.318**	-0.377**	1
	p	0.000	0.000	0.001	0.000	0.000	0.000	
	n	200	200	200	200	190	200	200

FTBUT – Fluorescein Tear Break Up Time; Sch I – Schirmer I; RB – Rose Bengal; TF – Tear Ferning; TMH – Tear Meniscus Height; LIPCOF – Lid Parallel Conjunctival Folds; r - Pearson's correlation coefficient; **p – significant at level < 0.01; n – number of eyes.

We analyzed the results of McMonnies and OSDI questionnaires and they were in a positive correlation (r = 0.644; $p < 0.001$). When we compared them with the inflammatory cell scores acquired with scraping of tarsal conjunctiva of worse eye, we found that the correlation coefficient was r = 0.315 for the McMonnies questionnaire which was highly significant ($p = 0.001$), and correlation with the OSDI questionnaire was significantly positive as well (r = 0.290; $p = 0.003$). The patients with a higher score of inflammatory cells in tarsal conjunctiva had a higher score on both questionnaires.

When comparing the results of conjunctival scraping of patients younger than 60, we found a positive correlation on the questionnaires that was highly significant (McMonnies r = 0.349; $p = 0.002$, OSDI r = 0.341; $p = 0.003$). For the patients over 60 years of age, we found no correlation between the scraping results and neither of two questionnaires (McMonnies r = 0.011; $p = 0.956$, OSDI r = 0.221; $p = 0.278$). The correlation between the results of two questionnaires in both age group was positive (Group ≤ 60 r = 0.684; $p < 0.001$, Group > 60 r = 0.619; $p = 0.001$).

The average score of conjuctival scraping was higher in the group over 60 years of age than in the group of subjects aged under 60 years, and the difference was statistically significant (t = -1.991, $p = 0.049$). For the over 60 years of age group, the average scraping score was 5.77, and for the under 60 years of age group, it was 4.74.

There was no difference between two age groups in the average scores of both questionnaires (McMonnies $t = 0.927$; $p = 0.356$, OSDI $t = -1.495$; $p = 0.138$).

Of all examined patients, 88% of them were women (88 out of 100 patients). In the group diagnosed with DED, 91.2% were women, which was statistically higher ($\chi^2 = 4.001$; $p = 0.045$) than in the control group (75%).

Discussion

In the vicious circle of DED, the inflammation is something that comes after tear film instability and hyperosmolarity, [1,2,16] which might explain why, in our study, the conjuctival scraping could not show the clear distinction between the normal and mild dry eyes. Other authors state that in moderately severe dry eye, there is an (often subclinical) inflammatory reaction of the ocular surface and the lacrimal gland [17, 18], and so was confirmed in our study. That suggests that an anti-inflammatory treatment is needed in all except mild stage. Still, confirmation of presence of inflammation should make our decision easier to add this treatment to already existing artificial tears.

The relation between the inflammation and some of clinical symptoms and signs of DED was suggested before [19]. The diagnostic value of the clinical DE tests has been evaluated many times so far [2, 20]. We were interested in their correlation with the DE-related inflammation.

FTBUT compared to the conjunctival scraping as a measure of DE-related inflammation in our study showed the best balance between sensitivity (93.6%) and specificity (77.9%). There was a strong correlation between the FTBUT and conjunctival scraping as well as with the RB and TF.

Alves et al. [20] also reported that the FTBUT sensitivity was 72.3% while specificity was 100%, and they correlated the best with other clinical tests they applied in diagnosing the dry eye in different diseases.

Versura et al. [6] found a strong correlation between FTBUT and tear osmolarity, although in their study, this correlation did not increase in its strength as dry eye severity did.

Discrepancy between the symptoms and signs is a reason why we cannot rely on questionnaires only when it comes to the DE diagnosis and staging of disease [21]. The new definition of DED, published within the DEWS II report, addresses this problem of discrepancy between the signs and symptoms in some patients through the recognition of role for the neurophysiology in the sensory aspect of the disease [22]. In our study, a poor correlation was evident in the group of patients over 60 years of age, where the average scraping score was higher. In their study, Vehof et al. [23] found that the increased age was a predictor of fewer symptoms than signs. This should make us more careful when ruling out, or staging DED in the older population.

Conclusion

FTBUT, though often used in many combinations of the DED tests, showed in our study a remarkably high sensitivity and specificity on its own, when correlated with the DED-related inflammation. RB and FTBUT had the highest correlation factor with the conjunctival scraping. A poor correlation was found between the symptoms and DE-related inflammation in the patients over 60 years of age. We share the opinion that it is the overall clinical judgment of a clinician that should still be the final judge of DE diagnosis and treatment, but we also believe that it is helpful to have a harder scientific evidence to guide our decision on an anti-inflammatory therapy inclusion in DE treatment.

REFERENCES

1. The definition and classification of dry eye disease: Report of the Definition and Classification Subcommittee of the International Dry Eye WorkShop (2007). Ocul Surf 2007; 5(2): 75–92.
2. *Baudouin C, Aragona P, Messmer EM, Tomlinson A, Calonge M, Boboridis KG*, et al. Role of hyperosmolarity in the pathogenesis and management of dry eye disease: proceedings of the OCEAN group meeting. Ocul Surf 2013; 11(4): 246–58.
3. *Aslan Bayhan S, Bayhan HA, Muhafiz E, Bekdemir Ş, Gürdal CC.* Effects of osmoprotective eye drops on tear osmolarity in contact lens wearers. Can J Ophthalmol 2015; 50(4): 283–9.
4. *Leonardi A, Flamion B, Baudouin C.* Keratitis in Dry Eye Disease and Topical Ciclosporin A. Ocul Immunol Inflamm 2017; 25(4): 577–86.
5. *Craig JP, Nichols KK, Akpek EK, Caffery B, Dua HS, Joo CK*, et al. TFOS DEWS II Definition and Classification Report. Ocul Surf 2017; 15(3): 276–83.
6. *Versura P, Profazio V, Campos EC.* Performance of tear osmolarity compared to previous diagnostic tests for dry eye diseases. Curr Eye Res 2010; 35(7): 553–64.
7. *Sambursky R, Davitt WF, Latkany R, Tauber S, Starr C, Friedberg M*, et al. Sensitivity and specificity of a point-of-care matrix metalloproteinase 9 immunoassay for diagnosing inflammation related to dry eye. JAMA Ophthalmol 2013; 131(1): 24–8.
8. *Messmer EM, von Lindenfels V, Garbe A, Kampik A.* Matrix Metalloproteinase 9 Testing in Dry Eye Disease Using a Commercially Available Point-of-Care Immunoassay. Ophthalmology 2016; 123(11): 2300–8.
9. *Versura P, Profazio V, Fresina M, Campos EC.* A novel scraping cytology score system (SCSS) grades inflammation in dry eye patients. Curr Eye Res 2009; 34(5): 340–6.
10. *Manthorpe R, Oxholm P, Prause JU, Schiødt M.* The Copenhagen criteria for Sjögren's syndrome. Scand J Rheumatol Suppl 1986; 61: 19–21.
11. *Höh H, Schirra F, Kienecker C, Ruprecht KW.* Lid-parallel conjunctival folds are a sure diagnostic sign of dry eye. Der Ophthalmologe 1995; 92(6): 802–8. (German)
12. *Michel M, Sickenberger W, Pult H.* The effectiveness of questionnaires in the determination of Contact Lens Induced Dry Eye. Ophthalmic Physiol Opt 2009; 29(5): 479–86.
13. *Messmer EM.* The pathophysiology, diagnosis, and treatment of dry eye disease. Dtsch Arztebl Int. 2015 Jan 30;112(5):71–81; quiz 82.
14. Methodologies to diagnose and monitor dry eye disease: report of the Diagnostic Methodology Subcommittee of the International Dry Eye WorkShop (2007). Ocul Surf 2007; 5(2): 108–52.
15. *Evans KS, North RV, Purslow C.* Tear ferning in contact lens wearers. Ophthalmic Physiol Opt 2009; 29(2): 199–204.
16. *Amparo F, Dastjerdi MH, Okanobo A, Ferrari G, Smaga L, Hamrah P*, et al. Topical interleukin 1 receptor antagonist for treatment of dry eye disease: A randomized clinical trial. JAMA Ophthalmol 2013; 131(6): 715–23.
17. *Stevenson W, Chauhan SK, Dana R.* Dry eye disease: An immune-mediated ocular surface disorder. Arch Ophthalmol 2012; 130(1): 90–100.
18. *Stern ME, Schaumburg CS, Pflugfelder SC.* Dry eye as a mucosal autoimmune disease. Int Rev Immunol 2013; 32(1): 19–41.
19. *Calonge M, Enríquez--Salamanca A, Diebold Y, González-García MJ, Reinoso R, Herreras JM,* et al. Dry eye disease as an inflammatory disorder. Ocul Immunol Inflamm 2010; 18(4): 244–53.
20. *Alves M, Reinach PS, Paula JS, Vellasco CA, Bachette L, Faustino J,* et al. Comparison of diagnostic tests in distinct well-defined conditions related to dry eye disease. PLoS ONE 2014; 9(5): e97921.
21. *Bartlett JD, Keith MS, Sudharshan L, Snedecor SJ.* Associations between signs and symptoms of dry eye disease: A systematic review. Clin Ophthalmol 2015; 9: 1719–30.
22. *Lewis R.* New New View of Dry Eye Stresses Mechanisms Over Manifestations. Medscape 2017. Available from: http://www.medscape.com/viewarticle/879675?nlid=114929_450&src=WNL _mdplsfeat_170516_mscpedit_opth&uac=159098SY&spon=36&impID=1348993&faf=1#vp_2 [cited 2017 May 8].
23. *Vehof J, Sillevis Smitt-Kamminga N, Nibourg SA, Hammond CJ.* Predictors of Discordance between Symptoms and Signs in Dry Eye Disease. Ophthalmology 2017; 124(3): 280–6.

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