Original Article

Short tear film breakup time-type of dry eye in India

Samrat Chatterjee, Deepshikha Agrawal

Purpose: The aim of this study was to describe the clinical characteristics and risk factors of short tear film break-up time (TBUT) type of dry eye disease and compare it with other types of dry eye diseases. **Methods:** This cross-sectional study included 570 patients (≥ 20 years) from the outpatient department using systematic random sampling. **Results:** The age-adjusted prevalence of short TBUT type of dry eye disease was 5.4% (95% confidence interval: 3.2–6.8%). There was no difference ($P > 0.05$) between the total and subscale scores of the Ocular Surface Disease Index® questionnaire between patients with short TBUT and those with aqueous tear deficiency. Both these groups differed significantly ($P < 0.05$) in the findings of TBUT, Schirmer I test, and Lissamine green staining score. The common symptoms in patients with short TBUT type of dry eye disease were eye fatigue (25.4%), heaviness in the eye (19.7%), and an uncomfortable sensation (14.1%). The symptoms in the aqueous tear deficiency group were light sensitivity (28.2%), dryness (19.2%), burning (13.0%), foreign body sensation (12.8%), and blurring of vision (14.1%). The risk factors associated with short TBUT type of dry eye disease were the presence of meibomian gland dysfunction (odds ratio: 3.759 [95% confidence interval: 2.135–6.618], $P < 0.0001$) and female sex [odds ratio: 1.954 (95% confidence interval: 1.042–3.667), $P = 0.037$]. **Conclusion:** Patients with short TBUT type of dry eye disease have symptom severity similar to aqueous tear-deficient dry eyes, but the pattern is different. The finding of this type of dry eye disease in India indicates its global presence, and ophthalmologists should consider it in their differential diagnoses.

Access this article online

Website: www.ijo.in

DOI: 10.4103/ijo.IJO_327_21

Quick Response Code:

Key words: Dry eye, evaporative dry eye, eye fatigue, short tear film break-up type of dry eye, tear film break-up time

In 1995, Toda *et al*.[1] described a singular type of dry eye disease in Japan characterized by symptoms of ocular discomfort and a tear film break-up time (TBUT) of ≤5 s, but a normal tear secretion rate and absence of significant epithelial staining. In Japan, this type of dry eye condition was described as short TBUT,[2,3] and subsequent studies reported it to be fairly common in the Japanese population.[4,5] In 2015, Yokoi *et al*.[5] reported that short TBUT was the most common type of dry eye disease among office workers. The severity of symptoms reported by patients with short TBUT was greater than symptoms reported by those with other types of dry eye diseases. Other studies reported that patients with short TBUT type of dry eye disease had sizably more higher order aberrations with poor quality of vision,[6] which further deteriorated following prolonged visual tasks.[7,8] The severity of symptoms in short TBUT type of dry eye disease was correlated with corneal hypersensitivity to an unstable tear film,[9] and abnormalities in the mucin layer were believed to cause the unstable tear film.[10] In Japan, short TBUT type of dry eye disease was treated at par with aqueous tear deficiency (ATD) type of dry eye disease even though it did not fulfill the older (2006) Japan Dry Eye Society criteria of "definite dry eye disease."[3] However, in 2016, the society revised its guidelines, replacing vital staining of the ocular surface and Schirmer's test with a TBUT of ≤5 s as the only clinical sign necessary for the diagnosis of dry eye disease.[11] Thus, great emphasis was placed on the measurement of fluorescein TBUT, which the society felt could be comfortably performed in the general ophthalmic clinic, and make the diagnosis of dry eye disease simple and easy.[2,3,11]

However, outside Japan, there remains little recognition of short TBUT type of dry eye disease,[12] with only a few reports from other countries.[13-15] Recent findings in studies from India indicate that evaporative dry eye disease[16-18] and meibomian gland dysfunction (MGD)[19] are widely prevalent in the country. MGD, which is the most common cause of evaporative dry eye disease,[20] is also associated with short TBUT type of dry eye disease.[11] Therefore, it is plausible that the latter may also be commonly present in the Indian population, but not yet reported. The aim of this study was to describe the clinical characteristics and risk factors of short TBUT type of dry eye disease in an Indian cohort, and compare it with other types of dry eye conditions. The findings of this study will increase awareness about this type of dry eye disease among Indian ophthalmologists, thereby improving the management of patients with dry eye symptoms.

Cornea and Anterior Segment Services, MGM Eye Institute, Raipur, Chhattisgarh, India

Correspondence to: Dr. Samrat Chatterjee, Cornea and Anterior Segment Services, MGM Eye Institute, 5th Mile, Vidhan Sabha Road, PO Mandhar, Raipur - 493 111, Chhattisgarh, India. E-mail: samrat@mgmeye.org

Received: 07-Feb-2021 Revision: 07-Jun-2021
Accepted: 10-Jul-2021 Published: 26-Nov-2021

Cite this article as: Chatterjee S, Agrawal D. Short tear film breakup time-type of dry eye in India. Indian J Ophthalmol 2021;69:3463-8.

Methods

Study design, setting, and participants

The present cross-sectional study was carried out at a tertiary eye care center in central India between 2017 and 2018 and was part of a larger study on MGD.[19] In this study,[19] 570 patients were selected using systematic random sampling for a comprehensive dry eye work-up from a pool of 3410 consecutive new patients aged 20 years or more attending the corneal clinic on 3 days of the week. Exclusion criteria included red eyes, ocular trauma, anatomical abnormalities on the eyelids or ocular surface, and intraocular surgery performed within the previous 3 months. The study was approved by the institute ethics committee (MGMEI/I/2016/22) and adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants before enrollment.

Dry Eye Work-up

All subjects underwent a comprehensive eye examination that included history-taking, slit-lamp examination, visual acuity measurement, applanation tonometry, and fundus evaluation [Appendix I]. Information on age, gender, place of residence, dietary preferences, use of smartphones or video display terminals (VDT), use of air-conditioning, presence of systemic comorbidities, and in female patients, a history of menopause were recorded. All clinical examinations were performed in a single examination room where the temperature (20–22°C) and humidity (50–60%) were uniformly maintained. The sequence of dry eye tests was history of generic symptoms, Ocular Surface Disease Index® (OSDI), fluorescein TBUT, Schirmer I test without the use of a topical anesthetic agent, Lissamine green staining score as per the Oxford scale, and meibomian gland expression. All the dry eye tests were carried out as per recommended guidelines [Appendix II].[21-25]

Diagnoses

Based on the findings of the dry eye evaluation, patients were classified into the following four groups: short TBUT group, ATD group, patients with >5 but <10 s TBUT group, and normal group. The details of all operational diagnoses are given in Appendix III. Briefly, dry eye disease (symptoms and any one clinical sign as per DEWS II report) was diagnosed if the OSDI score was ≥13, with either TBUT being <10 s or Lissamine green staining score ≥2.[26] Patients were diagnosed with short TBUT based on the following criteria: TBUT ≤5 s, Schirmer I test without the use of a topical anesthetic agent >5 mm and Lissamine green staining score <2.[1,2] In our study, we also considered patients with a TBUT >5 but <10 s with a normal Schirmer I test and no signs of epithelial staining as a separate group. The severity of symptoms was categorized as none (OSDI score 0–12), mild (OSDI score 13–22), moderate (OSDI score 23–32), and severe (OSDI score 33–100).[23]

Statistical analysis

All quantitative and qualitative variables have been expressed as mean ± standard deviation and percentages, respectively. The normality of the data was tested using the Shapiro–Wilk test. Dry eye tests between the groups were compared with the Kruskal–Wallis test and the Mann–Whitney U test. Categorical data was analyzed using the Pearson's Chi-square test. A linear logistic regression analysis was done to identify risk factors for short TBUT type of dry eye disease. The variables included age, sex, diet, menopause, place of residence, average daily time spent viewing a mobile phone, computer screen or VDT, average time spent in air-conditioning, and presence of MGD. The age-adjusted prevalence data was calculated by considering the census data of India in 2011.[27] All tests were computed using the software Statistical Package for Social Sciences version 23.0 for Macintosh (IBM Corporation, New York, USA). A two-tailed *P* value of less than 0.05 was considered statistically significant.

Results

Patient characteristics

Of the 570 patients who underwent dry eye evaluation, there were 71 patients in the short TBUT group, 78 patients in the ATD group, 247 patients in the group with >5 but <10 s TBUT, and 77 patients in the normal group. We excluded 97 patients from the analysis because they could not be categorized into any of the groups. All these patients had a positive symptom score (OSDI score ≥13), but their dry eye tests were normal.

The demographic and lifestyle characteristics of the four groups are given in Table 1. There was a significant intergroup difference in the age distribution ($P = 0.002$), use of VDTs ($P = 0.038$), and time spent in air-conditioning ($P = 0.028$). The patients with short TBUT type of dry eye disease were younger [Table 1 and Appendix IV] than the other dry eye groups, but the difference was statistically not significant. Across all the groups, there were more patients from an urban background, but the difference was only significant when comparing the short TBUT and ATD groups ($P = 0.009$). Similarly, the proportion of women who had attained menopause was higher in all the dry eye groups compared to the normal group ($P = 0.011$).

Symptom pattern and severity

The distribution of the most commonly reported symptoms by the patients are given in Fig. 1, while a more detailed analysis is provided in Appendix V. Symptoms like eye fatigue, heaviness in the eye, and uncomfortable sensations were more commonly reported in patients in the short TBUT group, while light sensitivity, dryness, burning sensation, foreign body sensation, and blurring of vision were more commonly reported in patients with ATD. Eye pain or soreness was reported equally between both the groups.

The total and subscale scores of the OSDI questionnaire [Table 2] were similar between the short TBUT and ATD groups ($P > 0.05$). The number of patients with an OSDI score of ≥13 was similar ($P = 0.555$) between the short TBUT group (26, 36.6%) and the ATD group (30, 38.5%) and was nearly twice ($P = 0.003$) that of the patients in the group with >5 but <10 s TBUT (48, 19.4%). There were 11 (15.5%) patients with mild symptoms, 7 (9.9%) patients with moderate symptoms, and 9 (12.7%) patients with severe symptoms according to the OSDI questionnaire score in the short TBUT group, and 6 (7.7%), 12 (15.4%), and 18 (23.1%) patients with mild, moderate, and severe symptoms, respectively, in the ATD group [Appendix VI]. The difference in the proportion of patients with severe symptom scores between the ATD and short TBUT groups was not significant ($P = 0.099$), but it was significant ($P = 0.0009$) between the ATD group and the group with >5 s but <10 s TBUT.

Dry eye tests

Overall, there was a statistically significant difference ($P < 0.05$) in TBUT, Schirmer I test and Lissamine green staining score between the various groups [Table 2]. As expected, TBUT was

Table 1: Comparison of demographic characteristics in patients with different categories of tear film abnormalities

Variables	Group 1 *n*=71	Group 2 *n*=78	Group 3 *n*=247	Group 4 *n*=77	*P*					
					Between all groups	Group 1 vs Group 2	Group 1 vs Group 3	Group 1 vs Group 4	Group 3 vs Group 4	Group 2 vs Group 3
Age in years	48.9±15.9	51.8±15.7	50.6±16.6	43.5±15.0	0.002	0.200	0.183	0.066	<0.001	0.200
Sex										
Male	34 (47.9)	35 (44.9)	131 (53.0)	46 (59.7)	0.259	0.744	0.501	0.187	0.760	0.243
Female	37 (52.1)	43 (55.1)	116 (47.0)	31 (40.3)						
Residence										
Urban	60 (84.5)	51 (65.4)	186 (75.3)	60 (77.9)	0.053	0.009	0.110	0.401	0.761	0.107
Rural	11 (15.5)	27 (34.6)	61 (24.7)	17 (22.1)						
Diet										
Nonvegetarian	36 (50.7)	41 (52.6)	122 (49.4)	48 (62.3)	0.259	0.870	0.893	0.185	0.051	0.697
Vegetarian	35 (49.3)	37 (47.4)	125 (50.6)	29 (37.7)						
Menstrual cycle										
Regular	12 (32.4)	11 (25.6)	54 (46.6)	18 (58.1)	0.011	0.500	0.131	0.034	0.255	0.017
Menopause	25 (67.6)	32 (74.4)	62 (53.4)	13 (41.9)						
Use of VDT (in hours)	4.2±3.8	3.5±2.2	3.7±3.0	4.3±2.7	0.038	0.837	0.683	0.147	0.004	0.837
Stay in air-conditioning (in hours)	2.1±3.9	0.5±2.0	1.3±2.9	1.1±3.0	0.028	0.006	0.361	0.113	0.258	0.006

Group 1: patients with short tear film break-up time; Group 2: patients with aqueous tear deficiency; Group 3: patients with >5 but <10 s TBUT; Group 4: normal patients; VDT: video display terminal; vs: versus. For categorical variables, Pearson Chi-square test, and for continuous variables, Kruskall-Wallis test (comparison between all the groups) and Mann-Whitney U test (for comparison between individual groups) were used. Numbers in parentheses are percentages

Table 2: Comparison of dry eye tests in patients with different categories of tear film abnormalities

Variables	Group 1 *n*=71	Group 2 *n*=78	Group 3 *n*=247	Group 4 *n*=77	P					
					Between all groups*	Group 1 vs Group 2†	Group 1 vs Group 3†	Group 1 vs Group 4†	Group 3 vs Group 4†	Group 2 vs Group 3†
OSDI Ocular symptom subscale	2.4±2.7	3.5±4.0	1.5±2.5	0.5±1.0	<0.0001	0.238	<0.0001	<0.0001	0.005	<0.0001
OSDI Vision-function-related subscale	1.1±2.1	1.2±2.1	0.8±2.0	0.4±1.1	0.016	0.572	0.125	0.034	0.274	0.017
OSDI Environmental trigger subscale	0.7±1.4	1.0±1.0	0.5±1.2	0.3±0.6	0.019	0.277	0.206	0.164	0.682	0.005
OSDI Total score	10.8±11.6	15.5±18.2	7.1±11.4	2.9±3.9	<0.0001	0.238	0.001	<0.0001	0.134	<0.0001
Tear film breakup time (seconds)	3.7±1.0	6.1±3.6	7.2±1.3	13.1±1.7	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Schirmer's 1 test (mm)	20.5±9.5	5.6±5.9	23.3±9.4	27.5±8.5	<0.0001	<0.0001	0.024	<0.0001	0.001	<0.0001
Lissamine green score	0.3±0.4	0.9±1.1	0.2±0.4	0.1±0.3	<0.0001	0.003	0.274	0.005	0.021	<0.0001

Group 1: patients with short tear film break-up time; Group 2: patients with aqueous tear deficiency; Group 3: patients with >5 but <10 s TBUT; Group 4: normal patients; and vs: versus. * Kruskall-Wallis test; † Mann-Whitney U test

the least in the short TBUT group, and Schirmer I test was the least in the ATD group. The patients in the short TBUT and ATD groups differed significantly in TBUT, Schirmer I test, and Lissamine green staining scores. The patients in the group with >5 but <10 s TBUT time differed significantly ($P < 0.05$) in all the dry eye parameters as compared with the normal group.

The distribution of MGD in different study groups is given in Table 3. The difference in frequency was significant between the short TBUT group, ATD group ($P < 0.0001$) and the normal group ($P < 0.0001$) but not with the group with >5 but <10 s TBUT ($P = 0.114$).

Dry eye disease (symptoms and signs) was present in 26 (36.6%) patients in the short TBUT group, 27 (34.6%) patients in the ATD group, and 48 (19.4%) patients in the group with >5 but <10 s TBUT. The difference was statistically significant between the short TBUT group and the group with >5 but <10 s TBUT ($P = 0.003$) and the short TBUT and normal groups ($P < 0.0001$), but not between the short TBUT and ATD groups ($P = 0.865$). The difference was also significant between the ATD group and the group with >5 but <10 s TBUT ($P = 0.006$), and between the group with >5 but <10 s TBUT and the normal group ($P < 0.0001$).

Prevalence of short TBUT type of dry eye disease

The age-adjusted prevalence of asymptomatic (OSDI score <13) and symptomatic (OSDI score ≥13) short TBUT type of dry eye disease was 12.3% (95% confidence interval: 9.6–15.0%) and 5.4% (95% confidence interval: 3.2–6.8%), respectively.

Risk factors

A multivariate logistic regression analysis was done to identify the various risk factors [Appendix VII]. MGD (odds

Table 3: Distribution of meibomian gland dysfunction in patients with different categories of tear film abnormalities

Variables	Group 1 *n*=71	Group 2 *n*=78	Group 3 *n*=247	Group 4 *n*=77	P				
					Group 1 vs Group 2	Group 1 vs Group 3	Group 1 vs Group 4	Group 3 vs Group 4	Group 2 vs Group 3
Meibomian gland dysfunction	46 (64.8)	10 (12.8)	134 (54.3)	31 (40.3)	<0.0001	0.114	<0.0001	0.359	<0.0001

Numbers in parentheses indicate percentages. Group 1: patients with short tear film break-up time; Group 2: patients with aqueous tear deficiency; Group 3: patients with >5 but <10 s TBUT; Group 4: normal patients; and vs: versus

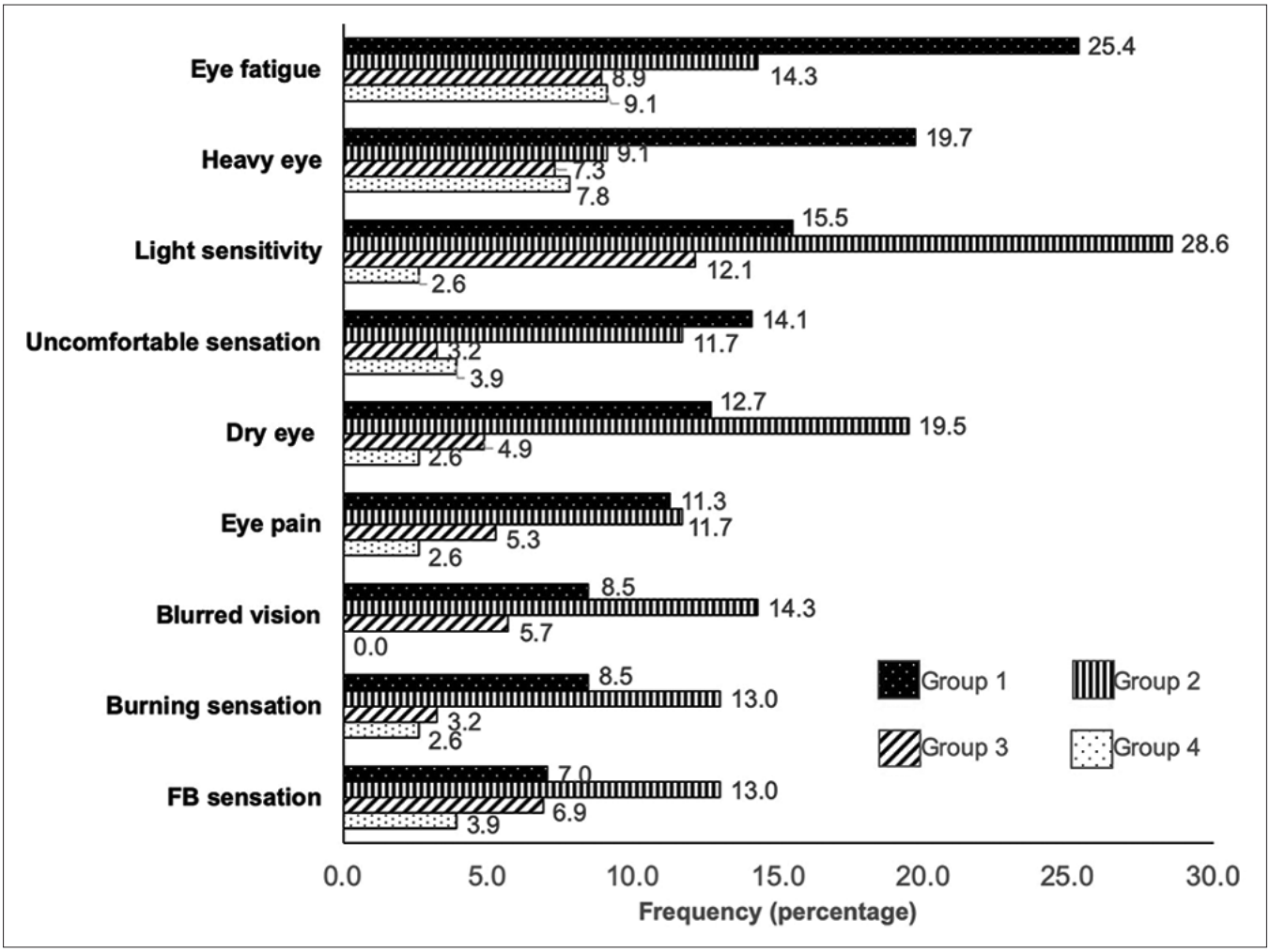


Figure 1: Common symptoms of dry eye reported by the patients with different categories of tear film abnormalities. Group 1: patients with short tear film break-up time; Group 2: patients with aqueous tear deficiency; Group 3: patients with >5 but <10 s TBUT; and Group 4: normal patients

ratio: 3.759 [95% confidence interval: 2.135–6.618], $P < 0.0001$) and female sex (odds ratio: 1.954 [95% confidence interval: 1.042–3.667], $P = 0.037$) were the two independent risk factors associated with short TBUT type of dry eye disease.

Discussion

In this study, we report a cohort of dry eye patients with short TBUT type of dry eye disease, who have clinical features distinct from other types of dry eyes, namely, a very unstable tear film (TBUT ≤5 s), no significant epithelial staining and a normal tear production. While the dry eye-related symptom severity was not very different from patients with ATD, the pattern was distinctive. Our patients were largely middle-aged adults of both sexes, and a significant proportion of the female patients had attained menopause. These clinical features distinguished short TBUT type of dry eye disease as a distinct subtype of evaporative dry eye disease, which was previously reported mostly from Japan, but now seems to be present outside that country.

One of the reasons why the short TBUT type of dry eye disease is regarded with importance in Japan[2] is its high prevalence in the urban population.[4,5] The age-adjusted prevalence of short TBUT type of dry eye disease in our study was less than the prevalence rate (43.5%) reported in a Japanese study conducted among office workers.[5] However, the prevalence of symptomatic disease (5.4%) in our study was

not greatly different from the prevalence rate of symptomatic disease (8.9%) in the Japanese study. The larger proportion of asymptomatic patients in our study may represent a preclinical disease stage. It is now hypothesized that chronic dry eye causes neurotrophic keratopathy.[28] Therefore, dry eye symptoms may be masked in these patients. Moreover, in elderly patients, there is reduced corneal sensitivity, which also masks symptoms of dry eye.[29] This may explain the high proportion of asymptomatic patients in the study.

Although the severity of symptoms between short TBUT type of dry eye and ATD type of dry eye did not seem to differ in this study, the pattern of symptoms was different. Eye fatigue, heaviness in the eyes, and uncomfortable sensations were present to a greater extent in the short TBUT group, while dryness, light sensitivity, burning or foreign body sensation, and blurred vision were largely present in the ATD group. Some of these differences were of borderline statistical difference. This difference in the pattern of symptoms appears to be related to different pathological mechanisms causing the two conditions – reduced tear secretion versus an unstable tear film. Symptoms like dryness, foreign body, and burning sensation have been predominant symptoms reported by patients with primary and secondary Sjogren's disease,[30] where there is reduced tear secretion. In contrast, eye fatigue, dry eye sensation, and uncomfortable sensation have been more commonly reported in patients with short TBUT type of dry eye,[5] where tear secretion is normal, but the tear film is unstable. Eye fatigue and its related symptoms, which are predominantly experienced in short TBUT type of dry eyes, are thought to be related to accommodation fatigue,[7-10] caused by the continuous effort of the ciliary muscles to focus the image (degraded due to an unstable tear film) on the retina.[15,31] A routine orthoptic examination was not done in patients complaining of eye fatigue. However, measurement of TBUT may play a diagnostic role in young adults complaining of eye fatigue. It is possible that some of these patients may have unrecognized short TBUT type of dry eyes and they may benefit if the unstable tear film is addressed. A measurement of functional visual acuity[8] in these patients may provide a better understanding of the mechanisms underlying their symptoms.

In their initial paper, Toda *et al*.[1] had described allergic conjunctivitis as a risk factor for short TBUT type of dry eye disease because of increased secretion of immunoglobulin-E and the presence of mucin abnormalities in their patients. In our study, MGD and the female sex were identified as independent risk factors. Tear film stability is maintained by both the lipid and the mucin layers.[20,32] MGD is more common in postmenopausal women,[19,20] and at the same time, mucin abnormality has also been reported more frequently in postmenopausal women with dry eye disease.[32] There are also reports that meibomian glands may regulate mucin secretion from the lacrimal glands and conjunctival goblet cells.[33,34] Therefore, multiple interrelated pathways may lead to a short TBUT type of dry eye state.

In this study, patients with a TBUT >5 but <10 s comprised the largest group of patients. They had a mild form of the disease as compared with the short TBUT type of dry eye disease but differed significantly from normal patients in the pattern of symptoms, severity, and dry eye test results. There were more reports of symptoms such as light sensitivity, dryness, eye pain, blurred vision, burning sensation, and foreign body sensation from these patients than those in the normal group. Interestingly, the dry eye diagnostic criteria of the Asia/Japanese dry eye society,[11] but not the DEWS II report,[25] exclude patients with a TBUT >5 s from the ambit of dry eye disease. In light of our findings, we believe that patients with a TBUT >5 but <10 s represent a preclinical or milder form of short TBUT type of dry eye disease, and excluding such patients may be counterproductive. Monitoring and treating these patients may prevent disease progression.

The cross-sectional clinic-based design of this study is a limitation in predicting the temporal course of the disease or generalizing the findings to the community. In our study, the association between short TBUT type of dry eye disease and the use of VDTs or other environmental factors were weak unlike the Japanese studies.[5,10] Our study included patients from both urban and rural settings, and this heterogeneous composition of the sample population may have mitigated the effect of urbanization and associated lifestyle risks. Despite these limitations, the findings of the present study bring forth a different perspective to our understanding of dry eye disease in India.

Conclusion

We have described a typical group of patients with specific characteristics that distinguish them from other types of dry eye disease. This study also emphasizes the importance of measuring TBUT, particularly in patients with symptoms of eye fatigue whose complaints may not primarily be due to anomalies of accommodation and/or convergence but due to an unstable tear film. The presence of short TBUT type of dry eye disease in Indian patients indicates a global presence of this disease, and ophthalmologists outside Japan should consider this in their diagnoses.

Acknowledgement

We acknowledge the contributions of Dr Arpit Sharma in data collection.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Toda I, Shimazaki J, Tsubota K. Dry eye with only decreased tear breakup time is sometimes associated with allergic conjunctivitis. Ophthalmology 1995;102:302-9.
2. Tsubota K. Short tear film breakup time-type dry eye. Invest Ophthalmol Vis Sci 2018;59:DES64-S70.
3. Shimazaki J. Definition and diagnostic criteria of dry eye disease: Historical overview and future directions. Invest. Ophthalmol Vis Sci 2018;59:DES7-12.
4. Uchino Y, Uchino M, Yokoi N, Dogru M, Kawashima M, Okada N, *et al*. Alteration of tear mucin 5AC in office workers using visual display terminals. The Osaka study. JAMA Ophthalmol 2014;132:985-92.
5. Yokoi N, Uchino M, Uchino Y, Dogru M, Kawashima M, Komuro A, *et al*. Importance of tear film instability in dry eye disease in office workers using visual display terminals: The Osaka study. Am J Ophthalmol 2015;159:748-54.
6. Koh S, Maeda N, Hori Y, Inoue T, Watanabe H, Hirohara Y. Effects of suppression of blinking on quality of vision in borderline cases of evaporative dry eye Cornea 2008;27:275-8.

7. Kaido M, Kawashima M, Ishida R, Tsubota K. Severe symptoms of short tear break-up time dry eye are associated with accommodative microfluctuations. Clin Ophthalmol 2017;11:861-9.
8. Kaido M, Kawashima M, Shigeno Y, Yamada Y, Tsubota K. Relationship of accommodation microfluctuation with dry eye symptoms in short tear break-up time dry eye. Plos One 2017;12:e0184296.
9. Kaido M, Kawashima M, Ishida R, Tsubota K. Relationship of corneal pain sensitivity with dry eye symptoms in dry eye with short tear break-up time. Invest Ophthalmol. Vis Sci 2016;57:914-9.
10. Shimazaki-Den, Dogru M, Higa K, Shimazaki J. Symptoms, visual function, and mucin expression of eyes with tear film instability Cornea 2013;32:1211-8.
11. Tsubota K, Yokoi N, Shimazaki J, Watanabe H, Dogru M, Yamada M, *et al*. New perspectives on dry eye definition and diagnosis: A consensus report by the Asia Dry Eye Society. Ocul Surf 2017;15:65-76.
12. Craig JP, Nichols KK, Akpek EA, Caffery B, Dua HS, Joo C-K, *et al*. TFOS DEWSII definition and classification report. Ocul Surf 2017;15:276-83.
13. Kim YH, Kang YS, Lee HS, Choi W, You IC, Yoon KC. Effectiveness of combined tear film therapy in patients with evaporative dry eye with short tear film breakup time. J Ocul Pharmacol Ther 2017;33:635–43.
14. Mun Y, Kwon JW, Oh JY. Therapeutic effects of 3% diquafosol ophthalmic solution in patients with short tear film break-up time-type dry eye disease. BMC Ophthalmol 2018;18:237.
15. Xi LC, Qin J, Bao Y. Assessment of tear film optical quality in a young short tear break-up time dry eye. Case-control study. Medicine 2019;98:e17255.
16. Tityal JS, Falera C, Kaur M, Sharma M, Sharma N. Prevalence and risk factors of dry eye disease in north India: Ocular surface disease index-based cross-sectional hospital study. Indian J Ophthalmol 2018;66:207-11.
17. Donthineni PR, Kammari P, Shanbag SS, Singh VS, Das VA, Basu S. Incidence, demographics, types and risk factors of dry eye disease in India: Electronic medical records driven big data analytics report I. Ocul Surf 2019;17:250-6.
18. Chatterjee S, Agrawal D, Sharma A. Dry eye disease in India. Indian J Ophthalmol 2020;68:1499-1500.
19. Chatterjee S, Agrawal D, Sharma A. Meibomian gland dysfunction in a hospital-based population in central India. Cornea 2020;39:634-9.
20. Knop E, Knop N, Miller T, Obata H, Sullivan DA. The international workshop on meibomian gland dysfunction: Report of the subcommittee on anatomy, physiology, and pathophysiology of the meibomian gland. Invest Ophthalmol Vis Sci 2011;52:1938-78.
21. Toda I, Fujishima H, Tsubota K. Ocular fatigue is the major symptoms of dry eye. Acta Ophthalmol 1993;71:347-52.
22. Methodologies to diagnose and monitor dry eye disease: Report of the diagnostic methodology subcommittee of the international dry eye workshop (2007). Ocul Surf 2007;5:108–52.
23. Miller KL, Walt JG, Mink DR, Satram-Hoang S, Wilson SE, Perry HD. Minimal clinically important difference for the ocular surface disease index. Arch Ophthalmol 2010;28:94-101.
24. Bron A, Evans VE, Smith JA. Grading of corneal and conjunctival staining in the context of other dry eye tests. Cornea 2003;22:640-50.
25. Tomlinson A, Bron AJ, Korb DR, Amano S, Paugh JR, Pearce EI, *et al*. The international workshop on meibomian gland dysfunction: Report of the diagnosis subcommittee. Invest Ophthalmol Vis Sci 2011;52:2006-49.
26. Wolfsohnn JS, Arita R, Chalmers R, Djalilian A, Dogru M, Dumbleton K, *et al*. TFOS DEWSII diagnostic methodology report. Ocul Surf 2017;15:539-74.
27. Office the Registrar General and Census Commissioner, India. Census of India website. Available from: http://www.censusindia.gov.in/2011census/C-series/C-13.html. [Last accessed on 2019 Mar 27].
28. Belmonte C, Nichols JJ, Cox SM, Brock JA, Begley CG, Bereiter DA, *et al*. TFOS DEWS II pain and sensation report. Ocul Surf 2017;15:407-40.
29. Shaheen BS, Bakir M, Jain S. Corneal nerves in health and disease. Surv Ophthalmol 2014;59:263-85.
30. Bjerrum KB. Test and symptoms in keratoconjunctivitis sicca and their correlations. Acta Ophthalmol Scand 1996;74:436-41.
31. Tutt R, Bradley A, Begley C, Thibos LN. Optical and visual impact of tear break-up in human eyes. Invest Ophthalmol Vis Sci 2000;41:4117-23.
32. Gipson IK, Spurr-Michaud SJ, Senchyna M, Ritter R, Schaumberg D. Comparison of mucin levels at the ocular surface of postmenopausal women with and without a history of dry eye. Cornea 2011;30:1346-52.
33. Mantelli F, Moretti C, Micera A, Bonini S. Conjunctival mucin deficiency in complete androgen insufficiency (CAIS). Graefes Arch Clin Exp Ophthalmol 2007;245:899-902.
34. Inaba T, Tanaka Y, Tamaki S, Ito T, Ntambi JN, Tsubota K. Compensatory increases in tear volume and mucin levels associated with meibomian gland dysfunction caused by stearoyl-CoA desaturase-1 deficiency. Sci Rep 2018;8:3358.

Appendix I. Method of comprehensive eye examination

History taking

A detailed information on demographics (gender, age, habitation), personal history (habits, nature and work setting, etc.), current and past ocular and medical history, history and medications was taken.

Measurement of visual acuity

Visual acuity measurements were performed for the right and then the left eye successively. Measurements were taken unaided, with patient's spectacles and through pinhole. Measurements were made on a modified high-contrast chart used in the Early Treatment of Diabetic Retinopathy study, which was designed for 3 m. The chart was retro-illuminated with four fluorescent bulbs of 2 feet long.

Slit-lamp evaluation

All patients were evaluated at the slit-lamp (BM 900, Haag Streit, Bern, Switzerland) using different illumination technique for examination of the eye lids and anterior segment.

Intraocular pressure measurements

Intraocular pressure was measured by Goldmann applanation tonometer (AT 900M/Q, Haag Streit, Berne, Switzerland) mounted on the slit lamp. Prior to the actual examination patients were comfortable seated at the slit lamp, and the procedure was explained. Topical anesthetic drops, Proparacaine 0.5% (Paracaine®, Sunways India Pvt Ltd., Mumbai, India) eye drops was instilled in the lower conjunctival cul-de-sac. A sterile fluorescein strip was gently applied and the patient was asked to blink several times following which the measurement was taken. Intraocular pressure was measured after the completion of all dry eye tests.

Fundus examination

Dilated fundus examination was performed after the completion of all dry eye tests and intraocular pressure measurements.

The optic disc and macula were examined with 90D lens at the slit lamp and the periphery of the retina was examined with a 20D lens and indirect ophthalmoscope.

Appendix II. Tests used to evaluate dry eye disease

Subjective symptoms

The list of 15 symptoms based on the questionnaire adopted by the Japanese Dry Eye Society. [21] The latter includes 12 symptoms: eye fatigue, uncomfortable sensation, heavy eye sensation, eye pain, foreign body sensation, discharge, itching, tearing, dry eye sensation, blurred vision, red eyes, and light sensitivity. To this, we added three other questions: burning sensation, excessive blinking, and history of chalazion. The responses were graded as ''constantly,'' ''often,'' ''sometimes,'' and ''never.'' A response of either ''constantly'' or ''often'' were considered positive for subjective symptoms.

Ocular Surface Disease Index[22]

The Ocular Surface Disease Index® (OSDI, Allergan Inc., Irvine, Ca., USA) is a 12-item patient reported outcome questionnaire designed to provide a rapid assessment of symptoms of ocular irritation consistent with DED and their impact on vision-related functions. The questionnaire consists of three domains: Ocular symptoms, vision-related functions, and environmental triggers. The 12-item questionnaire is graded on a Likert-type scale of 0–4 points, where 0 = none of the time, 1 = some of the time, 2 = half of the time, 3 = most of the time, and 4 = all the time. The total OSDI is then calculated with the formula:

$$OSDI\ score = \frac{Sum\ of\ score\ of\ all\ the\ questions \times 00}{No.\ of\ questions\ answered \times 4}$$

The OSDI score is on a scale 0–100 with higher scores indicating greater degree of disease. A score of ≥ 13 distinguished between symptomatic and asymptomatic individuals.[22,23]

Fluorescein tear film break-up time

The stability of the tear film was assessed by FTBUT and was measured by a standard technique that had been previously described.[22] Fluorescein sodium was instilled in the inferior palpebral conjunctiva using a fluorescein sodium ophthalmic strip (Fluorostrip®, Contacare Ophthalmics and Diagnostics, Vadodara, Gujarat, India). Following instillation, the subject was asked to blink naturally several times to distribute the fluorescein. After 10–30 s, the subject was asked to look straight ahead without blinking. The tear film was examined under cobalt blue filter of the slit-lamp viewed through 10x magnification. The time interval was recorded with a stopwatch and was the time between the last blink and the appearance of first random dark spot in the fluorescein-stained tear film. Three such readings were recorded and the average of three was considered as TFBUT. Times ≤10 s was considered as dry eye and >10 s was considered as normal. Time >15 s was recorded as 15 s.

Schirmer's I test

The Schirmer's test was carried out without anesthesia to assess tear production.[22] The subject was seated comfortably and asked to look straight ahead in slight up gaze. A Whatman paper no 41 (TearStrips®, Contacare Ophthalmics and Diagnostics, Vadodara, Gujarat, India) was placed at the junction of the outer and inner one-third of the lower eye lid carefully without touching the cornea and the subject was asked to normally blink his eyes. The reading was taken at 5 min. A reading of ≤5 mm at 5 min signified aqueous tear deficiency.

Lissamine green staining of ocular surface

Lissamine green stain was used to evaluate the corneal and conjunctival surface by instilling lissamine green ophthalmic strip (Lissamine Green Sterile Strips®, Contacare Ophthalmics and Diagnostics, Vadodara, Gujarat, India). The ocular surface was divided into three regions: corneal, nasal conjunctiva, and temporal conjunctiva. Staining was graded according to the panels of the Oxford scheme and was graded on a scale 0–5.[24] The grading of the Oxford scheme represented the lissamine green staining score and was abnormal if ≥ 2.

Meibomian gland expression

Meibomian gland expression was done by applying a firm pressure with the index finger at the central lower eye lid over the tarsal plate against the globe, maintaining the pressure for 15 s.[25] The area of focus was the central eight glands

Meibum quality was graded as: 0 = clear fluid, 1 = cloudy fluid, 2 = cloudy particulate fluid, and 3 = inspissated, toothpaste like. Meibum expressibility was graded as: 0 = all glands expressible, 1 = 3–4 glands expressible, 2 = 1–2 glands expressible, and 3 = no glands expressible. MGD was diagnosed based on a score of 1 for both quality and expressibility or a score of more than 1 for either quality or expressibility.

Appendix III: Study definitions

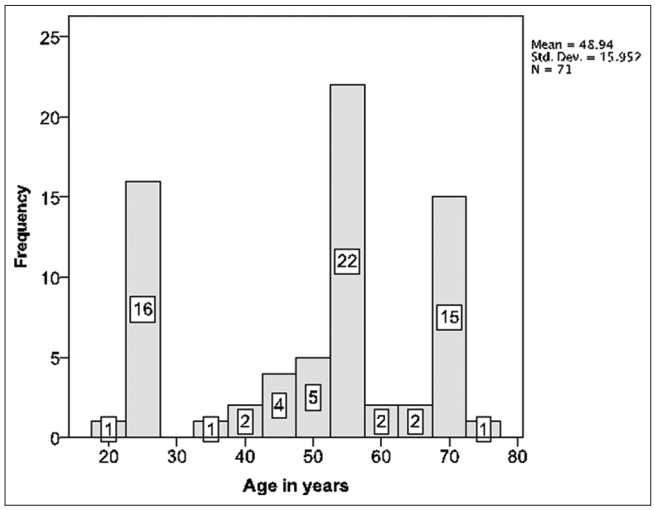
Diagnosis	Criteria
Normal patients	Ocular surface disease index <13+ Tear film break up time >10 s + Schirmer's I test >5 mm at end of 5 min + Lissamine green staining score <2 + No meibomian gland dysfunction
Aqueous tear deficiency (ATD)[22]	Schirmer's I test ≤5 mm at 5 min
Short tear film break-up (short TBUT)[1,2]	Tear film break up time ≤5 s + Schirmer's I test >5 mm at end of 5 min + Lissamine green staining score <2
>5 but<10 s tear film break-up time	Tear film break up time >5 s but <10 s + Schirmer's test 1 >5 mm at end of 5 min + Lissamine green staining score <2
Meibomian gland dysfunction[25]	A score of 1 for both meibomian gland expressibility and meibum quality or a score of more than 1 for either expressibility or quality
Dry eye disease[26]	OSDI score ≥13 + Tear film break up time<10 s or Lissamine green staining score ≥2
Aqueous tear deficiency dry eye disease[26]	Ocular surface disease index score ≥13 + Tear film break up time <10 s or Lissamine green staining score ≥2 + Schirmer's I test ≤5 mm at 5 min
Evaporative dry eye disease[26]	Ocular surface disease index score ≥13 + Tear film break up time <10 s and or Lissamine green staining score ≥2 + Schirmer's I test >5 mm at 5 min
Short tear film break-up dry eye disease (symptomatic)[1,2,26]	Tear film break-up time ≤5 s + Schirmer's I test >5 mm at end of 5 min + Lissamine green staining score <2+ Ocular surface disease index score ≥13

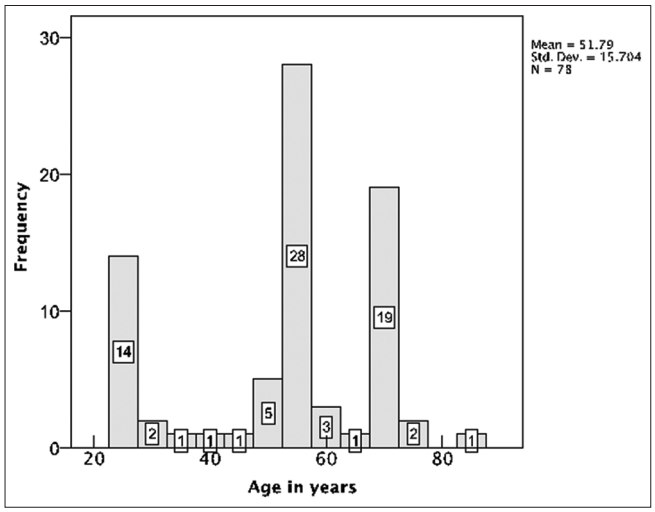
The concept of dry eye disease stems from the DEWSII report[26] that emphasizes on inclusion of both dry eye symptoms (positive dry eye questionnaire score) and signs to fulfill the criterion of a disease.

Appendix IV: Histograms showing the age distribution in different groups of patients

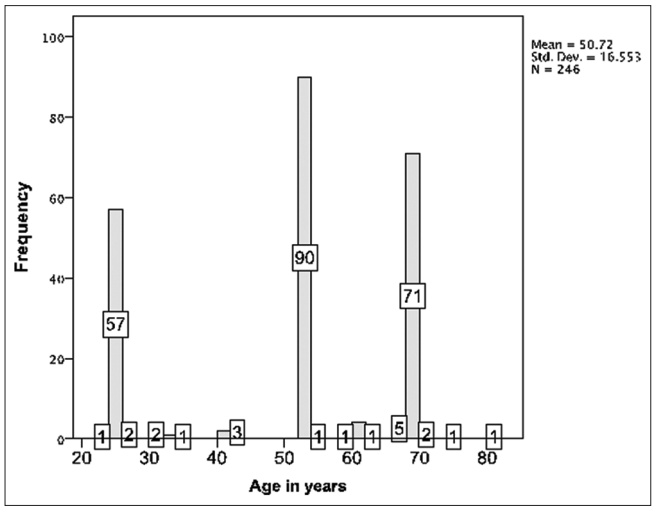
Age in years	Short tear film break-up time group	Aqueous tear deficiency group	>5 but <10 s tear film break-up time group	Normal group
Mean	48.9	51.8	50.7	43.6
Standard deviation	15.9	15.7	16.5	15.0
Median	53.0	53.0	53.0	50.0
Minimum	20	25	20	21
Maximum	75	85	75	68

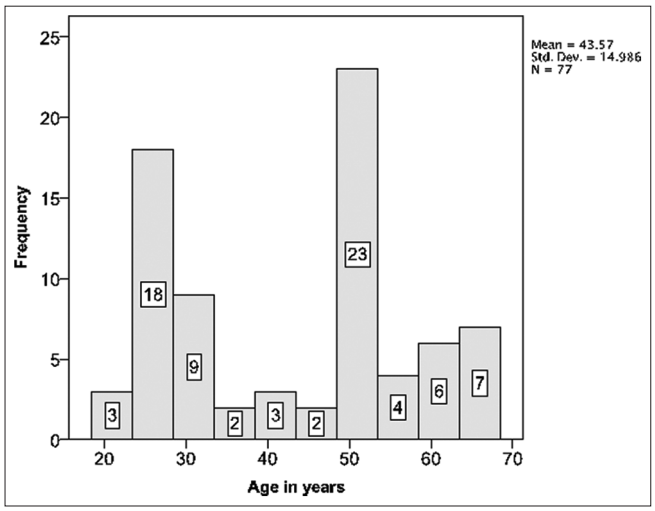
Short tear film break-up time group: **Aqueous tear deficiency group:**





>5 but < 10 s tear film break-up time group: **Normal group:**


Mean = 50.72
Std. Dev. = 16.553
N = 246
Frequency
Age in years
100
80
60
40
20
0
20
30
40
50
60
70
80
57
90
71
1
2
2
1
3
1
1
1
5
2
1
1


Mean = 43.57
Std. Dev. = 14.986
N = 77
Frequency
Age in years
25
20
15
10
5
0
20
30
40
50
60
70
3
18
9
2
3
2
23
4
6
7

Appendix V: Table showing the distribution of symptoms in different groups of patients

	Group 1 (*n*=71) *n* (%)	Group 2 (*n*=78) *n* (%)	Group 3 (*n*=247) *n* (%)	Group 4 (*n*=77) *n* (%)	P				
					1 vs 2	1 vs 3	1 vs 4	3 vs 2	3 vs 4
Eye fatigue	18 (25.4)	11 (14.1)	22 (8.9)	7 (9.1)	0.083	<0.001	0.008	0.185	0.961
Uncomfortable sensation	10 (14.1)	9 (11.5)	8 (3.2)	3 (3.9)	0.642	<0.001	0.029	0.004	0.781
Heavy eye	14 (19.7)	7 (9.0)	18 (7.3)	6 (7.8)	0.060	0.002	0.034	0.626	0.883
Eye pain	8 (11.3)	9 (11.5)	13 (5.3)	2 (2.6)	0.959	0.073	0.036	0.054	0.331
FB sensation	5 (7.0)	10 (12.8	17 (6.9)	3 (3.9)	0.242	0.963	0.398	0.098	0.342
Burning sensation	6 (8.5)	10 (13.0)	8 (3.2)	2 (2.6)	0.390	0.059	0.116	0.001	0.776
Discharge	2 (2.8)	5 (6.4)	2 (0.8)	2 (2.6)	0.301	0.217	0.934	0.003	0.215
Itching	9 (12.7)	12 (15.4)	24 (9.7)	8 (10.4)	0.635	0.471	0.663	0.164	0.863
Tearing	4 (5.6)	7 (9.0)	15 (6.1)	8 (10.4)	0.538	0.891	0.290	0.374	0.198
Dry eye sensation	9 (12.7)	15 (19.2)	12 (4.9)	2 (2.6)	0.277	0.019	0.020	<0.001	0.394
Blurred vision	6 (8.5)	11 (14.1)	14 (5.7)	0 (0)	0.278	0.395	0.009	0.015	0.033
Red eyes	5 (7.0)	5 (6.4)	10 (4.0)	1 (1.3)	0.878	0.294	0.077	0.386	0.245
Excessive blinking	2 (2.8)	6 (7.7)	4 (1.6)	0 (0)	0.187	0.513	0.138	0.007	0.261
Light sensitivity	11 (15.5)	22 (28.2)	30 (12.1)	2 (2.6)	0.062	0.458	0.006	0.001	0.014
History of chalazion	3 (4.2)	2 (2.6)	3 (1.2)	0 (0)	0.574	0.100	0.068	0.399	0.331

Group 1: patients with short tear film break-up time; Group 2: patients with aqueous tear deficiency; Group 3: patients with >5 but <10 s TBUT; and Group 4: normal patients; vs: versus.

Appendix VI: Table showing the severity of symptoms in different eye groups

	Group 1 (*n*=71)	Group 2 (*n*=78)	Group 3 (*n*=247)	Normal group (*n*=77)
Absent (OSDI score: 0-12)	44 (62.0)	42 (53.8)	192 (77.7)	74 (96.1)
Mild (OSDI score: 13-22)	11 (15.5)	6 (7.7)	20 (8.1)	2 (2.6)
Moderate (OSDI score: 23-32)	7 (9.9)	12 (15.4)	13 (5.3)	1 (1.3)
Severe (OSDI score: 33-100)	9 (12.7)	18 (23.1)	22 (8.9)	0 (0)

Group 1: patients with short tear film break-up time; Group 2: patients with aqueous tear deficiency; Group 3: patients with >5 but <10 s TBUT; Group 4: normal patients; and vs: versus.

Numbers in parentheses are in percentages. The difference of proportion of patients with severe symptoms score between Group 1 and Group 2 was not significant (P = 0.09894) but was significant (P = 0.0009) between Group 2 vs Group 3 groups (Z test for two population proportion).

Appendix VII: Binary logistic regression analysis of risk factors of short tear film break-up type of dry eye

Risk factors	Odds ratio	95% Confidence interval	*P*
Age	0.986	0.966-1.007	0.181
Female sex	1.954	1.042-3.667	0.037
Urban residence	1.901	0.926-3.902	0.080
Nonvegetarian diet	1.081	0.623-1.875	0.782
Menopause	2.051	0.818-5.143	0.126
Average daily use of VDT in hours	1.027	0.935-1.129	0.573
Average daily stay in air-conditioning in hours	1.068	0.980-1.163	0.133
Meibomian gland dysfunction	3.759	2.135-6.618	<0.0001