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ORIGINAL ARTICLE

COMPARISON OF TEAR FILM BREAKUP PATTERN IN ACTIVE AND INACTIVE THYROID EYE DISEASE PATIENTS

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ABSTRACT

Introduction: *Thyroid Eye Disease (TED) is an autoimmune inflammatory disease of the orbit that affects orbital fat, extraocular muscles, periocular tissue and lacrimal glands. TED activity can be assessed with a Clinical Activity Score (CAS) to identify active or inactive TED conditions. Dry Eye Diseases (DED) is one of the manifestations in patients with TED with a prevalence that varies from 27%-96%. The Asia Dry Eye Society (ADES) 2017 proposed a new concept for DED diagnosis and therapy, namely Tear Film Oriented Diagnosis (TFOD) and Tear Film Oriented Diagnosis Therapy (TFOT) with Tear Film Breakup Pattern (TBUP) examination. TBUP examination help in determine specific management of DED. The aim of this study is to determine the differences in TBUP in TED patients based on active and inactive.*

Methods*: This is an analytical observational study with a cross-sectional design. The subjects were TED patients who came to the Cicendo Eye Hospital and met the inclusion criteria. The study was conducted at the National Eye Center of Cicendo Eye Hospital in April - June 2022. The data were analysed with the Chi-Square Test.*

Result: *This study was conducted on 23 patients or 46 eyes. This study found a statistically significant differences in TBUP features in active and inactive TED patients (p=0.0001). The most common features of TBUP was found in active TEDs was dimples (55%).*

Conclusion: *There are differences of TBUP features in active and inactive TED patient.*

Keywords: *Thyroid Eye Disease, Dry Eye Disease, Tear Film Breakup Pattern.*

INTRODUCTION

Thyroid Eye Disease (TED) is an autoimmune inflammatory disease of the orbita that affects orbital fat, extraocular muscles, periocular tissue and the lacrimal gland of the orbita. The autoimmune condition will trigger an inflammatory process that causes ground substance expansion and induce tissue deposition and periorbital fat tissue fibrosis which causes cosmetic and functional defects.[1-3]

TED activity condition can be assessed by a modality called the Clinical Activity Score (CAS). CAS will divide the TED into 2 categories, which is active TED and inactive TED with a cut off value of its score is 3. The active CAS value provides an overview of the activity of the inflammatory process in the TED which cause many manifestations such as swelling of the

periorbita area, injection of the eyeball, and retro orbital pain that caused by inflammation. It also affect the cosmetic and functional aspects of vision. [4,5]

In addition, one of the clinical manifestations of TED is dry eye disease (DED). DED has a high prevalence of ocular disease due to autoimmune and thyroid disorders. The prevalence of DED in patients with TED is ranging from 27-96%. There are several hypotheses regarding the mechanism of TED causing DED conditions such as increased evaporation of the tear film surface due to mechanical factors (eyelid retraction, increased palpebral fissure height, and proptosis), changes in tear production due to immunological factors, ocular surface damage, changes in tear film composition. , and lacrimal gland damage. There are several guidelines of management of patients with DED, one of which is the guidelines from the Asia Dry Eye Society (ADES).[6,7,8]

ADES proposed a new concept for diagnosis and therapy of DED, such as Tear Film Oriented Diagnosis (TFOD) and Tear Film Oriented Diagnosis Therapy (TFOT). ADES classifies DED into aqueous deficiency, increased evaporation and decreased wettability as assessed by Tear Film Breakup Pattern (TBUP) using fluorescence. The new DED paradigm that is currently developing based on ADES 2017 to choose TFOT or TFOD by assessing TBUP. TBUP examination is expected to aid physician with specific dry eye management according to the disorders that occurs.[9,10]

This study aim to determine the differences in TBUP in TED patients based on active and inactive *condition* thus assisting in the selection of specific therapeutic modalities in TED patients with DED.

METHODS

This study is an analytical observational study with a cross-sectional design, with the research subjects being patients with TED who come to the Cicendo Eye Hospital and have met the inclusion criteria. The study was conducted at the National Eye Center of Cicendo Eye Hospital in April–June 2022 after approval from the Department of Ophthalmology and the Faculty Ethics Committee of Padjadjaran University of Medicine.

The inclusion criteria in this study were patients aged less than or equal to 50 years who had previously been diagnosed with TED. The exclusion criteria in this study were patients with corneal ulcers, corneal dystrophy, keratopathy, autoimmune disorders, or other diseases that can cause significant DED (e.g., Sjogren's syndrome, rheumatoid arthritis, systemic lupus erythematosus, sarcoidosis), diabetes mellitus, eyelid abnormalities such as entropion or ectropion, using contact lenses, history of orbital decompression surgery, history of orbital

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radiotherapy, receiving dry eye therapy, and anti-glaucoma therapy. Sampling was done by consecutive sampling.

Patients who are to participate in the study will sign an informed consent form, which contains an explanation of the examination procedure to be performed. Patient data was recorded, including name, age, gender, smoking history, and duration of suffering from TED. Research steps are: patients fill in the OSDI questionnaire and calculate the OSDI score; ophthalmological examination includes visual acuity examination, segments anterior with slit lamp biomicroscope, posterior segment with indirect ophthalmoscopy; clinical activity score (CAS); and proptosis; DED examination of DED includes TBUT; and description of TBUP is carried out in a random way concurrently by 1 ophthalmologist of the immunology infection unit. The method of examination is fluorescein paper that has been moistened, placed on the inferior fornix conjunctiva, and then released. The patient is asked to blink several times and then instructed to close his eyes slowly and open his eyes immediately. Evaluate using a cobalt blue filter on the slit lamp, then simultaneously look at the TBUP picture that appears and calculate TBUT, which is calculated from the time of the last flash until dry spots appear first.

A P value of 0,05 was interpreted as statistically significant. The data were analyzed with the Chi-Square Test using SPSS version 25.0 for Windows.

RESULTS

The study conducted from April 2022 until June 2022, a total of 46 eyes from 23 patients obtained from patients who came to National Eye Center Cicendo Eye Hospital who met the inclusion criteria and were not included in the exclusion criteria.

Characteristics of the subjects in this study are listed in Table 1. Subjects characteristics were divided into active TED and inactive TED. In the active TED group, the mean age was 35.60±9.216 years and based on its gender there were 4 male patients (40%) and 6 female patients (60%). The median duration of TED was 7 months. There were 2 patients who smoked in the active TED group (20%) and 8 patients who did not smoke (80%). In the inactive TED group, the mean age was 35.92±7.97 years and based on its gender there were 3 male patients (23.1%) and 10 female patients (76.9%). The median duration of TED was 2 months. There were 2 smoking patients (15.4%) in the inactive TED group and 11 patients (84.6%) who did not smoke.

Table 1 Subjects Characteristics in Active TED and Inactive TED Groups

Variables	Groups		P value
	Active TED N=10	Inactive TED N=13	
Age (years)			**0,93**
Mean ± SD	35,60 ± 9,22	35,92 ± 7,97	
Median	36	36	
Range (min-max)	24-49	20-49	
Sex			**0,65**
Male	4 (40%)	3 (23,1%)	
Female	6 (60%)	13 (76,9%)	
TED duration			**0,17**
(month)	11,80 ± 17,24	12,69 ± 23,74	
Mean ± SD	7	2	
Median	2-60	1-84	
Range (min-max)			
Smoke			**1,00**
yes	2 (20%)	2 (15,4%)	
no	8 (80%)	11 (84,6%)	

Note : TED : *thyroid eye disease*. Significance test value p value <0,05

Table 2 describes the comparison of proptosis, degree of proptosis, OSDI scores, CAS and TBUT scores in the active and inactive TED groups. From the results of the statistical analysis using the chi square test, it was found that the p value > 0.05 on the proptosis variable and the degree of proptpsis so that there was no significant difference between the active TED and inactive TED groups. The results of the statistical test in the research group above showed that the P value of the OSDI and CAS score variables was less than 0.05 (P value <0.05) using the Mann Whitney test, which means that there is a statistically significant difference between these groups. The TBUT test showed that the p-value was not statistically significant.

Table 2 Comparison of variables in active and inactive TED patients

Variabel	Groups		P value
	Active TED N=20	Inactive TED N=26	
Proptosis (mm)			**0,13**
Mean ± SD	20,85 ± 3,69	19,04 ± 3,74	
Median	22	18	
Range (min-max)	14-27	11-25	
Degree of			**0,10**
Proptosis	6 (30%)	16 (61,5%)	
No proptosis	9 (45%)	7 (27%)	
Mild proptosis	5 (25%)	3 (11,5%)	
Moderate proptosis	0 (0%)	0 (0%)	
Severe proptosis			
OSDI			**0,0001**
Mean ± SD	59,39 ± 15,73	37,53 ± 17,52	
Median	65,63	35	
Range (min-max)	33,30-82,10	15-68,75	

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CAS Score			**0,0001**
Mean ± SD	4,10 ± 0,85	1,08 ± 0,74	
Median	4	1	
Range (min-max)	3-6	0-2	
TBUT			**0,49**
Mean ± SD	4,90 ± 1,74	5,50 ± 1,86	
Median	5	5	
Range (min-max)	1-8	3-10	

Note: TED : *thyroid eye disease*; CAS : *clinical activity score*; OSDI *ocular surface disease index*; TBUT : *tear break up time.* Significance test value p value <0,05

Table 3 describes the comparison of TBUP in the active and inactive TED groups. TBUP analysis was tested using the Chi square test. The results of the statistical test show that the P value of the TBUP variable is smaller than 0.05 (P value <0.05) which means statistically significant. thus, it can be explained that there is a statistically significant difference between the TBUP variables in the active and inactive TED groups.

Table 3 Comparison of Tear Break Up Pattern in Active TED and Inactive TED

Variable	Groups		P value
	Active TED N=20	**Inactive TED N=1326**	
TBUP			**0,0001**
Area	5 (25%)	2 (7,7%)	
Dimple	11 (55%)	1 (3,8%)	
Line	2 (10%)	0 (0%)	
Random	2 (10%)	23 (88,5%)	
Spot	0 (0%)	0 (0%)	

Note: TBUP: *Tear Break Up Pattern*; Significance test value p value <0,05

DISCUSSION

Thyroid Eye Disease (TED) is an autoimmune inflammatory disease of the orbit that affects orbital fat, extraocular muscles, periocular tissue and the lacrimal gland of the orbita and one of its clinical manifestations of TED is dry eye disease (DED).[1,2]

The study found a statistically significant difference in TBUP features in active and inactive TED patients (p=0.0001). The most TBUP picture found in active TEDs was dimple (55%) indicating the occurrence of wettability-decreasing type of DED. The decrease in wettability can provide an overview of TBUP in the form of spots and dimples. research by Takahashi et al. they found more spot patterns in TBUP. The difference with this study is probably due to the tendency of higher CAS scores. Decreased wettability indicates an inflammatory process that occurs on the ocular surface which will damage goblet cells, thereby reducing membrane associated mucin and mucin secretion. Xu N et al conducted a cytological study on the conjunctiva and found that goblet cell damage in active TED was greater than in

inactive TED. This explains the decrease in wettability that occurs more in active TED patients.[9,11,12]

In this study, the random TBUP pattern was more common in inactive TEDs. A random pattern is common in evaporative DED, which means that tear evaporation occurs due to exposure to the ocular surface. Proptosis will increase the exposure of the ocular surface resulting in tear evaporation. So that in TED patients with proptosis there is greater evaporation. In this study, only 38.5% of inactive TED patients had proptosis. Other factors that contribute to the evaporative mechanism of TED are incomplete blinking and interference from the meibomian glands. Achtsidis et al stated that incomplete blinking occurs in TED patients with decreased corneal sensitivity and contributes to tear film instability, this can worsen dry eye symptoms. In this study, the evaporative type was the cause of DED in inactive TED without proptosis.[3,13,14]

This study found group of active TED has a mean age of 35.60 ± 9.22 years and inactive TED 35.92 ± 7.97 years. Allam et al's study reported the mean age of active TED was 40.75 years with inactive TED of 38.5 years. TED is more common in women than men with a ratio 5:1 and usually occurs between the 20 and 50 years, but it can occur in patients over 50 years. This is because women are considered to have more active immune responses than men. The studies of Kim et al and Lavaju et al reported 63.5% and 82.6% of TED in women, respectively.[15,16]

This study showed proptosis did not show a significant difference in both the active and inactive TED groups, which was similar to the study by Villani et al. This can be influenced by the onset of disease, the diagnosis and severity of TED. In this study, there was no significant difference in the duration of TED suffering between the two groups. Allam et al reported different results, there was a significant difference in proptosis in the active and inactive TED groups, namely the proptosis of the active TED was greater than that of the inactive TED.[16,17]

In this study, the OSDI scores were significantly different for active and inactive TEDs, where OSDI scores were higher for active TEDs. Huang et al reported similar result with this study, their study showed there was a significant difference in OSDI scores. which is greater in active TEDs than in inactive TEDs. Lo et al stated that an increase in the CAS score was associated with discomfort on the ocular surface. In this study, the CAS score of active TED was greater than that of inactive TED, causing increased discomfort on the ocular surface as indicated by the OSDI score..[18,19]

The results of TBUT in this study did not show a significant difference between active TED and inactive TED. Similar results were reported by Huang et al. ie active and inactive

TBUT TED were not significantly different. Selter et al reported that TBUT examination in TED was lower than in control patients, suggesting tear film instability in TED patients. In this study, it was possible that in active and inactive TEDs the tear film was unstable, so there was no significant difference between these groups.

The results of this study showed a significant difference in TBUP patterns in active TED and inactive TED, this indicates that there are different DED mechanisms that play a role in active TED and inactive TED. In an active TED, a dimple TBUP pattern was found, this explains the mechanism that causes DED, which is a decrease in wettability. The inactive TED shows a random TBUP pattern, this shows the type of DED that occurs is an evaporative mechanism. The difference in the mechanism of DED in TED may be decisive from DED therapy. Active TED patients can be treated with mucin segregate topical eye drops, autologous serum and rebamipide. Inactive TED patients can be given education to maintain eyelid hygiene, warm compresses and low-dose fat replacement eye ointment therapy.

This study has limitations, such as no quantitative assessment of the meibomian glands, which is a component in the assessment of evaporative DED. In this study, there were no DED patients as controls groups to see if there were differences in the mechanism of DED in TED and DED patients alone.

CONCLUSION

There are differences of TBUP features in active and inactive TED patient.

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