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RESEARCH ARTICLE **OPEN ACCESS**

Characteristics of Dry Eye Syndrome in Patients with Mild Graves' Ophthalmopathy

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Abstract:

Introduction: This study aimed to assess dry eye in patients with mild Graves' Ophthalmopathy (GO) at Vietnam National Eye Hospital.

Materials and Methods: This cross-sectional descriptive study evaluated dry eye syndrome in 40 eyes from 20 mild Graves' ophthalmopathy patients from January 2021 to December 2021 at the Vietnam National Eye Hospital. As an age-matched control group, 44 eyes of 22 adults without thyroid disease were selected. The Ocular Surface Disease Index (OSDI), Tear Break-up Time (TBUT), Schirmer I tear test, and Corneal Fluorescein Staining (CFS) were assessed.

Results: The results showed that dry eye in patients with mild GO disease was significantly higher (65%), *i.e*., 3.98 times compared to the control group (65% and 30%, p<0.001, OR=3.98). The mean Schirmer I tear test score, TBUT score, CFS score, and OSDI score had a significant difference between GO and controls. Dry eye indices (TBUT, Schirmer I test, CFS) in mild GO patients were linearly correlated with proptosis, Margin-to-reflex Distance 1 (MRD1), and Clinical Activity Score (CAS). In the group of patients with active GO, the results of TBUT, Schirmer I test, CFS, and OSDI were statistically significantly higher than the inactive group (p < 0.05). Dry eye in the inflammatory group was 5.14 times higher than the non-inflammatory group (85.7% *vs*. 53.8%, p< 0.001, OR = 5.14).

Conclusion: Dry eye syndrome was frequently found in patients with mild GO, 3.98 times higher than the control group. Dry eye findings and the ocular surface damage in GO were severe in the group with active mild GO and 5.14 times higher than the inactive group.

Keywords: Mild Graves' ophthalmopathy, Ocular surface damage, Dry eye, Tear film, Blurred vision, Patients.

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1. INTRODUCTION

Dry eye is a disorder of the tear film and ocular surface. This disease can be caused due to many reasons [1]. It can cause blurred vision, burning, itchiness, redness, or grittiness in the eye, and sensitivity to light [2]. This syndrome is determined when the patient shows signs of discomfort on the ocular surface, change in the tear film, and damage to the ocular surface. Dry eye syndrome is a common ophthalmic disorder and is increasingly prevalent among people with autoimmune disease and thyroid disorders [3].

Graves' Ophthalmopathy (GO), also known as thyroid

eye disease, is an autoimmune disease that causes inflammation and swelling of the orbital tissues. The disease has clinical manifestations depending on the stage of the disease, such as proptosis, eyelid retraction, restrictive extraocular myopathy, changes in the ocular surface, and mainly dry eye syndrome. Dry eye is the most frequent cause of ocular discomfort in GO and has been found to be present in 85% of patients [4]. However, Graves' disease has diverse manifestations, and dry eye can be neglected.

GO involves two phases: active and inactive [5]. The active phase may last for about 18 months to the first 3 years from the time the first manifestations of GO have occurred, and then the disease may self-limit, which is followed by the inactive phase. Mild thyroid eye disease may include an active phase [5]. In the active inflammatory phase, the patient may experience symptoms of swelling, redness, and pain in the orbit, eyelids, and conjunctiva. Changes in the ocular surface in GO patients may vary depending on the inflammatory status of Graves' eye disease. Cytological examination of the conjunctiva and tear film in patients with GO demonstrated the ocular surface in patients with active GO to be more damaged than in patients without inflammation [6, 7].

Dry eye syndrome in patients with GO occurs due to many causes, including decreased tear volume because the lacrimal gland is one of the target tissues of TSH, and increased eyelid gap and proptosis leading to rapid evaporation of the tear film [8]. Therefore, this study aimed to evaluate and compare dry eye and ocular surface parameter changes in active and inactive mild GO patients and age-matched controls.

2. MATERIALS AND METHODS

2.1. Study Design

This was an observational, clinical, cross-sectional study conducted with the control group. Twenty patients with mild-stage Graves' eye disease in 2021 (1/2021 to 12/2021) from Vietnam National Eye Hospital were enrolled.

2.2. Inclusion and Exclusion Criteria

Diagnostic criteria for determining Graves' eye disease were set according to the standards of the American Ophthalmological Association 1995 [9]. Each patient was examined and evaluated to classify thyroid eye disease according to the EUGOGO classification of the European Society of Endocrinology [10]. In this study, we only selected patients with mild GO. Our study excluded patients with other eye diseases, such as allergic conjunctivitis and glaucoma, diseases caused due to the use of contact lenses, having ophthalmic and orbital surgery, or patients with systemic diseases that can cause dry eye syndrome, such as Sjögren's syndrome. Similar exclusion criteria were defined for the control group.

2.3. Data Collection

All eyes were evaluated by two ophthalmology consultants and the results were recorded as the average value of these two doctors. A Hertel exophthalmometer was used to measure proptosis in both eyes. The degree of upper eyelid retraction was assessed by measuring MRD1 (vertical distance from corneal light reflex to the upper eyelid margin) [11]. The Clinical Activity Score (CAS), which evaluates the presence of classic features of inflammation, was calculated. A point was added for specific signs, symptoms, and progression of disease experienced by the patient. CAS scores ≥ 3 were defined to correlate with disease activity [12].

The tear film layer was evaluated mainly based on the results of microscopic examination with specific tests, including the Schirmer I test, Tear film Break-up Time (TBUT), and ocular surface staining with fluorescein. Each test was repeated three times and the value was taken as the average result of three measurements. Patients were diagnosed with dry eyes if they had functional symptoms accompanied by reduced Schirmer I test results below 10mm, reduced tear film breakdown time below 10 seconds, and fluorescein staining (CFS greater than 1) [2]. Corneal staining with fluorescein was performed according to the NEI index (National Eye Insitute) [1]. The corneal area was divided into five sections. Depending on the level of fluorescein staining from mild to severe, each section's CFS score was assigned from 0 to 3. The total score of the five sections was taken as the total CFS score of this eye. The questions of the OSDI were employed to evaluate the subjective symptoms of dry eye syndrome and its impact on visual function in the patient's daily life. According to the Schiffman study, the values of the OSDI questionnaire were obtained based on the following formula: (sum of severity of all the answers) x 100/number of replies x 4. The results of OSDI were classified as follows: normal ocular surface (0-12), mild (13-22), moderate (23-32), and severe (33-100) dry eye [1].

2.4. Statistical Analysis

T-test was used to compare mean tear film values between the two groups. To check whether the observed differences in the two groups in some variables were casual or not, the Mann-Whitney test was applied. To assess the associations, the Pearson test or Fisher's exact test was used when appropriate. Statistical significance was set at $p < 0.05$. Data were analysed using SPSS version 26.

2.5. Research Ethics

The research was approved by the medical ethics committee and the research subjects were clearly informed about the purpose and significance of the study. Study subjects were given the option to voluntarily participate in the study. The information collected was solely utilized for research purposes and kept confidential.

3. RESULTS

In this study, 40 eyes of 20 patients (16 females and 4 males) diagnosed with mild GO have been evaluated. The average duration of GO was 6.3 months (1-12 months) in all the patients. Of these, 70% of patients were diagnosed with hyperthyroidism at the time the first lesions of GO

appeared. All patients were of working age with a mean age of 38.2 ± 10.1 yrs (20-59). 22 euthyroid subjects (44 eyes) in the control group included 17 females and 5 males with a mean age of 40.2 ± 10.9 yrs (21-59). When comparing age and gender between the two groups, we found no differences.

Based on the assessment of the Clinical Activity Score (CAS), we defined the inflammation status of GO patients. Of the 40 eyes studied, 14 were active and 26 were inactive. Dry eye syndrome was present in 65% of eyes studied (26/40). This rate was higher than the dry eye rate in the control group (65% *vs*. 31.8%, p = 0.002, OR = 3.98).

The TBUT scores and Schirmer I tear test of 40 eyes studied and also 44 control eyes were normally distributed (Kolmogorov–Smirnov test; p>0.05), and therefore, the representative average was the mean ± Standard Deviation (SD) of the results. An abnormal distribution was found for the CFS (Kolmogorov–Smirnov test, p < 0.001 in both groups) and OSDI scores (Kolmogorov–Smirnov test, p = 0.01 in the study group and p < 0.001 in the control group), and therefore, the representative average was taken as the median (interquartile range). The mean±SD values for the TBUT scores, Schirmer I tear test and the median (IQR) for CFS and OSDI scores are shown in Table **1**.

Table 1. Average [mean ± standard deviation or median (interquartile range)] for the TBUT, Schirmer I tear test, CFS, and OSDI scores for the study and control groups.

Test	Average/median	
-	Study Group (N=40 eyes)	Control Group (N=44 eyes)
TBUT (second)*	8.25 ± 5.13	14.3 ± 6.72
Schirmer I (mm)*	7.95 ± 2.92	12.66 ± 4.11
CFS score*	4.5 (9.0)	2 (7)
OSDI score*	16.5 (19)	4.5 (13)

Note: * the difference is statistically significant with p<0.05.

The mean TBUT score of the study group was 8.25 ± 5.13 sec. While in the control group, the mean TBUT score was 14.3 ± 6.72 sec. When comparing the mean TBUT score between the two groups using the T-test, the research team found the TBUT score in the control group to be statistically significantly higher than the mild GO group (p<0.001). Reduced tear secretion was observed in the study group with a mean Schirmer I test of 7.95 ± 2.92 mm. This value in the study group was statistically significantly lower than the value of the control group (12.66 ± 4.11mm, p<0.001).

The median score for the OSDI in the study group represented mild dry eye condition [16.5 (19)], while the average score within the control group showed a normal eye condition [4.5 (13)]. The median score for the grades showed a moderated area of staining spots' CFS [4.5 (9.0)] within the study group and showed mild area of staining spots [2(7)] within the control group. When performing the Mann-Whitney U test to compare the two medians of OSDI score and CFS, both indexes in the study group were found to be statistically significantly higher than the control group (p <0.001).

The correlations between the scores related to dry eye status with proptosis, upper eyelid retraction (MRD1), and inflammation (CAS) within the study group are recorded in Table **2**. Generally, all scores exhibited a statistically linear correlation. The TBUT and Schirmer I tear test had negative strong correlations with proptosis, MRD1, and CAS, while OSDI scores and CFS had positive correlations with proptosis, MRD1, and CAS. OSDI scores, TBUT, Schirmer I test, and CFS have been closely correlated with CAS (p<0.001).

Table 2. Correlation of the OSDI, TBUT, Schirmer I tear test, and CFS scores with proptosis and MRD1 for the study group (N=40).

-	-	TBUT	Schirmer	CFS	OSDI
Proptosis	PC	-0.615	-0.598	0.609	0.592
-	Sig	<0.001	<0.001	<0.001	<0.001
MRD1	PC	-0.586	-0.512	0.377	0.435
-	Sig	<0.001	0.01	0.017	0.005
CAS	PC	-0.879	-0.911	0.753	0.872
-	Sig	<0.001	<0.001	<0.001	<0.001

Abbreviations: PC, Pearson correlation coefficient; Sig., significance (two-tailed).

By calculating the Clinical Activity Score (CAS), we divided mild GO patients into 2 groups. CAS scores ≥ 3 correlated with disease activity and the inactive group correlated with CAS scores <3 [12]. The mean±SD scores for the TBUT and Schirmer I tear tests and the median scores for the OSDI and CFS for both active and inactive GO patients are shown in Table **3**. All scores showed significant (p<0.001) differences between active and inactive GO patients. Dry eye was present in 85.7% of active mild GO patients (12/14), higher than the inactive group (85.7% *vs*. 53.8%, p< 0.001, OR = 5.14).

4. DISCUSSION

Dry Eye Syndrome (DES) is a common disease of the ocular surface with complex etiology. The disease can cause much discomfort to the patient [1]. In recent years, more and more studies have shown a relationship between dry eye syndrome and autoimmune diseases, especially GO [3, 13].

Our study showed 65% of eyes with mild GO to present dry eye syndrome. The rate of dry eye in the mild-stage GO patients was 3.98 times higher than in the control group. All dry eye indices were different from the control group. Dry eye syndrome is diagnosed on the basis of reduced tear film break-up time <10 seconds, a reduced Schirmer I test result ≤10mm after 5 minutes, and positive ocular surface irritation. This result has been found to be similar to many studies showing the proportion of patients with GO and dry eyes to be relatively large [14, 15]. In the complex clinical situation of GO, damage to the ocular surface, mainly dry eye, is not

Table 3. Average [mean±standard deviation or median (interquartile range)] OSDI, TBUT, Schirmer I tear test, and CFS scores, as well as thyroid function, TSH (Thyroid Stimulating Hormone), fT4 (thyroxine-free), and TRAb (TSH Receptor Autoantibodies) within active and inactive GO patients.

-	Active (n=14) (CAS ≥ 3)	Inactive (n=26) (CAS < 3)
OSDI*	31(15)	11.5 (7)
TBUT (sec)*	3.5 ± 2.35	10.81 ± 4.34
Schirmer I tear test (mm)*	4 .71 ± 1.77	9.69 ± 1.62
CFS*	12 (10)	4 (2)
Thyroid function	100% hyperthyroid	53.8% hyperthyroid (14/26) 46.2% euthyroid (12/26)
TSH (µUI/mL)*	0.11 ±0.12	0.97 ±1.47
fT4 (pmol/L)*	33.2 ±20.92	29.56 ±23.56
TRAb (UI/ml)*	16.45 ±12.34	11.58 ±11.12

Note: *: p-value < 0.05: statistically significant result.

given enough attention, but this is the damage seen in the majority of patients. Dry eye is also a lesion that causes discomfort and complaints in many GO patients, so correctly determining the dry eye condition is one of the important assessments for GO patients. In our study, the prevalence of dry eyes was lower than in some studies. This may be due to differences in patient selection. In other studies, the authors have evaluated dry eye status in groups of patients with all stages of GO, or patients with moderate-to-severe stages, while our study has only selected patients with mild GO. These mild GO patients had less proptosis and less eyelid retraction, so the prevalence of evaporative dry eye was reduced. Villani *et al*. also concluded the number and morphology of corneal epithelial cells in patients with GO to be more damaged than in controls [16].

Dry eye is a common lesion in patients with GO, but its pathogenesis remains unclear. Most authors believe that in patients with GO disease, dry eyes are mainly due to increased evaporation and inflammation on the ocular surface. In GO patients, the enlargement of the extraocular muscles and orbital tissues leads to proptosis. Contracture of the upper eyelid levator muscle complex due to inflammation and fibrosis is thought to be the cause of upper eyelid contracture. Upper eyelid retraction and exophthalmos increase the distance between the upper and lower eyelids, leading to increased contact area of the tear film with the environment. Dry eye due to increased evaporation in GO patients is also explained by insufficient oil in the tear layer. Meibomian glands located in the tarsal plate secrete the lipid layer of the tear film, helping to prevent too rapid evaporation of the tear film. Meibomian Gland Dysfunction (MGD) is a common cause of evaporative dry eyes. Inoue and colleagues conducted a study on dry eye status in 19 GO patients and compared them with a control group; the authors found a high proportion (84.2%) of patients diagnosed with DES [17]. More surprisingly, all patients in this study presented with obstructive MGD. This rate was higher than the rate of DES patients. The study also showed that patients presented with blepharitis and lid margin telangiectasia as well as thickening of the levator muscle, and in some patients, meibomian gland changes occurred in the central region of the eyelid, based on imaging of the meibomian gland. TBUT, vasculitis, dry eye-related quality-of-life score, and meibo-score (sum of upper and lower eyelid scores) in GO patients were significantly worse than controls. Many authors have reported that patients with GO exhibit morphological changes in the meibomian glands, correlating with proptosis and increased cleft height. The authors have attributed the decrease in the frequency of eye blinking due to proptosis and eyelid cleft height in GO patients to decreased secretion of meibomian glands, giving rise to obstructive MGD [18]. Other studies have reported oxidative stress to be associated with GO and that oxidative stress leads to changes in meibomian glands and meibum composition [19, 20]. In this study, we have evaluated the correlation of proptosis, upper eyelid retraction, and inflammation with the index of ocular surface damage. Research results have shown these indices to all be closely and linearly correlated with proptosis, upper eyelid retraction, and inflammation with $p<0.05$ and correlation coefficient $R > 0.5$. This result has been found to be similar to the study of Selter and Takahashi, which showed a high rate of patients with TBUT < 10 seconds and corneal damage in the group of patients with proptosis and upper eyelid retraction [21, 22]. Gürdal and colleagues also found a significant increase in the concentration of inflammatory substances at the ocular surface in GO patients with dry eyes [23]. The results of our study also showed that the Schirmer I test also positively correlated with proptosis and upper eyelid retraction. Allam and colleagues, when studying 40 patients with GO, also reached a similar conclusion [24]. This was explained by damage to the lacrimal gland due to the appearance of TSH-R receptors in GO patients. OSDI score and CAS have shown a strong linear correlation, suggesting GO activity status to affect the subjective symptoms of dry eye. However, patients with active inflammatory GO have been reported to have swelling on the eyelids, conjunctiva, and caruncle/plica, which may affect the question of roughness in the OSDI score.

GO is an autoimmune inflammatory disease caused by the appearance of autoantibodies. The main pathogenesis of GO is an internal inflammatory reaction that alters the orbital tissues, leading to a series of clinical manifestations. Changes in the ocular surface of patients with GO may be due to the inflammatory response of the lacrimal gland itself. There is much evidence showing the appearance of inflammatory mediators, such as interleukin, in the tear film layer as well. This may be secondary to the occurrence of other lesions, such as proptosis or eyelid retraction. In this study, we divided patients into two groups of active and inactive based on CAS score to compare changes in the ocular surface in the two groups. There was a statistically significant difference found between the two groups with $p < 0.05$. All the patients in the inflammatory group were hyperthyroid while nearly half of the non-inflammatory group was euthyroid. Consequently, there was a statistically significant difference between the two groups' thyroid function test values. In the active group, OSDI symptoms and corneal fluorescein staining were both statistically significantly greater than in the inactive group. The TBUT and tear secretion in the active group when compared to the inactive group were statistically significantly lower. The incidence of dry eyes in the active group was 5.14 times higher than that in the inactive group. Therefore, the rate of dry eyes has been found to be five times higher in patients having more than three clinical signs, such as pain, eyelid swelling or redness, conjunctival injection, chemosis, or inflammation of the caruncle/plica, than those having none or fewer of the above symptoms. Allam's research also showed similar results when the ocular surface damage indices were found to be different between the active and inactive groups, being different from the control group [24]. Increased proptosis and more eyelid retraction in the active group were considered to explain the increase in functional symptoms at the ocular surface as well as premature tear film breakdown. The goblet cells secrete mucus, which forms a gel layer on the ocular surface that binds with water to help maintain the stability of the tear film. In GO patients, there is a decrease in both membrane binding and mucus secretion due to inflammation leading to evaporative dry eye and, therefore, other ocular surface parameters, including tear film breakdown time. Lower Schirmer I tear secretion can be explained by the presence of proptosis and upper eyelid retraction. Furthermore, impaired tear secretion through lacrimal gland failure due to autoantibodies attacking the Thyroid-stimulating Hormone Receptor (TSH-R) found in the lacrimal gland contributes to reduced reflex tear secretion in GO patients. Inflammation of the ocular surface may increase the severity of dry eye in GO patients. The previous conception was that dry eyes are only caused by reduced tear secretion or an unstable tear film [2]. Many studies today have better understood the pathogenesis of dry eyes. In addition to the above two causes, changes in the ocular surface can lead to an imbalance between the components of the tear film layer, causing changes in the dynamics of the tear film layer. Inflammation at the ocular surface can alter cytokines and chemokines, leading to damage to corneal and conjunctival cells [25]. High concentrations of inflammatory substances, such as IL-1beta, IL-6, IL-8, and TNF alpha levels, in the tear film increase tear osmolarity [26].

The degree of dye staining on the cornea is evidence of damage to the ocular surface, a common sign in GO patients. In our study, the level of dye staining on the cornea in the active group was statistically significantly higher than that in the inactive group. Allam also found the level of dye staining in the active group to be higher than that in the control group [24]. This suggests that the degree of damage at the ocular surface is related to the activity of the orbit in patients with GO.

CONCLUSION

Dry eyes have been found to be common lesions in mild GO patients at a rate of 65%, being 3.98 times higher than the control group. Inflammation is a key factor in dry eye in mild GO patients. The group of patients with active GO had symptoms of more severe ocular surface damage (5.14 times higher) than the group without inflammation.

AUTHORS' CONTRIBUTIONS

It is hereby acknowledged that all authors have accepted responsibility for the manuscript's content and consented to its submission. They have meticulously reviewed all results and unanimously approved the final version of the manuscript.

LIST OF ABBREVIATIONS

GO	=	Graves' Ophthalmopathy
OSDI	=	Ocular Surface Disease Index
TBUT	=	Tear Break-up Time
CFS	=	Corneal Fluorescein Staining
MRD1	=	Margin-to-reflex Distance 1
CAS	=	Clinical Activity Score

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This cross-sectional study was approved by the ethics committee at Hanoi Medical University, Vietnam (IRB - VN01.001/IRB00003121).

HUMAN AND ANIMAL RIGHTS

All procedures performed involving human participants were in accordance with the ethical standards of institutional and/or research committee, and with the 1975 Declaration of Helsinki, as revised in 2013.

CONSENT FOR PUBLICATION

Informed consent was obtained from all participants of this study.

STANDARDS OF REPORTING

STROBE guidelines were followed.

AVAILABILITY OF DATA AND MATERIALS

he data supporting the findings of the article is available in the DryeyeGO at https://drive.google.com/file/d/12zKU6yh3ZpGtCmzTlJt1FFmh82IsuJ_J/view?usp=drive_link.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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