Dry eye evaluation in thyroid associated orbitopathy

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Abstract

Introduction: Many systemic autoimmune diseases are associated with dry eye; the autoimmune thyroid diseases are among them. One of the leading causes of ocular surface damage in thyroid associated orbitopathy (TAO) is dry eye syndrome (DES).

Aim: To evaluate the incidence and risk factors of dry eye and associated conjunctival morphological changes in TAO.

Materials and Methods: This is a cross sectional, non-interventional, non-comparative, observational study includes thirty patients (60 eyes) of clinically diagnosed TAO. The tear film and ocular surface were evaluated using the Schirmer- I test, Tear film break-up time (TBUT), Lissamine green staining and conjunctival impression cytology.

Results: Dry eye were found in 35 (58%) eyes based on dry eye severity grading **s**cheme (DEWS). Positive vital staining with Lissamine green was observed in 36 (60.0%) eyes. The average degree of staining was 4.28±3.81 (National Eye Institute Workshop grading system). The abnormal impression cytology was observed in 30 eyes (50.0%) of 18 patients. Impression cytology revealed the following changes: significant epithelial dystrophy with cell polymorphism, goblet cells deficiency or absence, excessive desquamation and epithelial keratinization with local leukocytic infiltration.

Conclusion: Significant risk factors of ocular surface damage in TAO were exophthalmos, palpebral fissure height, upper lid retraction, lower lid retraction and lagophthalmos. Histopathologic changes detected in conjunctiva are consistent with dry eye but were not specific for TAO.

Keywords: Dry Eye **S**yndrome, Impression cytology, Lissamine Green staining**,** Thyroid Associated Orbitopathy

Introduction

Dry eyeis one of the most frequently encountered ocular morbidities, a growing public health problem and one of the most common conditions seen by eye care practitioners.[1] Many systemic autoimmune diseases are associated with dry eye. Thyroid associated **o**rbitopathy (TAO), is a common autoimmune disease which is often associated with Dry **e**ye **s**yndrome (DES). Thyroid disease itself is a common condition, affecting approximately 1.5% of the adult population.[2] It is the most frequent cause of ocular discomfort in TAO patients.[3]

The incidence of DES in Thyroid associated orbitopathy (TAO) patients varies between 45% and 85% according to studies in the past.[3,4] Although the etiopathogenesis of dry eye in TAO remains unclear, previous studies have indicated that exophthalmos, palpebral fissure height widening, lagophthalmos, reduced tear production and accelerated tear film evaporation may contribute to the symptoms of dry eye.[5-8] Thyroid associated orbitopathy (TAO) constitutes a major clinical and therapeutic challenge.[9,10] The classic findings of TAO include eyelid retraction, lagophthalmos, exophthalmos, dysmotility and diplopia. However, some patients with TAO will have a more subtle presentation of ocular surface irritation and inflammation with injection and chemosis particularly overlying the rectus muscles. Although these later findings are well established, they are often overlooked, and therefore diagnosis of TAO may be delayed until the more classic features manifest leading to further ocular surface damage.

Thus the goal of our study was to evaluate the incidence and risk factors of dry eye and associated conjunctival morphological changes in TAO.

Material and Methods

This is a prospective, cross sectional, non-interventional, non- comparative study undertaken in 60 eyes of 30 patients of TAO, attending the ophthalmic plastic surgery clinic and-endocrinology clinic of a tertiary care hospital from January 2014 to November 2015. Patients included in the study were with clinical diagnosis of TAO and clinical activity score (CAS)$\geq$3/7[11,12] while patient unable to give consent or are unable to understand the requirement of the study, patients with other causes of dry eye, any recent ocular surgery, CAS $\leq$ 2/7 and hypersensitivity to lissamine green dye and fluorescein dye were excluded from this study.

The study was approved from the institutional ethical committee and was according to the declaration of Helsinki. Valid consent (informed consent) was taken from each of the patient after explaining them the procedure in detail before their inclusion in the study.

All patients included in this study underwent a detailed clinical evaluation for thyroid orbitopathy and dry eye syndrome evaluation based on Dry Eye Severity Grading Scheme (DEWS)[13] Detailed history and a comprehensive ophthalmological examination

was done which mainly includes Hertel Exophthalmometry, palpebral fissure height measurements, lagophthalmos, MRD1, MRD2, Schirmer test I, TBUT, Vital staining (using lissamine green) and Impression cytology.

Vital staining was performed using lissamine green. The degree of ocular surface damage was estimated according to National Eye Institute Workshop grading system.[14] In each eye the nasal and temporal bulbar conjunctiva is divided into 3 areas. The amount of staining in each area is graded on a scale of 0 to 3 according to the intensity of lissamine green staining. The maximum grading score is 18 for each eye with values of more than 3 being abnormal.

Conjunctival morphological changes were seen using impression cytology which was performed using millipore filter paper, pore size 45 micron (Sartorious Stedim Biotech, Germany) in each eye of the patients. It was gently pressed on the temporal inter-palpebral bulbar conjunctiva and strip was then removed with a peeling motion after 5 seconds, fixed with methyl alcohol and stain with Giemsa. Grading of cytology done according to Nelson's grading system.[15] The features evaluated from an impression cytology specimen included: area of epithelial cells, shape round or polygonal, size small or large, degree of squamous metaplasia and nucleus/cytoplasm ratio, goblet cells-density, shape, non-epithelial cells- inflammatory cells and microorganism.

Statistical analysis was performed using SPSS version 20 (Armonk, NY, IBM Corp., U.S.A.). The Pearson's correlation coefficient (r) and p-value were calculated to assess the risk factors associated with conjunctival changes in TAO. A p-value < 0.05 was considered statistically significant.

Results

There were 17(57.0%) female and 13(43.0%) male included in this study. The mean age of the patients was 35.9±13.75 years, 88.5% had symmetrical and 11.5% had asymmetrical TAO. The mean Schirmer test was 16.73±4.8 mm (range 5-24) (Table 1).

Table 1: Showing clinical descriptive data

		Minimum	Maximum	Mean	Std. Deviation
AGE	30	18	60	35.77	13.16
PROPTOSIS	60	16	30	20.85	3.26
PFH	60	10	20	12.70	2.50
MRD1	60	4	10	5.62	1.74
MRD2	60	5	10	7.05	1.14
LAGOPHTHALMOS	60	0	5	0.65	1.20
SCHIRMER	60	5	24	16.73	4.8
TBUT	60	3	16	9.85	3.27
LISSAMINE GREEN	60	0	14	4.28	3.81
IMPRESSION CYTOLOGY	60	0	3	1.42	1.10

The abnormal Schirmer test was observed in 12 eyes (20.0%), out of which mild dry eye was seen in 5 (8.33%), moderate dry eye was present in 1(0.66%) and severe dryness was found in 6 (10.0%) eyes. Schirmer test have statistically significant positive correlations with exophthalmos, upper eyelid retraction and lagophthalmos. (p value< 0.05) No statistically significant correlation was found with age, palpabral fissure height and lower eyelid retraction. (p value>0.05) (Table 2)

Table 2: Showing correlation of various Tests of Dry Eye

	Schirmer test I	P value	Tear Film Breakup Time	P value	Lissamine Green Stain	P value	Impression cytology	P value
Age	0.269	>0.151	-0.097	>0.611	-0.12	>0.576	-0.182	>0.336
Proptosis	0.302	<0.019	0.667	<0.001	0.692	<0.001	0.733	<0.001
PFH	0.205	>0.116	0.413	<0.001	0.776	<0.001	0.681	<0.001
MRD1	0.264	<0.042	0.605	<0.001	0.661	<0.001	0.673	<0.001
MRD2	0.238	>0.067	0.583	<0.001	0.752	<0.001	0.583	<0.001
Lagophthalmos	0.500	<0.001	0.528	<0.001	0.459	<0.001	0.529	<0.001

The mean TBUT observed was 9.85±3.27 seconds (range 3-16) (Table 1). The abnormal TBUT was observed in 30 eyes (50.0%) of 19 patients, out of which mild dry eye was seen in 15 (25.0%), moderate dry eye in 9 (15.0%) and severe dry eye in 6 (10.0%) eyes. TBUT had statistically significant positive correlations with exophthalmos,

palpebral fissure height, upper lid retraction, lower lid retraction and lagophthalmos(p value< 0.05) No significant correlation was found with age. (Table 2)

Positive vital staining with Lissamine green was observed in 36 (60.0%). eyes (Fig.1)

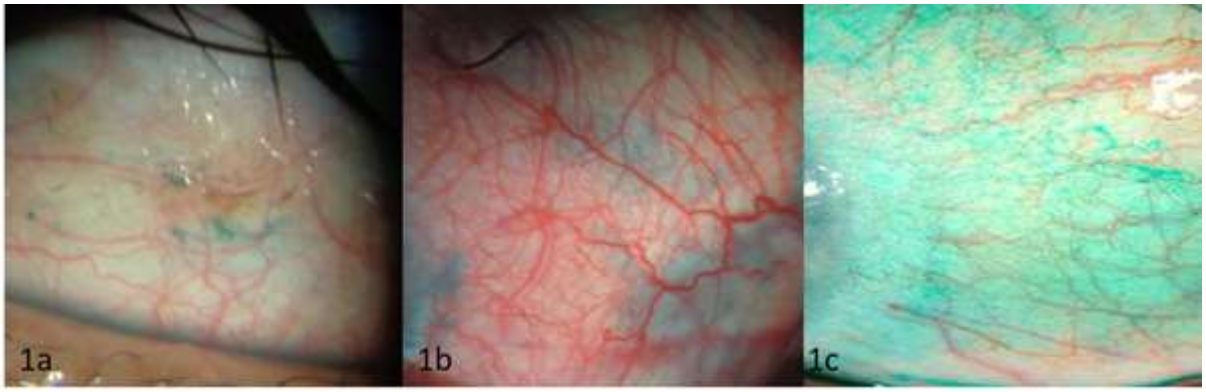

Fig. 1a showing grade 1, 1b grade 2 and 1c grade 3 of Lissamine green staining

The average degree of staining was 4.28±3.81 (range 0-14) (Table 1). In 8 eyes (13.33%) severe dryness was found with degree of staining exceeding 12. Conjunctival vital staining with lissamine green have statistically significant positive correlations with exophthalmos, lagophthalmos, palpebral fissure height, upper lid retraction and lower lid retraction. No correlation was found with age. (Table 2)

The mean impression cytology in all eyes was 1.42±1.1 (range 0-3) (Table 1). The abnormal impression cytology was observed in 30 eyes (50.0%) of 18 patients. Mild dry eye was found in 10 (16.66%), moderate dry eye was seen in 12 (20.0%) and severe dry eye was present in 8(13.33%) eyes. Impression cytology have statistically significant positive correlations with exophthalmos, palpebral fissure height, upper lid retraction, lower lid retraction, lagophthalmos and schirmer test. No correlation was found with age. (Table 2)

Impression cytology revealed the following changes: significant epithelial dystrophy with cell polymorphism, goblet cells deficiency or absence, excessive desquamation and epithelial keratinization with local leukocytic infiltration. (Fig. 2)

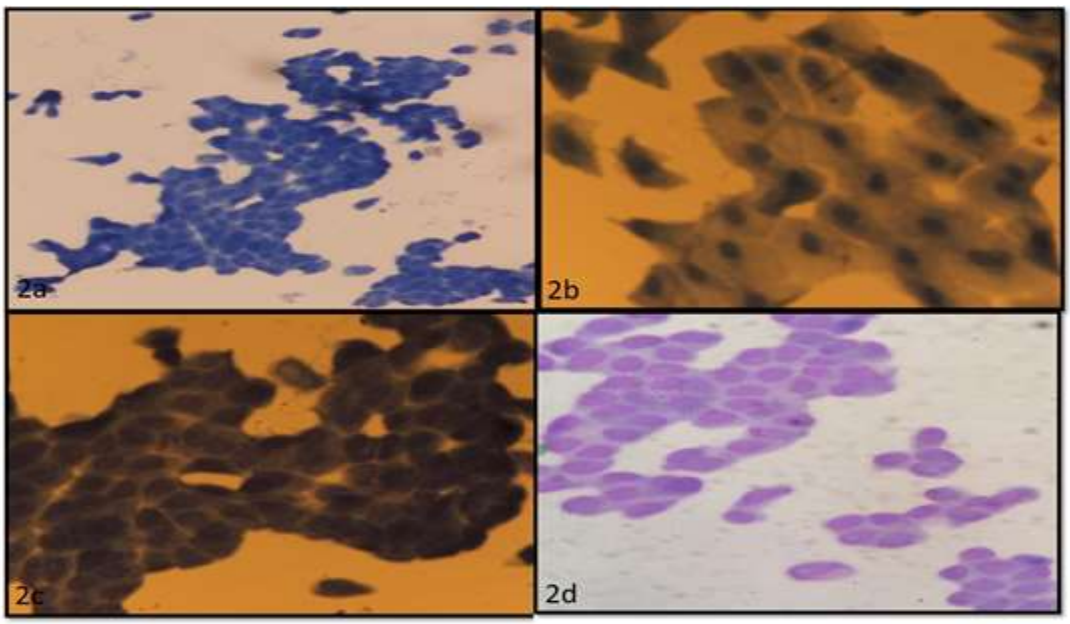

Fig. (2a): showing Grade 0, (2b): Grade 1, (2c): Grade 2 and (2d): Grade 3 of Impression cytology (Nelson's grading system)

In our study dry eye were found in 35 (58%) eyes out of 60 eyes based on Dry Eye Severity Grading Scheme (DEWS). Out of 60 eyes, 10 eyes (20.0%) had severe dry eye, 8 eyes (13.33%) had moderate dry eye, 17 eyes (28.33%) had mild dry eye and 25 eyes (42.66%) had no dry eye.

Discussion

Thyroid associated orbitopathy (TAO), is a disease often associated with Dry eye syndrome (DES) that is the most frequent cause of ocular discomfort in TAO patients. Various studies were performed in different population to find out correlation of dry eye with TAO and have provided some valuable information regarding prevalence of dry eye in TAO. This study was also based on the idea to study the incidence, risk factors of dry eye and ocular surface damage in TAO.

In our study 58.0% of eyes (70.0% of patients) were found to have dry eye, this corresponds with incidence reported by other authors.[3] The data of risk factor for ocular surface changes which we had come up with is different from other authors. Gilbard and Farrisdid not find any correlation of ocular surface damage with exophthalmos, upper lid lag or tear production, but found palpebral fissure height to be the only associated factor in their study.[6] The similar results were obtained by Brasil et al showed that patients with TED regardless of disease duration have more intensive conjunctival vital staining compared to control group and there is no difference in tear film pH, fluorescein staining and Schirmer test results.[16] Jae Ryun Kim et al found the risk factors for dry eye disease were palpebral fissure width and lagophthalmos.[17] Dilyara S. Ismailova et al found significant risk factors of ocular surface damage in TAO were exophthalmos, lagophthalmos, palpebral fissure height and lower lid retraction.[18] While in our study ocular surface damage correlated with degree of exophthalmos (<0.001), lagophthalmos (<0.001), palpebral fissure height (<0.001), upper eye lid retraction (<0.001) and lower eye lid retraction (<0.001). In our opinion these results show that ocular surface exposure does play a critical role in pathogenesis of ocular surface damage in TAO patients irrespectively of changes in tear production Ecksteinet al found that ocular surface damage during the active stage of TED associated with reduction of tear production, hypothesized to result from lacrimal gland involvement.[5] In our study patients with TAO have significantly lower Schirmer tests (16.73±4.8 mm), suggesting inadequate tear production and this corresponds with incidence reported by other authors.[3] Schirmer test have statistically significant positive correlations with exophthalmos (p <0.001), upper eyelid retraction (p <0.04) and lagophthalmos (p <0.001) in our study.

In the present study the TBUT in TAO patients was 9.85±3.27sec, significantly lower than normal, this corresponds with incidence reported by other authors suggesting an unstable tear film.[4,5] Brasil et al found that in TAO patients' palpebral fissure height correlates with their TBUT.[16] They showed that those patients with a wider palpebral fissure are more likely to have a shorter tear film breakup time, which leads to tear film instability. In our study, TBUT have statistically significant positive correlations with exophthalmos (p<0.001), palpebral fissure height (p<0.001), upper lid retraction (p<0.001), lower lid retraction (p<0.001) and lagophthalmos (p<0.001).

In our study 60.0% of eyes (70.0% of patients) were found to have positive conjunctival vital staining, this corresponds with incidence reported by other authors.[3] Lissamine green staining show significantly more ocular damage in patients with TAO with mean degree of staining of 4.28±3.81. Lissamine green too have statistically significant positive correlations with exophthalmos (p <0.001), lagophthalmos (p <0.001), palpebral fissure height (p <0.001), upper lid retraction (p <0.001) and lower lid retraction (p <0.001).

Impression cytology is an important option for the diagnosis of dry eye. The abnormal impression cytology was observed in 30 eyes (50.0%) of 18 patients (60.0%). This corresponds with incidence reported by other authors.[19] Impression cytology has statistically significant positive correlations with exophthalmos, palpebral fissure height, upper lid retraction, lower lid retraction, lagophthalmos and Schirmer test. This method has a number of advantages such as easy reproducibility, and is a non-invasive test. It allows the study of the ocular surface, especially the most superficial and desquamated conjunctival cells.

Three types of cells may be found in impression cytology: epithelial, inflammatory and goblet cells. Goblet cells deficiency and keratinization of epithelium are characteristic for dry eye syndrome. In the past too, we have found few studies devoted to morphological changes of bulbar conjunctiva in TED. Weiatel in their study on impression cytology of the conjunctival epithelium revealed decrease in goblet cells and significantly higher degree of squamous metaplasia in the TAO group.[19] It has positive correlation with MRD1, representing the severity of upper eyelid retraction, may play an important role in predicting the ocular surface changes in GO patients. While Dilyara et al in their study showed epithelial dystrophy with cell polymorphism, goblet cells deficiency, excessive desquamation and epithelial keratinization with local leukocytic infiltration which were also seen in our study.[18] These features characterize structural changes of conjunctiva typical to dry eye and is not specific for any particular disease.

Incisional biopsy of the area of stained bulbar conjunctiva was also performed to study the epithelium in above mentioned study, which only confirm the finding of impression cytology and did not reveal any further diagnostic morphological changes. Conjunctival biopsy being an invasive procedure and not adding anything further in the literature was excluded from our study. Thus, in our study dry eye syndrome was present in 70.0% of patients (58.0% of eyes) with TAO. Significant risk factors of ocular surface damage in TAO were exophthalmos, palpebral fissure height, upper lid retraction, lower lid retraction and lagophthalmos. Histopathologic changes detected in

conjunctiva are consistent with dry eye and are not specific for TAO.

References

1. O'Brien PD, Collum LM. Dry eye: Diagnosis and current treatment strategies. Curr Allergy Asthma Rep 2004;4:314-9.
2. Caturegli P, Kimura H, Rocchi R, et al. Autoimmune thyroid diseases. Curr Opin Rheumatol 2007;19:44–48.
3. Gürdal C, Saraç O, Genç I, Kırımlıoğlu H, Takmaz T, Can I. Ocular surface and dry eye in Graves' disease. *Curr Eye Res*. 2011;36(1):8–13.
4. Nowak M, Marek B, Kos-Kudla B, et al. Tear film profile in patients with active thyroid orbitopathy. Klin Oczna. 2005;107:479–482.
5. Eckstein AK, Finkenrath A, Heiligenhaus A, et al. Dry eye syndrome in thyroid-associated ophthalmopathy: lacrimal expression of TSH receptor-specific autoantibodies. Acta Ophthalmol Scand 2004;82:291–297.
6. Gilbard JP, Farris RL. Ocular surface drying and ocular tear film osmolarity in thyroid eye disease. Acta Ophthalmol (Copenh) 1983;61:108–116.
7. Khalil HA, De Keizer RJ, Kiljstra A. Secretory IgA and Lysozyme in tears of patients with Graves'ophthalmopathy.Doc Ophthalmol1989;72:329–334.
8. Khurana AK, Sunder S, Ahluwalia BK, Malhotra KC. Tear film profile in Grave's ophthalmopathy. Acta Ophthalmol (Copenh) 1992;70:346–349.
9. Wiersinga WM, Perros P, Kahaly GJ, Mourits MP, Baldeschi L, Boboridis K, Boschi A, Dickinson AJ, Kendall-Taylor P, Krassas GE, Lane CM, Lazarus JH, Marcocci C, Marino` M, Neoh C, Orgiazzi J, Pinchera A, Pitz S, Prummel MF, Sartini MS, Stahl M & von Arx G. Clinical assessment of patients with Graves' orbitopathy: the European Group on Graves' Orbitopathy recommendations to generalists, specialists and clinical researchers. European Journal of Endocrinology 2006; 155;387–389.
10. Perros P, Baldeschi L, Boboridis K, Dickinson AJ, Hullo A, Kahaly GJ, Kendall-Taylor P, Krassas GE, Lane CM, Lazarus JH, Marcocci C, Marino` M, Mourits MP, Nardi M, Orgiazzi J, Pinchera A, Pitz S, Prummel MF & Wiersinga WM. A questionnaire survey on the management of Graves' orbitopathy in Europe. European Journal of Endocrinology 2006;155:207–211.
11. Mourits MP, Koornneef L, Wiersinga WM, Prummel MF, Berghout A & van der Gaag R. Clinical criteria for the assessment of disease activity in Graves' ophthalmopathy: a novel approach. British Journal of Ophthalmology, 1989;73:639–644.
12. Mourits MP, Prummel MF, Wiersinga WM & Koornneef L. Clinical activity score as a guide in the management of patients with Graves' ophthalmopathy. Clinical Endocrinology, 1997;479–14.
13. The definition and classification of dry eye disease: report of the Definition and classification Subcommittee of the International Dry Eye Workshop. Ocul Surf 2007:5:88.
14. Lamp MA. Report of the National Eye Institute/Industry workshop on Clinical Trials in Dry Eyes. CLAO J;1995;21:221–232.
15. Nelson DJ, Havener VR, Cameron JD. Cellulose acetate impressions of the ocular surface: dry eye states. Arch Ophthalmol,1983;101:1869-1872.
16. Brasil MV, Brasil OF, Vieira RP, et al. Tear film analysis and its relation with palpebral fissure height and exophthalmos in Graves' ophthalmopathy. Arq Bras Of talmol 2005;68:615–618.
17. Jae Ryun Kim et al, Risk Factors for Dry Eye in Thyroid-Associated Ophthalmopathy J Korean Ophthalmol Soc. 2011 Jul;52(7):771-776.
18. Dilyara S. Ismail ova et al. Ocular Surface Changes in Thyroid Eye Disease, Orbit, 2013;32(2):87–90.
19. Wei YH, Chen WL, Hu FR, Liao SL. In vivo confocal microscopy of bulbar conjunctiva in patients with Graves' ophthalmopathy. J Formos Med Assoc. 2015;114(10):965-72.