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Presence of Inflammatory Dry Eye in Patients with Thyroid Disorders

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I. Introdution

According to the Dry Eye Work Shop (DEWS) definition, dry eye is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance and tears film instability, with potential damage to the ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface. [1]

Confirmation of the presence of inflammatory dry eye is helpful for initiation of appropriate therapy. Anti-inflammatory therapy has been reported to improve signs and symptoms of ocular surface disease and therefore is a more targeted and effective therapeutic option.[2,3]Often patients receive treatment only with artificial tears without consideration of the cause of the symptoms or the potential effectiveness of other treatments.Increased MMP-9 expression is one of the markers to diagnose inflammatory dry eye.[4]

Thyroid associated ophthalmopathy (TAO) is common in patients suffering from Graves' disease (80%), but it is not unusual in hypothyroid patients. Studies have shown that 45–85% of the TAO patients have dry eye syndrome. [5]

Two main types of dry eye are known, which are, namely, aqueous tear-deficient dry eye and evaporative dry eye. Aqueous tear-deficient dry eye is caused due to diseases of lacrimal gland while evaporative dry eye is due to disorders in the meibomian glands and lids. Thyroid disorders are known to cause DED by various mechanisms including the widening of palpebral fissure; exophthalmos, tear production deficiency, tear evaporation and inflammation.[6,7,8]

This study aimed at assessing the presence of DED by means of the OSDI Score, Schirmers test and TBUT in patients with thyroid disorders and compare it with that in healthy subjects. In addition, presence of inflammatory dry eye was assessed by means of MMP-9 in both groups. This would aid in treatment of inflammatory dry eye with appropriate anti-inflammatory therapy.

II. Materials And Methods

Patients were divided into following two groups.
Group 1: Thirty patients attending endocrine OPD of a tertiary care centre and diagnosed to be having hypo/hyperthyroidism.

Group 2: Thirty patients attending eye OPD of a tertiary care centre for cataract surgery. The patients had no ocular complaints besides diminution of vision and had been referred for cataract surgery.

The following tests were conducted on all patients in both groups.
1. Dry eye symptoms based Ocular Surface Disease Index (OSDI) questionnaire
2. Schirmer test
3. Tear break up time (TBUT)
4. Rapid diagnostic kit to assess MMP-9 level (Matrix Metalloproteinase-9)

It is a cross sectional study. After taking Institutional ethical clearance study was conducted at the Eye Out-Patient Department of a tertiary care centre on 30 subjects in each group. Patients were enrolled between Jan 2019- Jun2019.The data were tabulated using Excel (Microsoft™ Office 2010, Microsoft Corp., Redmond, USA) and was analyzed using the SPSS® statistical package, version 22.0 (SPSS Inc., Chicago, IL, USA) for Windows®.
The inclusion criteria were as under:

Group 1
1. Patients reporting to endocrine OPDfor evaluation of thyroid associated disorders.
2. Newly diagnosed with hypothyroidism/hyperthyroidism, based on the serum thyroid-stimulating hormone (TSH) and free thyroxine (T4) levels.
3. Age 35-80 years.
4. No ocular complaints.
5. No signs of exophthalmos, lid lag, lid retraction.
6. No findings of extraocular muscle enlargement on CT scan.

Group 2
1. Patients attending eye OPD of a tertiary care centre for cataract surgery.
2. No ocular complaints besides diminution of vision
3. Age 35-80 years

The exclusion criteria were as under:
1. Patients suffering from systemic conditions known to cause dry eyes and already on treatment
2. Recent history of ocular injury, contact lens use or ocular surgery
3. Chronic inflammatory or infectious disease.
4. Patients using topical or systemic medications known to suppress MMP-9.
5. Patients lost to follow up

All patients were evaluated at baseline with the following tests.

OSDI - Detailed history of onset and symptoms was taken based on Ocular surface disease index.The OSDI is a global assessment measure consisting of 12 questions, each scored by the patient. The test is self-administered. The 12 items are graded on a scale of 0 to 4. The OSDI score = [(sum of the scores for all questions answered x 100]/[(total number of questions answered) x4]. Thus scale is from 1 to 100. The OSDI scores range from 0 (no disability) to 100 (complete disability).

SCHIRMER TEST- A Schirmer test was performed by placing Schirmer test strips over the lower eyelid margin, at the junction of the lateral and middle thirds, for 5 minutes. The strip wetting was measured and recorded in millimeters.A score of < 5mm in 5 minutes (without anesthesia) is an indicator of severe dry eye.

FLUORESCEIN TEAR BREAK-UP TIME (TBUT)- The TBUT was evaluated 2 minutes after the inferotemporalbulbar conjunctiva was touched with a sodium fluorescein strip.Participants were instructed to blink, and the precorneal tear film was examined under blue-light illumination with a biomicroscope and 10X magnification. The interval between the blink and the appearance of the first dark spot or discontinuity in the precorneal fluorescein-stained tear layer was then recorded. TBUT value of < 10 seconds is considered to be abnormal.

MMP-9 LEVEL IN TEAR SAMPLE - The test was performed using rapid detection kit. It uses direct sampling microfiltration technology. Two antigen-specific antibodies captureMMP-9 antigens in the sample, and this complex is captured in a proprietary mode at the test result line, giving rise to a visually observable signal. The intensity of the visual test result line correlates with the amount of MMP-9 in the sample. The test is rapid, requiring only 10 minutes for a result.

The kit consists of 2 parts: a sterile sample collector and an immunoassay test strip in plastic test cassette housing. After the sample collector is used to collect the tear fluid, it is assembled to the test cassette. The test is initiated when the absorbent pad of the test strip is dipped into a buffer solution. After 10 minutes, the result is visible in a readout window. The presence of 1 blue line (control line) indicates a negative (MMP-9<40 ng/mL) result,whereas 2 lines (blue control line and red) confirms inflammation (MMP-9>40ng/ml)..

Data was tabulated on excel sheet, studied and subjected to statistical analysis.

III. Results

GROUP 1- The mean age was 40.31 years ± 13.26 years (range 35-64 years). 26 patients were females (86.67%) and 4 males (13.33%). The mean baseline OSDI score was 44.73± 18.09(range 10.4-83.3). The mean baseline Schirmer's value was 6.70±4.16mm (range 2-25mm). The mean TBUT was 6.44±2.44seconds (range 1-12 seconds. The MMP 9 was positive in 16 patients (53.3%). 25 patients were hypothyroid (83.33%) and 5 patients were hyperthyroid (16.67%). Table 1

GROUP 2- The mean age was 55.77 years ±13.5 years (range 35-86 years). 17 patients were females (56.66%) and 13 were males (43.33%). The mean baseline OSDI score was 24.99±20.40 (range 10.4-72.9). The mean baseline Schirmer's value was 10.08± 4.87mm (range 4-24mm). The mean TBUT was 10± 2.03 seconds (range 6-14 seconds). The MMP 9 was positive in 16 patients (53.3%).

In Group1, 26 patients had dry eye (86.67%). In Group 2, 13 patients had dry eye (43.33%). This was statistically significant ($p< 0.05$). The MMP-9 results were similar in both groups. However, they were increased significantly in women. The mean Ocular surface disease index score was significantly higher and mean Schirmer and mean Tear break-up time scores were significantly lower in patients with thyroid disorders compared to healthy control subjects. Table 1

Table 1. Characteristics of Group 1 and 2 subjects

	Patients/ Group 1(n=30)	Healthy Subjects/ Group 2(n=30)	P value
Age in years (mean±SD)	40.3 ± 13.26	55.77 ± 13.5	
Sex (F/M)	26/30(86.67%)	17/30(56.66%)	
Thyroid function Hyperthyroid Hypothyroid	 5/30 (16.67%) 25/30 (83.33%)		
OSDI Score(mean±SD)	44.73± 18.09	24.99±20.40	Mann Whitney test 0.0006
Schirmer(mean±SD) in mm	6.70±4.16	10.08± 4.87	Mann Whitney test 0.005
TBUT (mean±SD) in seconds	6.44±2.44	10± 2.03	Two sample t test 0.0000
MMP-9 positive (>40ng/ml)	16/30 (53.3%)	16/30 (53.3%)	No difference
DED (OSDI>12, Schirmer<10, TBUT<10, staining>1)	26/30(86.67%)	13/30 (43.33%)	0.0000

Table 2

Comparison with other studies- data for dry eye parameters in patients with thyroid disorders

Title	Journal	OSDI Score	Schirmer (mm)	TBUT (sec)	MMP9
Dry eye syndrome in thyroid eye disease patients: the role of increased incomplete blinking and meibomian gland loss	Acta Ophthalmologica 2018	Not done	8.3±2.0	4.1±1.9	Not done
Dry eye evaluation in thyroid associated orbitopathy	International Journal of ocular Oncology and Oculoplasty 2016	Not Done	16.73±4.8	9.85±3.27	Not Done
Presence of dry eye in patients with hashimoto's thyroiditis	Journal of Ophthalmology 2014	32.7±19.2	10.9±5.6	10.1±2.6	Not done
Our Study		44.73± 18.09	6.70±4.16	6.44±2.44	16/30 (53.3%)

IV. Discussion

Dry eye syndrome (DES) is a common ocular surface disease and affects10–30 % of the population, especially after 40 years of age.[1]The incidence of DES in thyroid disorders is between 45% to 85% according to various studies.

Various factors may cause the DES in these patients including exophthalmos, increased palpebral fissure height, lid lag, reduced tear production and increased tear film evaporation. These factors together disrupt the ocular surface and cause tear film instability and high tear osmolarity. The ultimate result isinflammation which further increases the dry eye.[9]

In our study 86.67% (26/30) were found to have dry eye. This was a high value compared to that reported by other studies. Table 2 [10,11]The OSDI score for patients with thyroid disorders was high (44.73± 18.09) compared with the score for the control group (24.99±20.40). In our study patients with thyroid disorders had significantly lower Schirmer tests (6.70±4.16mm), suggesting inadequate tear production compared to normal population (10.08± 4.87mm) and this corresponds with findings by other authors.[12]

In the present study the TBUT in Group 1 was6.44±2.44sec, significantly lower than Group 2 (normal), this corresponds with the incidence reported by other studies and is indicative of an unstable tear film.[13,14,15]

The most common types of thyroid disease are hypothyroidism and hyperthyroidism. In our study, 83.33% patients were hypothyroid (25/30). This suggests that dry eye has increased prevalence in hypothyroid patients also; although thyroid associated ophthalmopathy(TAO) occurs more commonly in patients with Grave's disease. This suggests the importance of screening patients with all thyroid disorders for the presence of dry eye, thereby enabling institution of appropriate therapy.

Testing for inflammatory markers (MMP-9) revealed similar results in both groups (53.3%). This suggests that inflammation is the final common pathway in patients suffering from DED in both thyroid disorders as well as the normal population. No other study has evaluated the correlation of inflammatory markers with DED in thyroid disorders to study the definitive role of inflammation. This aspect may need more detailed studies with a larger sample size.

V. Conclusion

Patients with thyroid disorders were found to have significantly high levels of DED compared to healthy subjects based on all the three assessment tests. The positivity of inflammatory markers was similar in both groups suggesting that inflammation is a common final pathway in causation of DED in all patients (both thyroid associated dry eye and others). However, the high positivity rate for inflammatory markers suggested the importance of the role of anti-inflammatory therapy in management of these cases in both groups. A more detailed study is needed in order to better understand the role of inflammatory markers in pathogenesis of thyroid associated dry eye.

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