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Original Research

Subjective versus objective dry eye disease in patients with moderate-severe thyroid eye disease

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ABSTRACT

Purpose: To compare the subjective versus Objective dry eye disease (DED) in patients with moderate-severe thyroid eye disease (TED).

Method: Included were the patients with moderate-severe TED and ≥ 18 years old. They completed the ocular surface disease index (OSDI) questionnaire and had Schirmer, Tear breakup time (TBUT), fluorescein staining, osmolarity, corneal aesthesiometry, and meibomian gland dysfunction (MGD) tests. Excluded were patients with history of any disease, surgery and or medications which might be affecting the ocular surface and incomplete tests results. Subjective DED was defined as OSDI score of ≥ 13 and objective as one abnormal sign (TBUT, Schirmer, Osmolarity, and Staining). Presence of both was defined as definite DED.

Results: Included were 38 patients (74 eyes) with mean age of 40 years. Subjective DED was detected in 77%, objective in 89.2%, and definite in 67.7% of the eyes. Severe subjective and objective DED were found in 36.5% and 24.3% of the eyes, respectively. TBUT was the most frequent positive test (63.5%). MGD was observed in 56.8% of the eyes. Mean clinical activity score, palpebral fissure, rundle grading, proptosis, corneal aesthesiometry, and presence of MGD were not significantly different between the eyes with and without subjective, objective, or definite DED.

Conclusion: Definite DED was found in more than 2/3 of the eyes with moderate-severe TED. While frequency of objective DED was higher, severe form of subjective DED was more frequent. No variable was significantly different between the eyes with and without subjective, objective and definite DED.

1. Introduction

Thyroid Eye disease (TED) is a common orbital inflammatory disease in which hypertrophy of the extraocular muscles, cellular infiltration of the interstitial tissues, and proliferation of orbital fat and connective tissue including lacrimal gland are observed [1]. It mostly associated with an autoimmune thyroid disease [1,2]. Its severity has been defined as mild, moderate-severe, and sight threatening by European group of Graves' ophthalmopathy (EUGOGO) [3].

Dry Eye disease (DED) is a multifactorial ocular surface disease resulting from damaged tear film homeostasis in which tear film hyperosmolarity, ocular surface inflammation, and neurosensory abnormalities have been reported [4].

Studies on DED in patients with TED are scarce [1,2,5–13]. It has been reported in 65%–85% of the patients with TED based on subjective symptoms (questionnaires) or objective signs (Schirmer test, tear breakup time, fluorescein and lissamine green staining test) [7,8,14]. For

example, Iskeleli et al. [1] reported tear film hyperosmolarity in 21 patients with TED. Furthermore, Bruscolini et al. [5] compared 25 non-exophthalmic TED patients with a control group and found that Schirmer I and II, tear break-up time, and ocular surface disease index (OSDI) questionnaire were significantly impaired. However, all previous studies have simultaneously included different severity grades of TED, not performed all the DED tests concurrently, and not compared subjective (OSDI) versus objective (tests) DED. Therefore, the aim of this study was to compare the subjective versus Objective DED in patients with the same severity of TED (moderate-severe) based on new definition of DED by International Dry Eye Workshop II [4].

2. Methods

This is a prospective comparative study (Rassoul Akram Hospital, 2013–2015) on patients (more than 18 years of age) with moderate-severe TED (unilateral or bilateral). Excluded were patients with

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Table 1
Frequency of different severity of dry eye disease (DED) related tests in 74 eyes (38 patients) with moderate-sever thyroid eye disease.

	Normal	Mild/Moderate	Severe
OSDI score [15]	0–12 14 (18.9%)	13–32 33 (44.6%)	≥ 33 27 (36.5%)
Schirmer [22]	> 10 37 (50.0%)	10–2 33 (44.6%)	< 2 4 (5.4%)
Tear break-up time [21]	> 10 27 (36.5%)	10–5 29 (39.2%)	< 5 18 (24.3%)
Osmolarity [20]	< 308 62 (83.8%)	308–318 8 (10.8%)	> 318 4 (5.4%)
Fluorescein staining	Negative 48 (64.8%)	Positive 26 (35.1%)	Positive

OSDI: Ocular Surface Disease Index.

previous ocular surgery, ocular surface disease, systemic diseases affecting the ocular surface, eyelid malposition, being on regular topical eye medications (except for artificial tear and antiglaucoma medications) within the past year, taking systemic medications affecting the tear film (anticholinergic, anti-histamine, and anti-depressant) in the last 3 months, wearing contact lenses, and incomplete DED questionnaire and tests. Study was approved by the Iran University Ethic Committee and informed consent was obtained from all the patients.

Diagnosis of TED [16] was made by the senior author (MBK). Special examination form was completed for all the patients in order to record the severity score (EUGOGO) [3], Rundle classification [17], and clinical activity score (CAS) [18] of TED. EUGOGO [3] has divided the severity of TED into 3 groups of mild (mild eyelid retraction and or proptosis), moderate-severe (severe eyelid retraction, severe proptosis, and or extraocular myopathy), and sight threatening (optic neuropathy). Furthermore, Rundle severity classification [17] was also recruited in this study in which patients with TED have been regarded as: Rundle A (just symptoms), B (proptosis and eyelid retraction), C (extraocular myopathy), and D (Optic neuropathy). In fact, moderate-sever grade of EUGOGO includes patients with Rundle B and C of TED.

OSDI questionnaire was employed to assess subjective DED (symptoms) whose validity and reliability in Farsi language have already been assessed and approved [19]. OSDI scores were then grouped into normal (0–12), mild-moderate (13–32), and severe (≥ 33) [15].

Furthermore, results of tear film osmolarity (TearLab Corp., San Diego, CA) [20], tear break-up time (TBUT) [21], and Schirmer test [22] were recorded and grouped into normal, mild-moderate, and severe (Table 1).

Fluorescein staining [23] was recorded as negative and positive (Table 1). Corneal aesthesiometry was measured with Cochet-Bonnet filament-type (Luneau Ophtalmologie, Paris, France) [24]. Presence of meibomian gland dysfunction (MGD) [25] was also documented. MGD was diagnosed based on plugged MG orifice, MG expression, and eyelid margin redness and debris in association with ocular surface symptoms which has been previously described [25].

All the tests were performed on 3 consecutive visits within 1 week. First visit comprised TBUT, ocular surface staining, and then MGD assessment. Second visit included osmolarity test and then corneal aesthesiometry. Finally, Schirmer test was performed on the third visit.

Subjective DED was defined as OSDI score of ≥ 13 and objective as

one abnormal sign (TBUT, Schirmer, osmolarity, or staining). Presence of both subjective and objective DED was considered definite DED [15].

Data were entered with SPSS software (version 16, SPSS Inc., Chicago, IL, USA). Independent sample *t*-test (comparing the means), Chi-square test (comparing nonparametric variables), Kappa coefficient (inter-rater agreement for qualitative items), and Generalized Estimating Equations (GEE) analysis (inter-eye correlation) were used for analyses.

3. Results

Initially, 48 patients (90 eyes) with unilateral or bilateral moderate-sever TED were included. Excluded were 16 eyes of 10 patients because of previous ocular surgery (2 eyes of 2 patients), taking anti-depressant in the last 3 months (4 eyes of 2 patients), wearing contact lenses (2 eyes of 1 patient), and incomplete data (8 eyes of 5 patients). Finally, 38 patients (74 eyes) with mean age of 40.08 (SD = 14.5) were included in whom 57.8% (22/38) were females. Hyperthyroidism was the underlying thyroid disorder in 97.3% (37/38). There were 25 patients (25/38, 65.8%) with Rundle B and 13 (13/38, 34.2%) with Rundle C. Associated systemic diseases were hypertension (2/38, 5.2%) and diabetes mellitus (3/38, 7.8%).

Subjective DED was observed in 77% (57/74) and objective in 89.2% (66/74) of the eyes. Two abnormal tests were observed in 50% (37/74) and ≥ 3 in 19% (14/74) of the eyes. More than 2/3 of the eyes (67.7%, 50/74) had definite DED (Table 1). Severe subjective (OSDI score of > 33) and objective (TBUT of < 5 s) DED were found in 36.5% (27/74) and 24.3% (18/74) of the eyes, respectively (Table 1). Mean OSDI score, osmolarity, and TBUT were 27.1 (SD = 16.3, range: 6.2–79.1), 295.91 (SD = 19.41, range: 260–387), and 7.95 (SD = 3.66, range: 1–15), correspondingly.

Positive OSDI score (≥ 13) was not significantly in agreement with any of positive objective tests ($-0.04 < \text{Kappa} < 0.03$; $0.1 < P < 0.5$).

The most prevalent positive test in general (63.5%, 47/74) and in definite DED (78%, 39/50) was TBUT (Tables 1 and 2). MGD was present in more than half of the eyes (56.8%, 26/74).

OSDI score did not have a significant correlation (Spearman test; $-0.02 < r^2 < +0.1$ and $0.2 < P < 0.8$) with DED tests (osmolarity, Schirmer, TBUT) nor with TED related measures (Hertel Exophthalmometry, palpebral fissure, CAS score).

Mean clinical activity score, palpebral fissure, rundle grading, Hertel Exophthalmometry, and corneal aesthesiometry as well as presence of MGD were not significantly different between the eyes with and without subjective DED ($0.2 < P < 0.9$), objective DED ($0.2 < P < 0.8$), and definite DED ($0.1 < P < 0.9$). In order to consider inter-eye correlation, GEE analysis was performed which showed the same results.

4. Discussion

TED is clinically evident in more than one third of patients with autoimmune thyroid diseases in whom different severity and activity of TED are detected [26,27]. Patients with TED are at increased risk of DED [8,9,28]. There are, to the best of our literature search, 11 studies on the issue of DED in TED since 1983 (Table 3) in which none has

Table 2
Frequency of positive dry eye tests in 74 eyes (38 patients) with moderate-severe thyroid eye disease with and without definite dry eye disease (DED).

	OSDI		Schirmer		TBUT		Osmolarity		FS	
	Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative	Positive	Negative
DED (50 eyes)	50 (100%)	0	26 (52%)	24 (48%)	39 (78%)	11 (22%)	11 (22%)	39 (78%)	19 (38%)	31 (62%)
NO DED (24 eyes)	7 (29.2%)	17 (70.8%)	11 (45.8%)	13 (54.2%)	8 (33.3%)	16 (66.7%)	1 (4.2%)	23 (95.8%)	7 (29.2%)	17 (70.8%)

OSDI, Ocular Surface Disease Index; TBUT, Tear Break Up time; FS, fluorescein staining.

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