Corneal surface and tear secretion parameters and their relation with clinical signs in patients with thyroid-associated ophthalmopathy

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Abstract

Background In patients with thyroid-associated ophthalmopathy (TAO), symptoms and signs of ocular dryness are common, these disorders may coincide and it is difficult to accurately identify and differentiate them early.
Aim To evaluate the symptoms and parameters of the ocular dryness in patients with TAO according to the severity and activity of the disease.
Methods
This study included 104 randomly selected patients with GD with an average age of 42.3 years old (SD 6.7). 62 patients (58.2%) were with TAO. The control group consisted of 75 subjects with an average age of 41.97 years old (SD 7.1). Ocular Surface Disease Index (OSDI), the mean of tear break-up time (TBUT), Schirmer‘s test (without topical anesthesia), corneal sensitivity were assesed.
Results
Patients with TAO had reduced the TBUT, Schirmer‘s tests value, increase of the frequency of corneal fluorescein staining and decrease of corneal sensitivity, compared with control and GD (without TAO) patients.
In moderate to severe form of TAO group TBUT, Schirmer‘s tear tests statistically significantly were reduced in comparison with the control group. More frequent corneal fluorescein staining and decreased corneal sensitivity were in moderate to severe and active forms of TAO patients group compared with mild and inactive TAO group and controls. Corneal surface and tears secretion tests correlated with proptosis, palpebral fissure width, CAS and TSHR Ab in active form of TAO.
Conclusion The significant difference of tear film functions was observed in moderate to severe and active form of TAO patients compared with control group. There was a significant correlation between TBUT, Shirmer‘s tests, OSDI data in an active TAO and clinical and biochemical data.

Key words: Thyroid-associated Ophthalmopathy,Ocular surface, Tears secretion

Introduction
Graves‘ disease (GD) is an autoimmune disease that affects the thyroid, microsoft tissue of the orbit and other connective tissues due to autoantibodies to thyroid-stimulating hormone receptor (TSH-R). Thyroid-associated ophthalmopathy usually is self-limiting autoimmune process associated with dysthyroid pathology [1, 2].The natural history of TAO consists of active inflammatory phase, stabilization and inactive remission phase. It can be progressed or regressed. In rare cases the active stage of TAO later can return [3].
Autoantibodies to the thyroid-stimulating hormone receptor induce the excess thyroid hormone production and cause inflammatory process in orbital tissues, thyroid and lacrimal glands [4].
From the clinical point of view, autoimmune process may increase the amount of orbit volume and mechanical pressure to the tissues that can lead to typical clinical signs: proptosis or exophthalmos, lid retraction, increased intraorbital pressure, lid lag, and ocular surface and tear film changes [1, 2, 5].
TAO has various inflammatory symptoms, including inflammatory infiltration of the orbital tissue, conjunctiva and caruncula, that are used to evaluate it‘s activity using Clinical Activity Score (CAS) [6]. Autoimmune thyroid disease is a risk factor for dry eye disease [7, 8], which is the most widespread cause of ocular discomfort in TAO patients [5]. Thus, about 65–85% patients with TAO exhibit symptoms and signs of the dry eye syndrome and the combination of both disorders makes difficult an early accurate diagnosis and differential diagnosis [2, 9, 10].
Dry eye syndrome symptoms may include visual disturbance, burning, itching, redness or grittiness in the eye, foreign body sensation, increased light sensitivity and excessive tearing [7, 8, 11]. The quality of life and visual functions are greatly impaired [10, 12].
Studies have noted that mechanisms, that cause dry eye symptoms and signs in patients with autoimmune thyroid diseases, include dysfunction of lacrimal gland, leading to hyposecretion or loss of tear secretion, increased evaporation of the tear film [5, 13, 14]. Increase of tear film osmolarity results in ocular surface damage [5, 15, 16]. Different proteins of tear fluid (inflammatory and protective) in TAO and dry eye were detected. These proteins might be a useful indicator for disease activity and ocular surface disease in patients with TAO [17].
Hormones also play an important role in the pathophysiology of dry eye [18]. Lacrimal acinar cells express thyroid-stimulating hormone receptor TSH receptor which is considered to be an autoantigen shared by both thyroid and lacrimal gland in patients with Graves’ disease [19].There is lack of data about TAO and dry eye, according to disease activity and severity [3, 11].There are still controversies over the link between these two diseases due to different literary data.
To evaluate the symptoms and parameters of the ocular dryness in patients with TAO according to the severity and activity of the disease.

Material and methods

The study was conducted at the Eye Clinic of Lithuanian University of Health Sciences. All subjects have signed informed consent form for participation in the study. The study protocol was aproved by Kaunas Regional Biomedical Research Ethics Commitee.

This study included 104 randomly selected patients with GD (78 women and 26 men with a ratio of 3 to 1) diagnosed between 2009 and 2016 years. Average patient age was 42.3 years old (SD 6.7) (range 17.5 to 61.5 years). Euthyroid status was found in 26 patients (25%), 71 were hyperthyroid (68.3%), and 7 were hypothyroid (6.7%). 62 patients (58.2%) were with TAO.

Eligibility criteria for patients were as follows:

Inclusion criteria: patients with clinical and serologic diagnosis of Graves' disease and TAO (lid retraction, proptosis, stare, lid lag).

Exclusion criteria: patients with ocular inflammations and other diseases, using eye drops, contact lens, after ophthalmologic surgery, chemical burn, if patients have previously been diagnosed Sjogren's or Stevens Johnson syndromes, the disorder of meibomian gland function.

The control group consisted of 75 subjects, 62 women (82.67%) and 13 men (17.33%) with an average age of 41.97 years old (SD 7.1) (range 19.0 to 59.7 years). Controls were recruited from ophthalmology clinics without clinical and serologic diagnosis of Graves'disease and with no history of dry eye syndrome.

Diagnosis of GD was based on patients' anamnesis, the thyroid status examination and blood serum biochemical indices – free thyroxine (FT4), free triiodo-thyronine (FT3), thyroid stimulating hormone (TSH), thyrotropin hormone receptor antibodies (TSHR Ab), antibody against thyroperoxidase (anti-TPO) and antibodies to thyroglobulin (anti-Tg) evaluation.

Diagnosis of TAO was based on the basis of the criteria of the European Group on Graves' Orbitopathy (EUGOGO) Consensus. All subjects were examined to establish thyroid eye signs, and severity was classified as mild, and moderate to severe according to the EUGOGO [6]. According to the clinical activity score (CAS), TAO patients were divided into inactive (CAS < 3) and active (CAS ≥ 3) groups.

All patients and control subjects underwent a a complete ophthalmic examination of both eyes, including visual acuity testing, proptosis (Hertel exophthalmometry) and palpebral fissure width measurements, slit-lamp and fundoscopic examination. Ocular Surface Disease Index (OSDI) [20], the mean of tear break-up time (TBUT), Schirmer's test (without topical anesthesia), corneal sensitivity were assesed.

Statistical Analysis

Statistical analysis was performed using SPSS (Statistical Package for Social Sciences Inc., Chicago, Illinois, USA) version 20.0. All continuous variables were presented as mean±SD, if they were normally distributed. Categorical variables were described with absolute and relative (percentage) frequencies. Comparison between groups was performed with the unpaired t-test and with the Fisher's exact testo or theχ2– test for categorical variables. Correlation between the quantitative parameters was determined by Pearson's correlation coefficient (r). A probability level of ≤ 0.05 was considered as statistical significant.

Results

The mean GD duration of symptoms was 37.4 months (between 4–120 months). 42 out of 104 patients with GD (40.38%) had no thyroid eye sign. Comparing time since symptoms onset among groups GD (withou TAO) and TAO there was statistically significant difference (table 1). The values of the levels were compared between patients with Graves' disease (without ophthalmopathy) and TAO: FT4, FT3, TSHR Ab and Anti-TPO concentrations at diagnosis were found to be significantly higher in TAO group compared with GD (without TAO).

Table 1. Data of thyroid function parameters in patients with GD (without TAO) and TAO

Parameters	GD (without TAO) n=42	TAO n=62	P
Time since symptoms onset, months	41.37 ± 13.26	16.71± 7.23	0.05
Time since diagnosis, months	32.19± 19.29	14.27± 9.26	0.14
Hyperthyroid state, n (%)	31 (92.86)	40 (64.52)	0.32
Euthyroid state, n (%)	15 (35.71)	11 (17.74)	0.04
Hypothyroid state, n (%)	5 (11.9)	2 (3.23)	0.08
TSH, mIU/L	0.03 ± 0.12	0.01 ± 0.14	0.25
FT4, pmol/L	37.87 ± 3.17	58.18 ± 6.51	0.01
FT3, pmol/L	11.69 ± 2.86	19.37± 2.43	0.006
TSHR Ab, IU/L	22.89±3.16	39.58±8.97	0.04
Anti-TPO, IU/ml	69.53±13.8	143.63 ±37.28	0.03
Anti-Tg, IU/ml	89.92±21.71	50.06±15.22	0.16

29 (46.77%) of patients with TAO had active form of ophthalmopathy (table 2). We found that in TAO group palpebral fissure width and proptosis were significantly higher than in control group (p=0.04; p=0.05, respectively). CAS was significantly higher in active compared with inactive TAO and control groups (p= 0.01; p=0.0005, respectively).

Table 2. Clinical features in patients according to the activity of thyroid-associated ophthalmopathy

Clinical features	Active TAO n=29	Inactive TAO n=33	Control n=75	p1	p2	p3
Visual acuity	0.81 ± 0.41	0.75 ± 0.29	0.92 ± 0.32	0.58	0.56	0.37
Proptosis, mm	18.82 ± 1.61	17.16 ± 2.21	16.3±1.07	0.43	0.05	0.39
CAS	4.37 ± 0.94	1.33 ± 0.75	0.08±0.24	0.01	0.0005	0.06
Palpebral fissure width, mm	14.92 ± 1.16	13.18 ± 1.28	12.01±0.97	0.08	0.04	0.38

p1 – the difference between values of active TAO and inactive TAO, p2 – the difference between values of active TAO and control group, p3 – the difference between values of inactive TAO and control group

Patients complaints statistically significantly ($p<0.01$) more frequently occured in active form of TAO than in inactive (pain of the eye in 75.86% of patients vs. 12.12 % , tearing 65.52% vs. 18.18%, itching 65.52% vs. 6.06% , foreign body sensation 34.48% vs. 9.09%, photophobia 58.62% vs. 15.15%, respectively).

OSDI score was statistically significantly higher in GD and TAO groups than control group (p=0.05, p=0.005, respectively), (table 3). More frequent corneal fluorescein staining and decreased corneal sensitivity were found in TAO comparing with GD, and the control group (p=0.0001). Patients with TAO had significantly lower Schirmer‘s test (7.83± 2.89 mm) compared with controls ($p = 0.04$). The TBUT in TAO patients was significantly

lower than controls (p=0.01), suggesting an unstable tear film, there was no statistical difference between the mean of TBUT in the GD and control groups. The corneal sensitivity was decreased in patients with TAO comparing with the control group (p=0.0001)

Table 3. Comparison of the corneal surface and tears secretion parameters between patients with GD (without TAO), TAO and control groups

	GD (without TAO) n=42	TAO n=62	Control n=75	p1 p2 p3
OSDI score	21.18±12.72	28.8±10.59	0.72± 0.35	0.36 0.05 0.005
Corneal fluorescein staining, n (%)	3 (7.14)	27 (43.55)	0	0.0001 0.09 0.0001
TBUT, sec	6.74 ± 1.81	4.67± 1.47	10.84±1.96	0.16 0.06 0.01
Decrease of corneal sensitivity, n (%)	2 (4.76)	14 (22.58)	0	0.013 0.26 0.0001
Schirmer's test, mm	9.54 ± 2.91	7.83± 2.89	15.58± 3.32	0.09 0.07 0.04

p1 – the difference between values of GD and TAO, p2 – the difference between values of GD and control group, p3 – the difference between values of TAO and control group

A mild degree severity was found in 34 patients (54.84%), and 28 patients (45.16%) had a moderate to severe form of TAO. OSDI was higher not only in moderate to severe form, but also in mild TAO in comparison with the control group (table 4). In moderate to severe form of TAO group TBUT, Schirmer's tears tests statistically significantly were reduced in comparison with the control group (p=0.007, p=0.025, respectively). More frequent corneal fluorescein staining and decreased corneal sensitivity were determined in moderate to severe form of TAO patients group compared with mild TAO group (p =0.0001; p =0.0005, respectively) and controls (p =0.0001).

29 (46.77%) patients were with active TAO. The OSDI score was significantly higher in both forms of TAO comparing with control subjects (respectively p=0.0006; p= 0.028). Fluorescein corneal staining and decreased corneal sensitivity occured significantly more frequently in active than in inactive TAO group.

Table 4. Comparison of the corneal surface and tear secretion parameters according to TAO severity and activity

	Mild TAO n=34	Moderate to severe TAO n=28	Control n=75	p1 p2 p3
OSDI	22.39 ± 9.83	35.21 ± 11.34	0.72± 0.35	0.51 0.024 0.002
Corneal fluorescein staining, n (%)	1 (0.03)	26 (92.86)	0	0.0001 0.56 0.0001
TBUT, sec	6.01±2.16	3.33±1.98	10.84±1.96	0.19 0.08 0.007
Decrease of corneal sensitivity, n (%)	2 (5.88)	12 (42.86)	0	0.0005 0.17 0.0001
Schirmer's test, mm	9.2 ± 2.75	6.46± 3.03	15.58±3.32	0.17 0.07 0.025
p1 – the difference between values of mild TAO and moderate to severe TAO, p2 – the difference between values of mild TAO and control group, p3 – the difference between values of moderate to severe TAO and control group				
	Active TAO	Inactive TAO	Control group	p1 p2 p3

	n=29	n=33	n=75	
OSDI score	38.36 ± 11.98	19.24 ± 9.19	0.72± 0.35	0.09 0.0006 0.028
Corneal fluorescein staining, n (%)	23 (79.31)	4 (12.12%)	0	0.0001 0.0001 0.01
TBUT, sec	3.25±1.98	6.09±2.16	10.84±1.96	0.28 0.008 0.01
Decrease of corneal sensitivity, n (%)	11 (37.93)	3 (9.09)	0	0.007 0.0001 0.05
Schirmer's test, mm	6.37±2.57	9.29±3.21	15.58±3.32	0.22 0.02 0.07
p1 – the difference between values of active TAO and inactive TAO, p2 – the difference between values of active TAO and control group, p3 – the difference between values of inactive TAO and control group				

TBUT, Shirmer's test results were negatively correlated with proptosis, interpalpebral distance, CAS and TSHR Ab in active form of TAO (table 5). OSDI value positively correlated with these clinical and biochemical data (r = 0.42, p= 0.023; r=0.53, 0.003; r=0.46, p=0.012; r=0.37, p=0.048, respectively).

Table 5. Correlations between the corneal surface, tears secretion parameters and clinical and biochemical data in patients with TAO

Clinical and biochemical data		TBUT	Shirmer's test	OSDI
Active TAO				
Age	r	-0.18	-0.07	0.14
	p	0.345	0.718	0.469
Proptosis	r	-0.41	-0.37	0.42
	p	0.027	0.048	0.023
Palpebral fissure width	r	-0.39	-0.4	0.53
	p	0.042	0.032	0.003
CAS	r	-0.4	-0.37	0.46
	p	0.032	0.048	0.012
TSH	r	0.19	0.12	-0.13
	p	0.323	0.535	0.501
fT4	r	-0.13	-0.16	0.12
	p	0.501	0.407	0.535
fT3	r	-0.12	-0.18	0.21
	p	0.535	0.350	0.274
TSHR Ab	r	-0.36	-0.39	0.37

	p	0.055	0.036	0.048
Anti-TPO	r	-0.29	-0.22	0.21
	p	0.127	0.251	0.274
Anti-Tg	r	-0.18	-0.12	0.14
	p	0.345	0.535	0.469
Inactive TAO				
Age	r	-0.05	-0.14	0.10
	p	0.782	0.437	0.58
Proptosis	r	-0.24	-0.13	0.28
	p	0.179	0.471	0.115
Palpebral fissure width	r	-0.26	-0.29	0.13
	p	0.144	0.102	0.471
CAS	r	-0.15	-0.07	0.09
	p	0.405	0.699	0.618
TSH	r	0.18	0.23	-0.24
	p	0.316	0.198	0.179
fT4	r	-0.17	-0.11	0.19
	p	0.344	0.542	0.29
fT3	r	-0.23	-0.27	0.25
	p	0.198	0.129	0.161
TSHR Ab	r	-0.16	-0.18	0.13
	p	0.374	0.316	0.471
Anti-TPO	r	-0.06	-0.12	0.26
	p	0.740	0.506	0.144
Anti-Tg	r	-0.03	-0.07	0.04
	p	0.868	0.699	0.825

There were no correlations between corneal surface, tears secretion parameters and clinical, biochemical data in patients with inactive TAO.

Discussion

The association between thyroid-associated ophthalmopathy and dry eye syndrome long time is the object of medical literature [3, 9-11, 13, 15, 19, 21]. Several publications show that autoimmune thyroid disease is one of the risk factors for dry eye disease [2, 16].

The purpose of our study was to identify the symptoms and parameters of the ocular dryness in patients with TAO according to the severity and activity of the disease.

In our study, women were more likely than men to have the Graves‘ disease (ratio 3:1). Age range was from 17.5 to 61.5 years, the mean − 42.3 years old, it is similar to other studies where they show that the age is usually between 20 and 50 years old [2 22].

We found greater dry eye association in TAO group than in the case of GD (without TAO) that showed a higher corneal surface exposure. However, no differences authors have found between these parameters of ocular surface and tears secretion between Graves' disease (without TAO) and thyroid-associated ophthalmopathy patients groups [5],TAO and control group [11], GD and controls [14].

In moderate to severe TAO patients statistical significantly decreased TBUT, and Shirmer‘s tests values comparing with normal people. Interestingly, that OSDI in mild TAO was significant increased in comparison with control group. This suggests that patients with mild TAO should also be evaluated for both the severity of the disease and the dryness of ocular surface.

Compared to previous studies [10, 19, 23] we found an increased OSDI score and reduced TBUT in both forms of thyroid-associated ophthalmopathy than controls. Howewer, other publications demonstrate that there is no difference between these parameters and activity of TAO [3, 11], these data change in moderate to severe forms of TAO [24].This may be explained by the damage of homeostasis of ocular surface in the active TAO caused by inflammation of the orbit, proptosis, lagophthalmos and evaporation of corneal surface [3, 11, 15, 12, 23, 24]. Our study showed more frequent fluorescein corneal staining and decreased corneal sensitivity in active TAO than in inactive form of this disease.

Several changes are similar to those that have been described recently. Tirakunwichchaa et al. noted that the prevalence of dry eye in autoimmune thyroid diseases was 96% by TBUT, 69% by ocular surface staining, but only 27% by OSDI, and 18% using a Schirmer‘s test [24]. Authors confirmed that fluorescein staining of the cornea is the most common result of eye surface inflammation in thyroid eye disease [9-11, 19, 22].We found that in active TAO Schirmer’s test value was reduced comparing with the control group. A mechanism that would explain the weakening of tear secretion is lacrimal gland disorder due to an attack of autoantibodies to the thyroid-stimulating hormone receptor, which was found in lacrimal glands [8, 19]. Based on our eye surface and tears secretion tests findings, we believe that reduced tears secretion should be included into the mechanism of eye dryness in patients with TAO, as well as suggested by other authors [3, 5, 10, 19, 22]. Decreased production of tears is also due to the inflammatory process in TAO [18]. However, other investigators did not demonstrate tears hyposecretion in TAO [11].

In active form of our patients with TAO, TBUT, Shirmer‘s test results inversely correlated with proptosis, interpalpebral distance, CAS and TSHR Ab and positively correlated with OSDI. Our study showed that in active TAO proptosis and lagophthalmos, CAS, TTHR Ab affects the reduced TBUT, Shirmer‘s tests.Those who have exophthalmos, a wider palpebral fissure are more likely to have a shorter time of tear film break-up, which results in instability of the tear film. Although, there were no correlations between corneal surface, tears secretion parameters and clinical, biochemical data in our patients with inactive TAO form. These data are controversal with Ha et al. where TBUT was correlated with proptosis and palpebral fissure width in both (active and inactive) forms of TAO [23].Authors noted that one of corneal exposure parameters, TBUT, inversely correlates with proptosis in TAO [23, 24]. The prevalence of proptosis,was 68%. as a risk factor for dry eye in autoimmune thyroid disease [24]. However, few published works are controversal, they did not find correlation between proptosis and reduce of TBUT [22].Also there was found greater correlation between increase of interpalpebral distance and decrease of TBUT in TAO [11, 15, 22-24]. Dry eye in autoimmune thyroid disease was found to be associated with lagophthalmos and proptosis [24]. Eckstein et al.found that more often, patients with TAO and lagophthalmos, impaired Bell's phenomenon had reduced ocular surface and tears secretion parameters [19]. Mechanical disorders related to orbital muscles and immune-mediated lacrimal gland dysfunction may be the causes of dry eye in TAO patients [13].There was found correlation between the active process of TAO, increase of CAS and corneal staining [25]. Patients without excessive proptosis may also suffer from decreased corneal sensitivity due to inflammation of ocular surface, which could properly explain the nature of the dry eye disease in thyroid-associated ophthalmopathy [3, 16].

Recent research has increased our understanding of the mechanism of dry eye symptoms in TAO. It seems that the ocular surface of TAO patients is affected by few mechanisms: lacrimal gland dysfunction (reduced tears secretion, decreased Shirmer‘s test value), ocular inflammation (increased CAS; TBUT, Shirmer‘s tests, OSDI correlation with CAS), ocular surface exposure, tear film evaporation, corneal damage (TBUT, corneal fluorescein staining, decrease of corneal sensitivity) due to lid retraction, proptosis and increased palpebral fissure width (relation with TBUT, Shirmer‘s test, OSDI) and relation with autoimmune process (correlation of TTHR Ab with TBUT, Shirmer‘s tests, OSDI). Patients with GD should also be screened for dry eye syndrome in order to assess possible changes. As well as patients with dry eye syndrome should be investigated for thyroid pathology. It may be helpful to plan thyroid and eye examinations. In summary, we believe that the data of our study provide interesting opportunities for further research.

Conclusions

Among the GD patients dry eye findings were found in patients with TAO compared with GD (without TAO) and control group.The significant difference of tear film functions was observed in moderate to severe and active form compared with mild and inactive disease forms of TAO patients and control group. Analysis revealed statistically significant correlation of TBUT, Shirmer‘s tests, OSDI data with proptosis, palpebral fissure width, CAS and TSHR Ab in active TAO.

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