

Brief communication (Original)

Prevalence of dry eye disease in autoimmune thyroid disease and the association of dry eye with clinical signs of thyroid associated ophthalmopathy: observational, noncomparative, cross-sectional study

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Background: Autoimmune thyroid disease (AITD) is a risk factor for dry eye disease. The prevalence of dry eye in AITD is not definitely known.

Objectives: To determine the prevalence of dry eye in AITD and its association with clinical signs of thyroid associated ophthalmopathy (TAO).

Methods: We enrolled a cross-section of 92 patients with AITD between May 1 and August 31, 2013. All were examined to establish thyroid eye signs, and severity was classified as none, mild, and moderate–severe according to the European Group on Graves' orbitopathy. Dry eye disease was verified using an Ocular Surface Disease Index (OSDI) questionnaire, tear break-up time (TBUT), Schirmer test, and ocular surface fluorescein staining. Features of meibomian glands were inspected. This observational study was registered at www.clinicaltrials.in.th, No. TCTR20130713001.

Results: The prevalence of dry eye in AITD was 27% by OSDI questionnaire (95% confidence interval (CI), 16%–34%); 96% (95% CI, 93%–99%) by TBUT; 69% (95% CI, 62%–75%) by ocular surface staining; and 18% (95% CI, 12%–23%) using a Schirmer test, which associated dry eye and proptosis with an odds ratio (OR) of 9.3 (95% CI, 1.2–70.6, $P = 0.031$), and lagophthalmos by ocular surface staining with an OR of 5.8 (95% CI, 1.2–27.7, $P = 0.026$). Dry eye in patients with or without clinical signs of TAO was not significantly different.

Conclusions: The prevalence of dry eye varied by criteria, but was not different in AITD patients with or without TAO. Proptosis and lagophthalmos were associated more strongly with dry eye disease in AITD with TAO, than without.

Keywords: AITD, autoimmune thyroid disease, dry eye, TAO, thyroid associated ophthalmopathy

Autoimmune thyroid disease (AITD) is a common disorder, ranging from hypothyroidism (Hashimoto's thyroiditis) to hyperthyroidism (Graves' disease). It is the most common cause of unilateral and bilateral proptosis. Nearly 60% of patients with AITD develop thyroid associated ophthalmopathy (TAO) [1]. The presence of autoantigens in the thyroid gland and extrathyroidal sites induces autoantibodies that assault the thyroid gland, lacrimal glands, and orbital

fibroblasts, resulting in thyroid ophthalmopathy. Common findings are ocular surface disease, proptosis, lagophthalmos, eyelid retraction, restrictive strabismus, and compressive optic neuropathy [2-4]. Ocular discomfort results mainly from dry eye disease [3-5]. A report of the Epidemiology Subcommittee of the International Dry Eye Workshop (2007) reported dry eye as a multifactorial disease and risk factors were demonstrated [6, 7]. Based on explicit data, autoimmune thyroid disease (AITD) is one of the risk factors of dry eye. The present study was to find the prevalence of dry eye in patients with AITD, and the clinical manifestations that might be associated with dry eye.

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Materials and methods

This observational, noncomparative, cross-sectional study was approved by the Institutional Review Board, Research Affairs, King Chulalongkorn Memorial Hospital and Faculty of Medicine, Chulalongkorn University (approval No. 187/55). The protocol was registered at www.clinicaltrials.in.th No. TCTR20130713001. The study adhered to the informed consent regulations (both written informed consent and documented verbal consent in cases of illiteracy) and the principles of the most recent revisions of the Declaration of Helsinki. We recruited patients older than 20 years of age who were diagnosed with AITD, and were treated, and followed in the Endocrinology Unit, Department of Medicine between May 1 and August 31, 2013. All medical records and the patients' medical history were reviewed. Well-known risk factors for dry eye disease, such as pregnancy, postmenopausal hormone therapy, postradiation of the head or neck region, hematopoietic stem cell transplantation, vitamin A deficiency, androgen deficiency, hepatitis C infection, postexcimer laser surgery, connective tissue diseases, and antihistamine intake within two weeks, were excluded from the study. None of the patients had used any eye drops within 48 h before the ocular examinations. We enrolled 92 patients. Ocular examination was performed to verify dry eye by using the Ocular Surface Disease Index (OSDI) Thai version-questionnaire, Schirmer test, tear break-up time (TBUT), fluorescein staining of the ocular surface, and meibomian glands were inspected by a corneal specialist (RU), and fluorescein staining of the ocular surface. Meibomian glands were inspected by a corneal specialist (RU), then followed by an oculoplastic specialist (TS) to establish thyroid eye signs. Demographic data were gathered, and ocular disease or systemic disease history was elicited. The onset, duration, diagnosis and treatment of autoimmune thyroid disease were also recorded.

Dry eye in the study was defined as an OSDI score of >20%, TBUT <10 s, ocular surface staining (Oxford schema; panels B–E), and Schirmer test of

<5 mm. The appearance of meibomian glands was examined and the quality of meibum. Meibomian gland dysfunction (MGD) was graded as none, mild, moderate, or severe. Thyroid eye examination was performed and classified into activity score and severity adhered to the consensus statement of the European Group on Graves' orbitopathy (EUGOGO) on management of Graves' orbitopathy [8]. Statistical analysis used the SPSS for Windows (version 17.0, SPSS, Chicago, IL, USA). Prevalence of dry eye disease in AITD was reported as percentage, and 95% confidence interval. The association between variables was determined using a Chi-square test, and multiple logistic regression was used to determine risk factors for dry eye and AITD. $P < 0.05$ was considered to be significant.

Results

There were 92 patients (184 eyes), 76 women and 16 men with a ratio of 4.75 to 1. The age range was 20–70 years with the mean age of 43.6 years old (SD 11.3). We diagnosed 88 patients (96%) with Graves' disease, 4 patients (4%) with Hashimoto's thyroiditis. Euthyroid status was found in 38 patients (41%), 21 were hyperthyroid (23%), and 33 were hypothyroid (36%). A disease duration of 1–5 y was found in 39 patients (42%). About one-third (62 out of 184 eyes, 34%) had no thyroid eye sign. Of the remaining (122 eyes, 66%), 50% had one thyroid eye sign, the other half had multiple eye signs. Most cases (136 out of 184 eyes, 74%) were inactive, in which clinical activity score was 0/7, the remaining 48 eyes (26%) had activity score ≤ 2 . A mild degree severity was found in 115 eyes (63%), only 29 eyes (16%) had a moderate-to-severe form. The ocular manifestations were ptosis (MRD1 <4) in 59 eyes (32%), eyelid swelling in 42 eyes (23%), proptosis and eyelid retraction were equally found in 35 eyes (19%), lagophthalmos in 19 eyes (10%), strabismus in 14 eyes (8%), and conjunctival injection in 12 eyes (7%). The prevalence of dry eye in all 92 AITD patients is shown in **Table 1**.

Table 1. Prevalence of dry eye in AITD patients

Criteria	AITD patients (%)	95% CI (%) of prevalence		All AITD patients presented with (%)		Difference in prevalence
		Lower	Upper	Clinical TAO	No TAO	
Ocular Surface Disease Index	25 (27%)	16	34	18 (30%)	7 (23%)	7%
Tear break-up time	176 (96%)	93	99	114 (93%)	62 (100%)	7%
Ocular surface staining	126 (69%)	62	75.2	87 (71%)	39 (63%)	8%
Schirmer test	33 (18%)	12	23.4	19 (16%)	14 (23%)	7%

AITD, autoimmune thyroid disease; OSDI, Ocular Surface Disease Index Thai version-questionnaire; TAO, thyroid associated ophthalmopathy; TBUT, tear break-up time.

By univariate analysis, thyroid eye signs were found to be associated with dry eye in **Table 2**.

When calculated by multiple logistic regression only proptosis was shown to be a risk factor in developing superior staining, which represents dry eye (**Table 3**).

There was an association of dry eye with moderate-to-severe form TAO by TBUT (**Table 4**).

By multivariate analysis, the association of dry eye with AITD is shown in **Table 5**.

Table 2. Univariate analysis, association of the thyroid eye signs with various dry eye criteria

Eye signs	OSDI in AITD		Tear break-up time in AITD		Schirmer test in AITD		Ocular surface staining in AITD		Superior staining only in TAO	
	Frequency (%)	<i>P</i>	Frequency (%)	<i>P</i>	Frequency (%)	<i>P</i>	Frequency (%)	<i>P</i>	Frequency (%)	<i>P</i>
Proptosis	6 (35%)	0.55	32 (91%)	0.18	1 (3%)	0.02	25 (71%)	0.83	7 (20%)	0.01
Eyelid swelling	7 (32%)	0.77	41 (98%)	0.69	8 (19%)	>0.9	33 (79%)	0.16	4 (10%)	0.75
Eyelid injection	1 (100%)	0.27	2 (100%)	>0.9	0 (0)	>0.9	2 (100%)	>0.9	0 (0)	>0.9
Ptosis	9 (33%)	0.55	56 (95%)	0.71	11 (19%)	>0.9	41 (70%)	0.97	1 (2%)	0.02
Eyelid retraction	6 (38%)	0.36	33 (94%)	0.65	2 (6%)	0.06	23 (66%)	0.85	6 (17%)	0.08
Lagophthalmos	4 (50%)	0.21	16 (84%)	0.04	1 (5%)	0.21	17 (90%)	0.07	2 (11%)	0.67
Conjunctival injection	0 (0)	0.32	8 (80%)	0.06	0 (0)	0.21	7 (70%)	>0.9	6 (60%)	<0.001
Conjunctival swelling	1 (100%)	0.27	3 (100%)	1.00	0 (0)	>0.9	3 (100%)	0.55	1 (33%)	0.25
Strabismus	5 (71%)	0.02	13 (93%)	0.48	2 (14%)	>0.9	11 (79%)	0.55	0 (0)	0.36

AITD = autoimmune thyroid disease, OSDI = Ocular Surface Disease Index Thai version-questionnaire, TAO = thyroid associated ophthalmopathy (significant differences are shown in bold)

Table 3. Multiple logistic regression; association of superior staining with thyroid eye signs in autoimmune thyroid disease (thyroid associated ophthalmopathy) (adjusted by proptosis, eyelid retraction, lagophthalmos, eyelid swelling, eyelid injection, MGD)

Thyroid eye signs	<i>P</i>	Odds ratio	95% Confidence interval	
			Lower	Upper
Proptosis	0.04	4.5	1.1	17.9
Eyelid retraction	0.13	2.9	0.7	11.3
Lagophthalmos	0.90	1.1	0.2	6.4
Eyelid swelling	0.96	1.0	0.2	4.8
Eyelid injection	>0.99	0	0	
Meibomian gland dysfunction	0.52	0.6	0.1	3.0

Table 4. Association of dry eye with severity of thyroid associated ophthalmopathy

		Severity of TAO		<i>P</i>
		Mild	Mod-severe	
OSDI	≤20%	43 (77%)	8 (57%)	0.18
	>20%	13 (23%)	6 (43%)	
TBUT	≥10	1 (0.9%)	3 (10%)	0.03
	<10	114 (99%)	26 (90%)	
Ocular surface staining (Oxford scheme)	A	13 (11%)	6 (21%)	0.22
	B-E	102 (89%)	23 (79%)	
Schirmer test	≥5	87 (76)	27 (93%)	0.07
	<5	28 (24%)	2 (7%)	

OSDI, Ocular Surface Disease Index; TBUT, tear break-up time; TAO, thyroid associated ophthalmopathy

Table 5. Multiple logistic regression; association of dry eye with autoimmune thyroid disease (adjusted by proptosis, eyelid retraction, lagophthalmos and eyelid injection, MGD)

		<i>P</i>	Odds ratio	95% Confidence interval	
				Lower	Upper
Ocular surface staining	Lagophthalmos	0.03	5.8	1.2	27.7
	Meibomian gland dysfunction	0.004	3.0	1.4	6.3
Schirmer test	Proptosis	0.03	9.3	1.2	70.6

Only three features in patients with AITD: lagophthalmos, proptosis, and MGD were demonstrated to be risk factors for dry eye. The prevalence of MGD in patients with AITD was 68% (125/184 eyes) (95% CI, 61–75), but there was no significant difference in MGD between AITD patients with and without TAO ($P = 0.53$), and also within the subgroup analysis of the severity ($P = 0.65$) (data not shown).

Discussion

In the present study, women with AITD were more numerous than men with the disease. The sex ratio was similar to previous studies, which were approximately 5–10:1 and the age range in AITD is typically between 20 and 50 years [9, 10]. Patients may present without or with ocular symptoms or signs. The present study found that the prevalence of dry eye in AITD was 96% by TBUT, but only 27% by OSDI criteria. We showed higher prevalence of dry eye revealed by TBUT when compared to previous studies showing the prevalence in normal populations with different criteria [11, 12]. However, even excluding patients with risk factors highly suggestive of dry eye in the present study, we still needed an age and sex matched design to avoid confounding factors when comparing dry eye in patients with AITD and normal populations. The criteria for clinical symptoms of dry eye by OSDI are less than for TBUT and ocular surface staining criteria, which might reflect subclinical dry eye in patients with AITD. Gupta et al. [13] reported occult thyroid eye disease in patients presenting with dry eye symptoms. Interestingly, ptosis was found in 32%, which was not consistent with the characteristics of TAO and was unanticipated. However, this could be a racial characteristic associated with small orbits, or involutional ptosis because of age ≥ 30 years old with normal levator function and minimal amount of ptosis (1–2 mm). Similarly, Naseem et al. [14] reported an AITD patient

presenting with ptosis, but as a sign of severe Graves' orbitopathy. Most patients (74%) were inactive (including all strabismic patients who were in the burn-out stage), only 26% were active with activity score of only 2 or less, and 63% had a mild degree of severity. Nowak et al. [15] found that 85% of ocular discomfort in active thyroid orbitopathy came from dry eye proven by TBUT, Schirmer test, and ocular surface staining. Dryness can be caused by evaporation or a reduction in tear secretion. A mechanism that would explain an attenuation of tear secretion is lacrimal gland impairment because of the attack of autoantibodies to the thyroid-stimulating hormone receptor found in lacrimal glands [16, 17]. The prevalence of dry eye shown by a Schirmer test in the present study was only 18%. We need to consider that, according to the International Dry Eye Workshop definition, dry eye is a multifactorial disease and the Schirmer test alone is not adequate to evaluate dry eye disease. Many patients might present with tearing secondary to a continuous reflex corneal irritation because of increased palpebral height. Therefore, Schirmer measurements are not especially reduced in these patients. Considering this, there is evidence that patients without excessive exophthalmos might suffer from diminished corneal sensitivity because of the ocular surface inflammation, which could satisfactorily explain the occult character of the dry eye disease in Graves' ophthalmopathy [18, 19]. Dry eye in AITD was also found to be associated with lagophthalmos by ocular surface staining with an OR of 5.8, and TAO with proptosis had OR of 9.3. Lagophthalmos, which usually accompanies proptosis caused more exposure of the eyeball, results in dryness. Iskeleli et al. [20] also found that dry eye in thyroid ophthalmopathy was related to increased palpebral fissure width and proptosis, resulting in increment of tear film osmolarity and decrement of TBUT. Although strabismus was significant in univariate analysis by OSDI, we could not elucidate

how the patients were getting dryness; they might be getting discomfort from the strabismus and misreported this as having dry eye. The present study showed the association of dry eye in AITD with lagophthalmos, proptosis, and MGD. These three features appear to be risk factors for dry eye in patients with AITD and TAO. However, dry eye seems to be present even in mild active disease and occult disease, which is difficult to diagnose. It might be beneficial to schedule a routine eye examination both for thyroid severity and activity, and for the ocular surface dryness test to prevent severe ocular inflammation and ocular surface damage. The prevalence of MGD, which was found as a risk factor in AITD, was 68%. MGD might be a coincidence, or it could be sequelae of inflammation in AITD. We found greater association of dry eye in the moderate-to-severe group than in the group with a mild degree of AITD with TAO, which represented more exposure from proptosis as shown by superior staining, but not with eyelid retraction. However, according to the primary objective in reporting the prevalence of dry eye in AITD, the sample size and study design might not be appropriate in verifying the association of dry eye disease and the thyroid eye signs because of the wider range of the confidence interval. Another limitation was a nonhomogenous population of AITD patients with different stages and activity of the disease. More subjects should be included and a subgroup analysis should be performed to clarify these points.

The prevalence of dry eye varied by the criteria setting. There was no significant difference in dry eye between AITD with and without TAO. Proptosis and lagophthalmos were more strongly associated with dry eye disease in AITD with TAO.

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Conflict of interest statement

The authors declare that there is no conflict of interest in this research.

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