Evaluation of the Relationship between Serum TSH Receptor Antibody and Dry Eye Syndrome in Graves' Disease : A Cross-sectional Study

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Abstract

Background: This study aimed to evaluate the relationship between serum TSH receptor antibody levels and dry eye syndrome in Graves' disease patients without graves' orbitopathy.

Materials and Methods: This cross-sectional study encompassed 28 eyes of 14 individuals diagnosed with Graves' disease. Serum TSH receptor antibodies were measured followed by dry eye parameters assessed via the OCULUS Keratograph® 5M specifically Non-Invasive Keratograph Break-Up Time, tear meniscus height, and redness score. Dry eye symptoms were assessed with OSDI score.

Results: The majority of Graves' disease patients exhibit moderate severity of dry eye symptoms (Mean OSDI score = 25.05) and high TSH receptor antibody level (Mean TRAb level = 9.61). The TSH receptor antibody level shows a significant association primarily with the redness score ($r = 0.410$, $p = 0.030$). However, no significant correlations were observed between the TSH receptor antibody level and tear meniscus height, NIKBUT, or OSDI score.

Conclusion: In Graves' disease patients without Graves orbitopathy, a correlation was observed between Serum TSH receptor antibody levels and the redness score. However, there was no correlation between TSH receptor antibody levels and other dry eye parameters or symptoms associated with dry eye syndrome.

Conflicts of Interest: no financial interest in any products or instruments mentioned in this study.

Keywords: TSH Receptor Antibody, Dry Eye Syndrome, Graves' Disease

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Introduction

In Graves' disease, the most prevalent cause of hyperthyroidism in iodine-replete regions, various systemic manifestations occur. Notably, ocular symptoms affect 25-50% of Graves' disease patients, ranging from mild dry eye and irritation to severe conditions like dysthyroid optic neuropathy or corneal breakdown.[1] Graves' orbitopathy's pathogenesis involves autoantibodies, specifically the TSH receptor antibody, which binds to TSH receptors found ubiquitously in orbital structures such as extraocular muscles, adipocytes, and lacrimal glands, leading to an inflammatory cascade and eventual tissue remodeling.[2] Numerous studies underline the significance of TSH receptor antibody (TSHR-Ab, TRAb), revealing a strong correlation (Positive predictive value 100%) with Graves' orbitopathy in individuals whose antibody titer exceeds 4.[3] Additionally, TRAb aids in prognostication and treatment response assessment.[1,2,4,5,7]

Dry eye syndrome and ocular surface abnormalities commonly occur in Graves' disease patients, irrespective of the presence of Graves'

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orbitopathy.[6] This is primarily due to the inflammatory changes around the widened palpebral fissure, proptosis, lid retraction, and poor Bell's phenomenon, resulting in increased exposure of the ocular surface to the environment.[6, 8] Consequently, dry eye symptoms manifest, ranging from mild to severe. Research underscores the relationship between TSH receptor antibody levels and proptosis along with the clinical activity score, suggesting a plausible hypothesis that higher TSH receptor antibody levels might exacerbate dry eye symptoms.

Hence, this study aims to investigate the correlation between TSH receptor antibody levels and dry eye syndrome in Graves' disease patients without Graves' orbitopathy. The objective is to evaluate the severity of dry eye symptoms in patients lacking Graves' ocular signs and plan long-term management based on TSH receptor antibody levels. High antibody levels may indicate the need for early aggressive treatment. Furthermore, the relationship between autoantibodies and dry eye might redirect dry eye management strategies in hyperthyroid patients with elevated antibody levels, potentially considering steroid/immunomodulatory eye drops for more targeted and effective treatment.

Materials and Methods

Study Design

A cross-sectional study is effective for evaluating the relationships between variables at a single point in time. Its feasibility and efficiency are generally superior to those of longitudinal studies, as it is less time-consuming and resource-intensive. Given the study's scope and the specific population (patients without Graves' orbitopathy), this design allowed the researchers to collect and analyze data in an efficient manner.

Patients

Patients diagnosed with Graves' disease, without Graves' orbitopathy, totaling 14 individuals (n = 28 eyes), were invited to participate in a research study at Thammasat Chalermprakiat Hospital from May 2023 to September 2023.

Inclusion Criteria

1. Individuals diagnosed with Graves' disease
2. Experience symptoms of dry eyes
3. Aged 18 years or older

Exclusion Criteria

1. Patients diagnosed with Graves' orbitopathy
2. Patients with other ocular conditions (such as eyelid disorders, glaucoma, pterygium, pinguecula, and other ocular surface diseases)
3. Patients who have undergone eye surgery or experienced eye trauma
4. History of prior treatment for dry eye symptoms

Sample Size

According to the research by Allam IY et al. in 2021, "Ocular Surface Changes in Patients with Thyroid Eye Disease: An Observational Clinical Study", a significant correlation was found between Anti-TSH receptors AB and OSDI, with a correlation coefficient of $r = 0.838$ ($p < 0.001$). Additionally, a significant correlation was observed between Anti-TSH receptors and NTBUT, with a correlation coefficient of $r = 0.745$ ($p < 0.001$). Consequently, the value of r between TSH and NTBUT was substituted into the equation to achieve the maximum number of n, encompassing all variables.

$$C = 0.5x\ ln\left[\frac{1+0.745}{1-0.745}\right],\ C = 0.962$$

$$n = \frac{(1.96+0.842)^2}{0.962^2} + 3$$

$$n = 12 + \text{Drop out } 10\%$$

$$n = 14$$

Research Methodology

1. Patients undergoing examination at the General Medicine, General Practice, and Ophthalmology Departments of Thammasat Chalermprakiat Hospital, diagnosed with Graves' disease and experiencing dry eye symptoms, will receive initial guidance and be referred to the investigator.
2. Collection of demographic data including gender, age, and completion of the OSDI questionnaire.
3. Ocular examination using the OCULUS Keratograph® 5M apparatus to gather tear meniscus height, NIKBUT (noninvasive keratograph break-up time), and redness score data.
4. Ocular examination using slit lamp with fluorescein dye to analyze the Fluorescein staining Oxford scheme grading.
5. Upon completion of the eye examination, patients will undergo a venipuncture to test for TSH receptor antibodies (3rd generation, with a positive cutoff at 1 IU/L).

Statistical Analysis

Statistical analysis was performed using SPSS version 23.0. Descriptive statistics included counts, percentages, means, standard deviations (SD), medians, interquartile ranges (IQR), and the maximum and minimum values. These statistics characterized data related to sex, age, OSDI score, and dry eye parameters.

For analytical statistics, a significance level of $p < 0.05$ was set. Correlation analysis involved examining the correlation coefficient (r) between serum TSH receptor antibody and OSDI score, redness score, NIKBUT, and tear meniscus height, utilizing Pearson's correlation coefficient.

Results

Patient Characteristic

The total of 14 individuals (28 eyes) diagnosed with Graves' disease, all of whom did not manifest Graves' orbitopathy. Among these individuals, 13 (92.9%) were female, while 1 (7.1%) was male. The mean age was 44 ± 11.52 years. The average TSH receptor antibody levels were notably elevated, averaging at 9.61 IU/L. On average, participants exhibited moderate symptoms of dry eye syndrome, indicated by a mean OSDI (Ocular Surface Disease Index) score of 25.05 as assessed using the OCULUS Keratograph® 5M. The Non-Invasive Keratograph Break-Up Time (NIKBUT) yielded an average value of 12.38, with a mean redness score of 1.42. The mean tear meniscus height was recorded at 0.26 mm. Additionally, the majority exhibited a fluorescein staining grade of 0. (75%) (Table 1) (Figure 1-3)

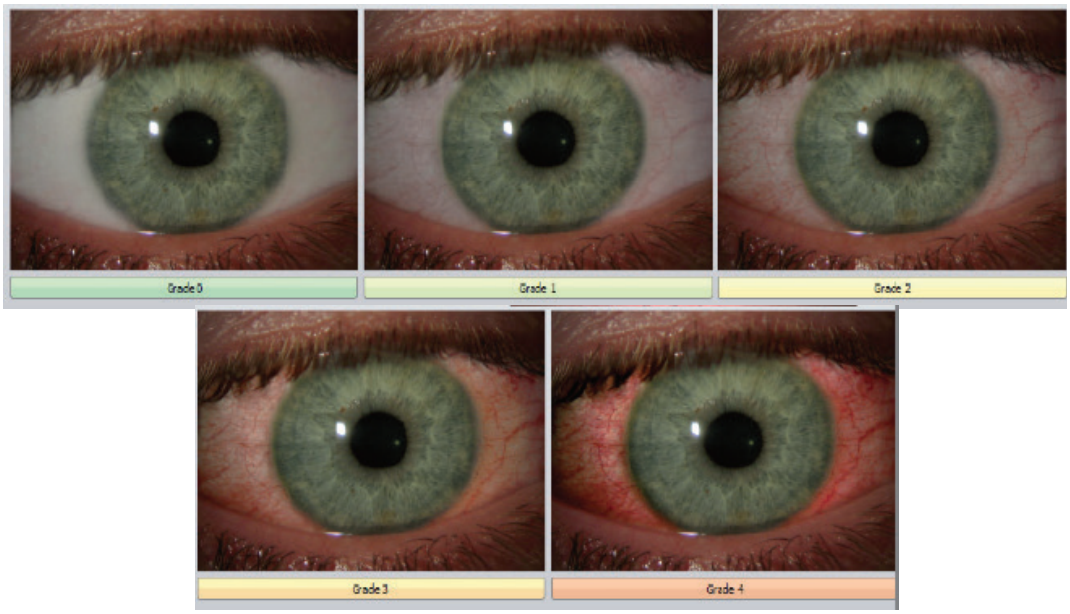

Figure 1: R-Scan result including automatic redness grading according to JENVIS

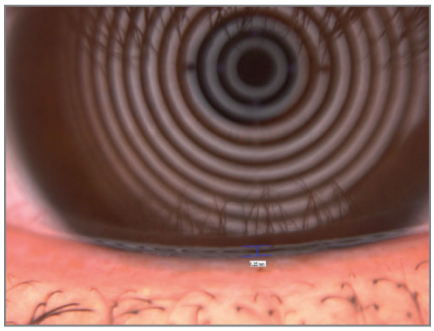

Figure 2: Keratograph 5M TMH normal eye

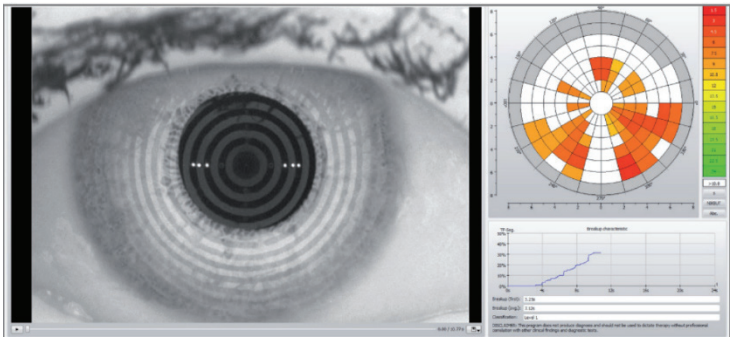

Figure 3: NIKBUT results

Table 1: Demographic and clinical characteristics of patients (n = 14)

Characteristics	Total (n = 14)	
	n	%
Sex		
Female	13	92.9%
Male	1	7.1%
Age (years)		
mean ± SD	44.14	± 11.52
min - max	28	- 64
TRAb level	9.61	± 8.81
OSDI score	25.05	± 11.46
NIKBUT (n = 28 eyes)	12.38	± 4.61
Redness (n = 28 eyes)	1.42	± 0.21
Tear meniscus (n = 28 eyes)	0.26	± 0.08
Fluoresceine staining (n = 28 eyes)		
grade 0	21	75.0%
grade 1	7	25.0%

Relationship between TSH Receptor Antibody and Dry Eye Parameters

The analysis revealed that the TSH receptor antibody levels exhibited the strongest positive correlation with the redness score (r = 0.41, p = 0.03), which was statistically significant. Subsequently, the OSDI score (r = 0.18, p = 0.349) and NIKBUT (r = 0.04, p = 0.841) showed weaker positive correlations with TSH receptor antibody levels, although these correlations did not reach statistical significance. Additionally, a negative correlation was observed between TSH receptor antibody levels and tear meniscus height (r = -0.252, p = 0.196), which, however, did not attain statistical significance.

Furthermore, a statistically significant positive correlation was identified between OSDI score and redness score (r = 0.37, p = 0.05). (Table 2)

Table 2: Correlations (n = 28 eyes)

Parameters		TRAb level	OSDI score	NIKBUT	Redness	Tear meniscus
TRAb level	r	1	0.184	0.040	0.410*	-0.252
	p-value		0.349	0.841	0.030	0.196
OSDI score	r		1	-0.172	0.370	0.250
	p-value			0.381	0.05	0.200
NIKBUT	r			1	-0.034	-0.186
	p-value				0.865	0.344
Redness	r				1	-0.260
	p-value					0.181
Tear meniscus	r					1
	p-value					

Pearson's Correlation Coefficient
* Correlation is significant

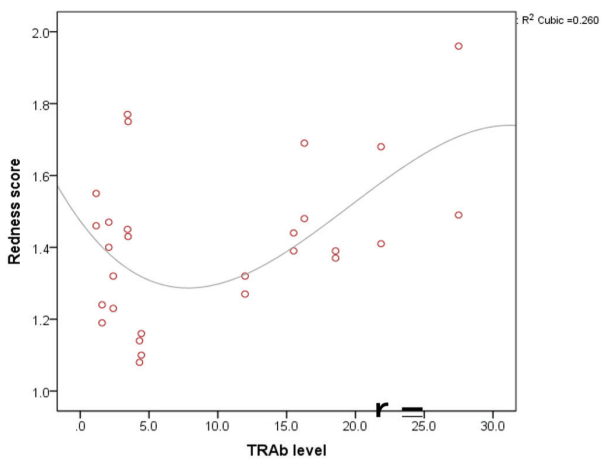

Figure 4: Conjunctival redness score and TRAb level

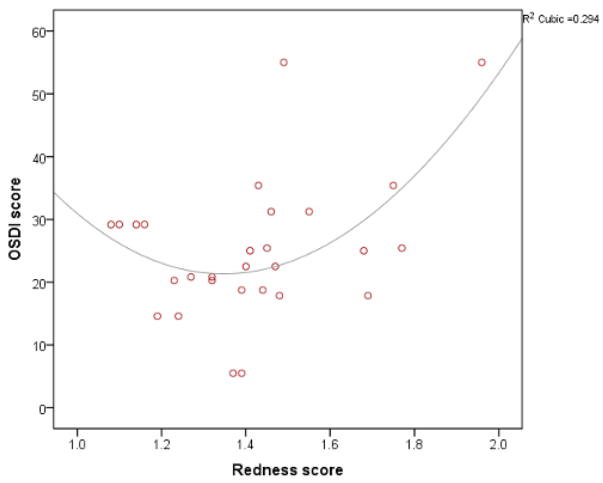

Figure 5: Conjunctival redness score and OSDI score

Discussion

Graves' disease is an autoimmune disorder known for causing significant inflammation in three key areas: the thyroid gland (thyrotoxicosis), the tissue surrounding the eyes (Graves' orbitopathy), and the skin (dermopathy and acropachy).[1, 2] The TSH receptor antibody plays a pivotal role in provoking inflammation. In this study, we investigated the correlation between TSH receptor antibodies and dry eye syndrome in Graves' disease patients without Graves' orbitopathy, aiming to eliminate factors contributing to dry eye symptoms originating from eyelid and orbit abnormalities.

Our findings revealed that TSH receptor antibodies exhibited the strongest correlation with the redness score ($r = 0.41$, $p = 0.03$), followed by a weaker correlation with tear meniscus height ($r = -0.252$, $p = 0.196$), OSDI score ($r = 0.184$, $p = 0.349$), and the least correlation with NIKBUT ($r = 0.04$, $p = 0.841$). This suggests that in the early stages of Graves' disease, elevated TSH receptor antibodies might predominantly affect the conjunctiva, leading to conjunctival bulbar redness. Additionally, we observed deteriorating changes in the tear film, including reduced tear meniscus height and an increase in dry eye symptoms measured by the OSDI score, although statistical significance was not reached.

These findings align with a study by Canan Gürdal et al.[6] which demonstrated greater ocular surface damage and an increased rate of dry eye, evaluated by Schirmer test in Graves' disease patients compared to the control group. Notably, these patients did not exhibit abnormal proptosis or lid signs. The observed dry eye symptoms are consistent with the characteristics of ocular surface inflammation.

When compared to the research conducted by Ibrahim Y Allam et al., which analyzed the correlation between TSH receptor antibodies and patients diagnosed with Graves' orbitopathy using a total of 60 eyes, it was found that serum TRAb had a significant association with dry eye symptoms. This was reflected in the OSDI score ($r = 0.838$, $p = 0.0001$) and NTBUT ($r = -0.745$, $p = 0.0001$).[8] This association can be explained

by the ocular surface deterioration observed in Graves' orbitopathy, characterized by lid retraction and exophthalmos, leading to more pronounced dry eye symptoms and signs.

Although this study identified the strongest correlation between serum TSH receptor antibodies and the conjunctival redness score, conjunctival redness is not a specific characteristic solely indicative of dry eye conditions. Moreover, despite observing a decline in tear film parameters, statistical significance was not achieved. Consequently, it remains inconclusive whether dry eye in Graves' disease patients can be attributed to elevated TSH receptor antibodies. The researchers anticipate that increasing the number of volunteers in future studies could enhance statistical significance and provide clearer insights into the observed correlations.

Conclusion

This study found a significant association between serum TSH receptor antibodies and conjunctival redness scores. Additionally, positive correlations were observed with tear film parameters such as OSDI score and NIKBUT, while a negative correlation was noted with tear meniscus height, although statistical significance was not achieved. However, it is important to note that conjunctival redness is not a specific characteristic solely indicative of dry eye conditions. Therefore, it remains inconclusive whether dry eye in Graves' disease patients can be wholly attributed to elevated TSH receptor antibodies.

Limitation

The study was conducted with a relatively small sample size of 14 individuals (28 eyes). This limited number of participants might affect the generalizability of the findings and could lead to a lack of statistical power to detect significant differences or correlations.

Inconclusive Correlations: While there were positive correlations observed between serum TSH receptor antibodies and conjunctival redness scores, statistical significance was not achieved for all parameters, indicating that the relationship between these variables may not be as strong or consistent.

Specificity of Redness Score: The study found a significant association between serum TSH receptor antibodies and conjunctival redness scores. However, conjunctival redness is not a specific indicator solely for dry eye conditions and can be influenced by various other factors, which makes it difficult to attribute redness exclusively to dry eye or elevated TSH receptor antibodies.

Confounding Variables: The study attempts to control for factors contributing to dry eye symptoms originating from eyelid and orbit abnormalities by excluding patients with Graves' orbitopathy. However, other potential confounding variables, such as environmental factors, concurrent medications, or systemic health conditions, might still influence the results and were not fully accounted for in the study design.

Potential Conflicts of Interest

Researchers have no financial interest in any products or instruments mentioned in this study.

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