Original Research Report

SIGNIFICANT ROLE OF THYROID STIMULATING HORMONE IN THE CLINICAL ACTIVITY SCORE OF THYROID EYE DISEASE AT A TERTIARY HOSPITAL IN SURABAYA, INDONESIA

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ABSTRACT

Thyroid eye disease is an autoimmune disorder characterized by inflammation of the orbital and periorbital tissues. This condition can lead to vision impairment, which is a notable manifestation of thyroid disease. The symptoms of thyroid disease reflected the level of inflammatory activity, whereas the clinical activity score was indicative of active and inactive phases. This retrospective analysis explored the intricate association between thyroid status and clinical activity score in thyroid eye disease patients, with the hope of providing a foundation for further research on the association between thyroid status and the occurrence of TED. This study utilized medical records from the years 2019 to 2022 from the Outpatient Department of Ophthalmic Oncology of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia. The variables examined in this study were thyroid status and the clinical activity score of thyroid eye disease. The statistical analysis was performed using Phi and Cramer's V as well as Spearman's correlation test ($p<0.05$). A total of 88 patients were diagnosed with thyroid eye disease during the study period. Thyroid eye disease primarily affected female patients (58%) and those who had a mean age of ≥41 years (58%). The Phi and Cramer's V analyses indicated no significant association ($p > 0.05$) between thyroid status and clinical activity score in thyroid eye disease patients. Intriguingly, the results exhibited the presence of euthyroidism as well as both overt and subclinical hypothyroidism and hyperthyroidism, regardless of the clinical activity score. Additionally, the Spearman test that incorporated the levels of thyroid hormones, i.e., triiodothyronine (T3), thyroxine (T4), thyroid stimulating hormone (TSH), and free thyroxine (FT4), showed a significant negative correlation ($p<0.05$) between TSH and clinical activity score. In conclusion, THS plays a crucial role in determining the clinical activity score of thyroid eye disease patients. This study underscores the imperative for further research to comprehensively elucidate the intricate correlation between TSH and clinical activity score.

Keywords: Thyroid eye disease; clinical activity score; thyroid hormone; thyroid stimulating hormone (TSH); human and health

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Highlights:
1. This study, conducted at a tertiary hospital, was the first to analyze the correlation between thyroid status and clinical activity score in thyroid eye disease.
2. This study offers valuable information regarding the crucial role of thyroid stimulating hormone (TSH) in determining the clinical activity score of thyroid eye disease.

INTRODUCTION

The thyroid gland produces thyroid hormones, which have a vital function in the human body, specifically in regulating growth and metabolism. Abnormalities in the thyroid gland can result in a variety of health issues (Geetha & Baboo 2016). Thyroid eye disease (TED) is one of the clinical manifestations of thyroid disorders. This disease is an autoimmune inflammatory disorder that affects orbital and periorbital tissues. Additionally, this disease poses a risk to eyesight, causing weakening

and potential deformity of the eye structure (McAlinden 2014, Savitri et al. 2019).

Thyroid eye disease affects approximately 25–50% of individuals who suffer from thyroid disorders (Şahlı & Gündüz 2017). The prevalence of this disease in Asia is 34.7% with women being the primary demographic affected with female-to-male ratio ranging from 3:1 to 14:1 (Muralidhar et al. 2020, Yu et al., 2022). In some cases, thyroid eye disease has the potential to cause vision loss (Rashad et al. 2022). The Ophthalmic Oncology Division of Dr. Soetomo General Academic Hospital in Surabaya, Indonesia, documented as many as 154 cases of thyroid eye disease from 2014 to 2019. The ratio of female to male patients was approximately 10 to 3.1. Between 2017 and 2019, a total of 33 patients with thyroid eye disease in the active phase required inpatient care due to complications that posed a threat to their vision (Fatmariyanti et al. 2022).

Insulin-like growth factor 1 (IGF-1R) and thyroid stimulating hormone receptor (TSH-R) are autoantibodies targeting the thyroid gland, orbital fibroblasts, and skin. These autoantibodies bind to and activate the same receptors in the serum of thyroid eye disease and Graves' disease patients. Antibodies, T lymphocytes, and B lymphocytes then identify and target similar antigens present in the thyroid gland and ocular adnexa. Thyroid eye disease is influenced by various contributing factors, including genetic, hormonal, and environmental, with smoking being particularly significant (Fatmariyanti et al. 2022). Thyroid eye disease manifests differently in each individual. Therefore, the clinical activity score (CAS) is used to assess inflammation activity levels in thyroid eye disease and distinguish between active and inactive phases of the disease (Barrio-Barrio et al., 2015).

The management of thyroid eye disease is greatly influenced by factors such as age, thyroid status, disease activity, and severity. Immunosuppressive therapy can be administered during the active phase, while rehabilitative surgery is the only option during the inactive phase (Salvi & Campi 2015, Gandhi et al. 2024). This study aimed to investigate the correlation between thyroid status and clinical activity score, specifically during the active and inactive phases of thyroid eye disease. The analysis of patient medical records acquired from the Outpatient Department of Ophthalmic Oncology of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, was expected to yield significant findings that can contribute valuable data and establish a foundation for further research.

MATERIALS AND METHODS

This present study used a retrospective analysis approach, with a statistical analysis utilizing the medical records of thyroid eye disease patients in the Outpatient Department of Ophthalmic Oncology, Dr. Soetomo General Academic Hospital, Surabaya, Indonesia. The data were collected between November 2022 and February 2023. Consecutive sampling was performed by selecting medical records that met specific criteria (Nagai et al. 2023). These criteria included patients diagnosed with thyroid eye disease between January 2019 and December 2021, and their medical records had to have all the relevant information, such as laboratory results for the thyroid status and clinical activity score. This study excluded patients with thyroid eye disease who had previously undergone therapy, as well as those with other autoimmune disorders, a history of eye surgery, and other eye abnormalities. Throughout the data collection period, a total of 88 patients were gathered. This study received ethical approval from the Health Research Ethics Committee of Dr. Soetomo General Academic Hospital (No. 1185/LOE/301.4.2/I/2023) on 11/1/2023.

Data related to thyroid laboratory results, clinical activity score, age, and sex were extracted from the medical records. The thyroid laboratory results were classified according to the criteria set by the Clinical Pathology Laboratory of Dr. Soetomo General Academic Hospital. The laboratory provided the following normal ranges of: 0.35–4.94 µIU/mL for thyroid stimulating hormone (TSH), 0.35–1.93 ng/mL for triiodothyronine (T3), 4.87–11.72 µIU/dL for thyroxine (T4), and 0.70–1.48 ng/mL for free thyroxine (FT4). The thyroid status was classified into five different categories: subclinical hypothyroidism (high TSH levels and normal FT4 levels), overt hypothyroidism (high TSH levels and low FT4 levels), euthyroidism (either high- or low-normal TSH and FT4 levels), subclinical hyperthyroidism (low TSH levels and normal FT4 levels), and overt hyperthyroidism (low TSH levels and high FT4 levels) (Rhee et al. 2016, Kannan et al. 2018). The early diagnostic tests employed to identify thyroid disorders were TSH and FT4 examinations. The purpose of these tests was to ascertain whether the disorder originated from the thyroid gland (primary disorder), the pituitary gland (secondary disorder), or the hypothalamus (tertiary disorder) (Shahid et al. 2024).

The clinical activity score was determined by assigning one point for each finding of the characteristics. According to the European Group on Graves' orbitopathy (EUGOGO), an inactive phase of thyroid eye disease was characterized by the presence of less than three symptoms on the seven-

point scale of clinical activity score. Conversely, an active phase of the disease was indicated when there were three or more symptoms on the seven-point scale of clinical activity score (Bartalena et al. 2021, Wang et al. 2022). The statistical analysis utilized Phi and Cramer's V to assess the association between thyroid status and clinical activity score, while Spearman's correlation test was employed to examine the correlation between thyroid hormone levels and clinical activity score. The data were analyzed using IBM SPSS Statistics for Macintosh, version 26.0 (IBM Corp., Armonk, N.Y., USA).

RESULTS

During the data collection period, 138 patients were gathered as potential research subjects. However, only 88 patients met the inclusion criteria following the exclusion process. A total of 22 subjects were excluded from the analysis for having other autoimmune disorders, a history of eye surgery, and unspecified medical records. Additionally, as many as 28 subjects were excluded for having a thyroid status without adequate data on their thyroid laboratory results.

Table 1. General characteristics of the patients.

	n	%	Mean±SD
Sex			
Male	37	42	
Female	51	58	
Age (y.o.)			
≤20	5	5.7	40.65±13.22
21–30	18	20.4	
31–40	14	15.9	
≥41	51	58	
Thyroid status			
Overt hypothyroidism	2	2.3	
Subclinical hypothyroidism	2	2.3	
Euthyroidism	22	25	
Subclinical hyperthyroidism	12	13.6	
Overt hyperthyroidism	50	56.8	
Thyroid lab results			
T3	42	47.73	2.08±1.61
T4	29	32.95	17.83±20.21
TSH	82	93.18	3.15±15.57
FT4	77	87.5	3.18±5.81
CAS			
Inactive phase	73	82.9	
Active phase	15	17.1	

Legends: T3=triiodothyronine; T4=thyroxine; TSH=thyroid stimulating hormone; FT4=free thyroxine; CAS=clinical activity score.

Table 1 presents the general characteristics of the patients (n=88). The majority of thyroid eye disease patients in the Outpatient Department of Ophthalmic Oncology of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia, were female (58%) and had a mean age of 40.65±13.22. Furthermore, thyroid eye disease was predominantly observed in those aged 41 years or older (58%). Most of the patients exhibited overt hyperthyroidism (56.8%) and were in the inactive phase of thyroid eye disease (82.9%) according to the clinical activity score.

Table 2. Statistical analysis of the thyroid status and clinical activity score.

CAS	Thyroid status (n, %)					
	Overt hypothyroidism	Subclinical hypothyroidism	Euthyroidism	Sub-clinical hyper Thyroidiim	Overt hyperthyroidism	Total
In- active phase	1 (1.1%)	2 (2.3%)	20 (22.7%)	10 (11.4%)	40 (45.4%)	73 (82.9 %)
Ac- tive phase	1 (1.1%)	0 (0.0%)	2 (2.3%)	2 (2.3%)	10 (11.4%)	15 (17.1 %)
Value						0.192
Approximate significance				0.518		

Legends: CAS=clinical activity score.

Table 2 displays the result of the statistical analysis conducted on the thyroid status and clinical activity score of thyroid eye disease patients. The data were analyzed to identify any presence of correlation between the variables using Phi and Cramer's V. The analysis revealed no significant value, with p=0.518 (p>0.05). Hyperthyroidism was found to be the most common thyroid status among thyroid eye disease patients.

Table 3. Statistical analysis of hyperthyroid and clinical activity score.

Hyperthyroid status	CAS	(n, %)	Value	Approximate significance
Subclinical hyperthyroid	Inactive phase	10 (11.4%)	0.004	0.970
	Active phase	2 (2.3%)		
Overt hyperthyroid	Inactive phase	40 (45.4%)	0.090	0.398
	Active phase	10 (11.4%)		

Table 3 displays the result of the statistical analysis conducted on hyperthyroid and clinical activity score of thyroid eye disease patients. The analysis of subclinical hyperthyroidism and clinical activity score showed that the correlation coefficient was not statistically significant, with p=0.970 (p>0.05). Similarly, the correlation coefficient between overt hyperthyroidism and clinical activity score was also not significant, with p=0.398 (p>0.05).

Table 4. Correlational analysis between the thyroid hormone levels and clinical activity score.

Thyroid hormones		CAS	Mean±SD	Range (min-max)
T3	ρ Sig.(bilateral) n	0.52 0.743 42	2.08±1.61	0.52-9.74
T4	ρ Sig.(bilateral) n	-0.091 0.639 29	17.83±20.21	5.30-117.04
TSH	ρ Sig.(bilateral) n	-0.349** 0.001 82	3.15±15.57	0.001-111.044
FT4	ρ Sig.(bilateral) n	0.100 0.385 77	3.18±5.81	0.19-46.16

Legends: CAS=clinical activity score; T3=triiodothyronine; T4=thyroxine; TSH=thyroid stimulating hormone; FT4=free thyroxine.

Table 4 summarizes the results of the statistical analysis performed to examine the correlation between thyroid hormone levels and clinical activity score. The data were analyzed for correlation using the Spearman test. The analysis indicated that clinical activity score was not significantly correlated with T3 (p=0.743), T4 (p=0.639), and FT4 (p=0.386). In contrast, the analysis revealed a statistically significant correlation (p=0.001) between TSH and clinical activity score, with a correlation coefficient of -0.349.

DISCUSSION

Characteristics of thyroid eye disease patients

This study found that the majority of the subjects were female (58%), proving a high prevalence of thyroid eye disease among women. A previous study reported similar findings, with 84% of thyroid eye disease patients being female (Iñiguez-Ariza et al. 2021). In a separate study conducted by Eshraghi et al. (2023), it was also shown that 59.1% of thyroid eye disease patients were female. Thyroid dysfunction is notably more prevalent in women than in men. Women experience a higher occurrence of metabolic and endocrine alterations, with distinct clinical trajectories and outcomes present in each of the conditions. The prevalence ratio of functional changes between women and men is 8:5, and this ratio tends to rise with advancing age. Women exhibit a higher occurrence of hyperthyroidism in comparison to men, with Graves' disease being seven times more prevalent in women. The impact of age is evident in both women and men, as the prevalence of these conditions rises as they age (Meng et al. 2015, Castello & Caputo 2019).

The patients in this study were divided into four age groups: ≤20, 21–30, 31–40, and ≥41 years. The majority of the patients belonged to the age group of 41 years or older (58%), with a mean age of 40.65±13.22 years. Previous studies have documented comparable results, indicating that the largest proportion of individuals affected by thyroid eye disease were above the age of 40, with a particular concentration within the age range of 41–60 years. The prevailing age categories consisted of individuals over 40 years old and under the age of 80 (Muralidhar et al. 2020, Levy et al. 2022).

Correlation between thyroid status and clinical activity score

Thyroid eye disease is a condition characterized by progressive inflammation and tissue damage around the eyes, particularly affecting the extraocular muscles, connective tissue, and fat tissue (Douglas et al. 2020). The inflammatory process will gradually subside over time and transition into a chronic phase, marked by a probable decrease in the clinical activity score. This phase is referred to as the non-inflammatory or inactive phase (Douglas et al. 2020, Wang et al. 2022). The improvement of thyroid eye disease occurs during the inactive phase as a result of the diminished inflammatory activity. However, changes in physical appearance may remain due to proptosis and persistent alterations in the eye muscles and eyelids (Cockerham et al. 2021).

The data obtained from this study revealed prevalence rates of 17.1% for active cases of thyroid eye disease and 82.9% for inactive cases of thyroid eye disease. These results indicated a higher prevalence of inactive thyroid eye disease in comparison to active thyroid eye disease. A similar study reported a similar finding, with only 22.6% of patients having active thyroid eye disease (Muralidhar et al. 2020). Most cases of thyroid eye disease manifest in patients with hyperthyroidism. However, thyroid eye disease can also manifest in individuals with a thyroid status other than hyperthyroidism, although the incidence rate was found to be low (10%) (Schattner et al. 2023). In a separate study conducted by Muñoz-Ortiz et al. (2020), the majority of thyroid eye disease patients were found to have hyperthyroidism (86.2%). However, the remaining patients exhibited hypothyroidism (10.36%) and euthyroidism (7.9%). This study uncovered comparable findings, indicating that hyperthyroidism was the predominant thyroid status among thyroid eye disease patients. Despite that, euthyroidism (25%) was also observed in 25% of the patients, which is a larger prevalence rate compared to hypothyroidism (4.5%).

The analysis using Phi and Cramer's V in this study revealed no significant association (p=0.518) between thyroid status and clinical activity score. A study conducted by Eshraghi et al. (2023) at an ophthalmology hospital in Iran found a higher

incidence of hyperthyroidism compared to hypothyroidism among thyroid eye disease patients. The study revealed a relatively low occurrence of active thyroid eye disease, with 25 out of 341 cases occurring in individuals with hyperthyroidism and 5 out of 33 cases occurring in individuals with hypothyroidism. However, the study results indicated no significant association between thyroid eye disease and either hyperthyroidism or hypothyroidism. As previously stated, this suggests that thyroid eye disease can develop not only in hyperthyroidism but also in hypothyroidism and euthyroidism (Iñiguez-Ariza et al. 2021).

Correlation between thyroid hormone levels and clinical activity score

This study divided the patients' thyroid status into five categories: overt hyperthyroidism, subclinical hyperthyroidism, euthyroidism, subclinical hypothyroidism, and overt hypothyroidism. Overt and subclinical hyperthyroidism share a common feature of low TSH levels. However, they exhibit variations in terms of thyroid hormones. Overt hyperthyroidism is characterized by elevated T3 and T4 levels, whereas subclinical hyperthyroidism typically exhibits normal T3 and T4 levels (Mathew et al. 2024). In contrast, overt and subclinical hypothyroidism share a common feature of high TSH levels. The distinguishing factor also lies in the levels of thyroid hormones. Overt hypothyroidism tends to exhibit low FT4 levels, whereas subclinical hypothyroidism typically presents normal FT4 levels (Calsolaro et al. 2019).

Euthyroidism represents a non-thyroidal syndrome marked by changes in thyroid hormone levels but without any dysfunction of the thyroid gland. In individuals with euthyroidism, the most common hormonal condition is low or normal TSH and T4 levels, with a tendency for low T3 levels (Ganesan et al. 2024). The analysis using Spearman's correlation coefficient method in this study was performed to examine the correlation between thyroid hormone levels and clinical activity score. The analysis results indicated no significant correlation between the levels of three thyroid hormones (T3, T4, and FT4) and clinical activity score ($p>0.05$). On the other hand, the correlational analysis between TSH and clinical activity score revealed a significant result ($p=0.001$), with a negative correlation strength of -0.349.

Strength and limitations

This study provides additional information regarding how clinical activity score is correlated with both thyroid status and thyroid hormone levels in thyroid eye disease patients. The findings of this study can serve as a reference for future research. However, this study encountered constraints in acquiring data from the thyroid eye disease patients. Further research is expected to employ a prospective approach to obtain more accurate and representative data on the conditions of the research subjects.

CONCLUSION

Thyroid status and clinical activity score were not correlated in the occurrence of thyroid eye disease. Overt hypothyroidism, subclinical hypothyroidism, euthyroidism, subclinical hyperthyroidism, and overt hyperthyroidism can be present during both the inactive and active phases of thyroid eye disease. Nevertheless, thyroid stimulating hormone (TSH) and clinical activity score were correlated. The clinical activity score was likely to increase as the TSH level decreased.

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Conflict of interest

None.

Ethical consideration

This ethical approval for this study was acquired from the Health Research Ethics Committee of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia (No. 1185/LOE/301.4.2/I/2023 on 11/1/2023).

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Author contribution

HSA contributed to the concept and design, drafting and final approval of the article, critical revision of the article for important intellectual content, provision of study materials and patients, statistical expertise, acquisition of funding, provision of administrative, technical, and logistic support, as well as data collection, analysis, and interpretation. DL, SAS, and RP contributed to the concept and design, drafting and final approval of the article, critical revision of the article for important intellectual content, provision of study materials and patients, statistical expertise, as well as data collection, analysis, and interpretation.

REFERENCES

Barrio-Barrio J, Sabater AL, Bonet-Farriol E, et al (2015). Graves' ophthalmopathy: VISA versus EUGOGO classification, assessment, and management. Journal of Ophthalmology 2015. doi: 10.1155/2015/249125

Bartalena L, Kahaly GJ, Baldeschi L, et al (2021). The 2021 european group on graves' orbitopathy (EUGOGO) clinical practice guidelines for the medical management of graves' orbitopathy. European Journal of Endocrinology 185**,** 43–67. doi: 10.1530/EJE-21-0479.

Calsolaro V, Niccolai F, Pasqualetti G, et al (2019). Overt and subclinical hypothyroidism in the elderly: When to treat?. Frontiers in Endocrinology. doi: 10.3389/fendo.2019.00177.

Castello R, Caputo M (2019). Thyroid diseases and gender. Journal of Sex- and Gender-Specific Medicine 5**,** 136–141. doi: 10.1723/3245.32148.

Cockerham KP, Padnick-Silver L, Stuertz N, et al (2021). Quality of life in patients with chronic thyroid eye disease in the United States. Ophthalmology and Therapy 10**,** 975–987. doi: 10.1007/s40123-021-00385-8.

Douglas RS, Kahaly GJ, Patel A, et al (2020). Teprotumumab for the treatment of active thyroid eye disease. New England Journal of Medicine 382**,** 341–352. doi: 10.1056/NEJMoa1910434.

Eshraghi B, Pourazizi M, Abbasi M, et al (2023). Hypo vs. hyperthyroid eye disease: is there any difference? BMC Ophthalmology 23**,** 58. doi: 10.1186/s12886-023-02806-7.

Fatmariyanti S, Lutfi D, Sidohutomo A (2022). Waspada mata menonjol. Mimbar 26**,** 14–15. Available at: https://rsudrsoetomo.jatimprov.go.id/storage/files/pkrs/mimbar/mimbarVol26no2.pdf

Gandhi R, Durairaj VD, Shah K (2024). Thyroid eye disease. MediaWiki. Available at: https://eyewiki.aao.org/Thyroid_Eye_Disease#Diagnostic_procedures.

Ganesan K, Anastasopoulou C, Wadud K (2024). Euthyroid sick syndrome. Available at: http://www.ncbi.nlm.nih.gov/pubmed/30325734.

Geetha K, Baboo SS (2016). An empirical model for thyroid disease classification using evolutionary multivariate bayseian prediction method. Global Journal of Computer Science and Technology 16**,** 1–9. Available at: https://computerresearch.org/index.php/computer/article/view/1353.

IBM Corp (2019). IBM SPSS Statistics for Macintosh, Version 26.0. Armonk, NY: IBM Corp. Avaliable at: https://www.ibm.com/id-id/products/spss-statistics.

Iñiguez-Ariza NM, Sharma A, Garrity JA, et al (2021). The "quiet TED"—a special subgroup of thyroid eye disease. Ophthalmic Plastic & Reconstructive Surgery 37**,** 551–555. doi: 10.1097/IOP.0000000000001942/

Kannan L, Shaw PA, Morley MP, et al (2018). Thyroid dysfunction in heart failure and cardiovascular outcomes. Circulation: Heart Failure doi: 10.1161/CIRCHEARTFAILURE.118.005266.

Levy N, Leiba H, Landau K, et al (2022). Clinical profile of 80-year-old and older thyroid eye disease patients. Graefe's Archive for Clinical and Experimental Ophthalmology. doi: 10.1007/s00417-022-05627-4.

Mathew P, Kaur J, Rawla P (2024). Hyperthyroidism. Available at: http://www.ncbi.nlm.nih.gov/pubmed/27521067.

McAlinden C (2014). An overview of thyroid eye disease. Eye and Vision 1**,** 9. doi: 10.1186/s40662-014-0009-8.

Meng Z, Liu M, Zhang Q, et al (2015). Gender and age impact on the association between thyroid-stimulating hormone and serum lipids. Medicine (Baltimore) 94**,** e2186. doi: 10.1097/MD.0000000000002186.

Muñoz-Ortiz J, Sierra-Cote MC, Zapata-Bravo E, et al (2020). Prevalence of hyperthyroidism, hypothyroidism, and euthyroidism in thyroid eye disease: a systematic review of the literature. Systematic Reviews 9**,** 201. doi: 10.1186/s13643-020-01459-7.

Muralidhar A, Das S, Tiple S (2020). Clinical profile of thyroid eye disease and factors predictive of disease severity. Indian Journal of Ophthalmology 68**,** 1629. doi: 10.4103/ijo.IJO_104_20.

Nagai H, Amemiya T, Suzuki H (2023). Risk factors for amiodarone-induced liver injury: A retrospective analysis of medical records. Int. Journal of Clinical Pharmacology and Therapeutics 61**,** 455–459. doi: 10.5414/CP204428.

Rashad R, Pinto R, Li E, Sohrab, et al (2022). Thyroid eye disease. Life *12*, 1-17. doi: 10.3390/LIFE12122084

Rhee CM, Ravel VA, Streja E, et al (2016). Thyroid functional disease and mortality in a national peritoneal dialysis cohort. The Journal of Clinical Endocrinology & Metabolism 101**,** 4054–4061. doi: 10.1210/jc.2016-1691.

Şahlı E, Gündüz K (2017). Thyroid-associated ophthalmopathy. Turkish Journal of Ophthal mology *47*, 94. doi: 10.4274/TJO.80688

Salvi M, Campi I (2015). Medical treatment of graves' orbitopathy. Hormone and Metabolic Research 47**,** 779–788. doi: 10.1055/s-0035-1554721.

Savitri AD, Sutjahjo A, Soelistijo SA, et al (2019). Comparison of thyroid stimulating hormone receptor antibody (Trab) in graves' disease patients with and without ophtalmopathy. New Armenian Medical Journal 13**,** 39–46. Available at: https://scholar.unair.ac.id/en/publications/comparison-of-thyroid-stimulating-hormone-receptor-antibody-trab-.

Schattner A, Voichanski S, Pollack R, et al (2023).

Euthyroid graves' ophthalmopathy. Q QJM: An International Journal of Medicine 116**,** 942–943. doi: 10.1093/qjmed/hcad176.

Shahid MA, Ashraf MA, Sharma S (2024). Physiology, thyroid hormone. Available at: http://www.ncbi.nlm.nih.gov/pubmed/29652955.

Wang Y, Padnick-Silver L, Francis-Sedlak M, et al (2022). Inflammatory and noninflammatory thyroid eye disease: Comparison of disease signs, symptoms, and quality of life in patients in the United States. Endocrine Practice 28**,** 842–846. doi: 10.1016/j.eprac.2022.06.003.

Yu CY, Ford, RL, Wester ST, et al (2022). Update on thyroid eye disease: Regional variations in prevalence, diagnosis, and management. Indian Journal of Ophthalmology 70, 2335. doi: 10.4103/IJO.IJO_3217_21