Medical Journal of Bakırköy

Med J Bakirkoy 2025;21(4):398-404
DOI: 10.4274/BMJ.galenos.2025.2025.7-11

Research

Evaluation of the Prevalence and Activity of Thyroid Ophthalmopathy in Patients with Thyroid Disease (Graves' Disease)

Tiroid Hastalarında (Graves Hastalığı) Tiroid Oftalmopati Sıklığı ve Aktivitesinin Değerlendirilmesi

Mehmet Özbaş, Sümeyye Selay Ersoy Şenel

University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Ophthalmology, İstanbul, Türkiye

ABSTRACT

Objective: To evaluate the prevalence, activity status, and clinical spectrum of thyroid associated ophthalmopathy (TAO) in patients with Graves' disease (GD), and to investigate the incidence of TAO activation and treatment approaches employed during follow-up.

Methods: This retrospective observational cohort study included 371 patients with GD who were referred from the endocrinology clinic to an the ophthalmology department and followed for at least 6 months. Thyroid function status at presentation (euthyroid, hypothyroid, or hyperthyroid), treatments for GD, thyroid-stimulating hormone receptor antibody (TRAb) levels, systemic comorbidities (diabetes mellitus, hypertension), and smoking status were recorded. Ocular involvement was evaluated using the clinical activity score (CAS), with CAS ≥3 indicating active TAO.

Results: Active TAO developed in 17.5% of GD patients. While most of these patients were in the hyperthyroid phase, a considerable proportion were in the euthyroid or hypothyroid phases. Patients with active TAO exhibited higher TRAb levels. Smoking emerged as a significant risk factor for TAO development. The most commonly administered treatment was intravenous methylprednisolone, followed by thyroidectomy, orbital radiotherapy, radioactive iodine therapy, and orbital decompression surgery.

Conclusion: Patients with GD, there is a risk of developing TAO during follow-up, even in those asymptomatic at presentation. Regular ophthalmologic assessment is recommended, particularly for patients who smoke or have elevated TRAb levels. CAS remains a valuable tool for evaluating disease activity and guiding treatment decisions.

Keywords: Graves' disease, thyroid associated ophthalmopathy, clinical activity score

ÖZ

Amaç: Graves hastalığı (GH) olan hastalarda tiroid ilişkili oftalmopatinin (TİO) prevalansını, aktivite durumunu ve klinik spektrumunu değerlendirmek ve takip süresince TİO aktivasyon insidansını ve uygulanan tedavi yaklaşımlarını araştırmaktır.

Gereç ve Yöntem: Bu retrospektif gözlemsel kohort çalışmasına, endokrinoloji kliniğinden göz hastalıkları bölümüne yönlendirilmiş ve en az 6 ay takip edilmiş 371 GH hastası dahil edildi. Başvuru anındaki tiroid fonksiyon durumu (ötiroidi, hipotiroidi veya hipertiroidi), GH tedavileri, tiroid uyarıcı hormon reseptör antikoru (TRAb) düzeyleri, sistemik komorbiditeler (diabetes mellitus, hipertansiyon) ve sigara içme durumu kaydedildi. Oküler tutulum klinik aktivite skoru (KAS) kullanılarak değerlendirildi; KAS ≥3 olan hastalar aktif TİO olarak kabul edildi.

Bulgular: GH hastalarının %17,5'inde aktif TİO gelişti. Bu hastaların çoğu hipertiroidi evresinde olsa da, önemli bir kısmı ötiroidi veya hipotiroidi evresindeydi. Aktif TİO'su olan hastalarda TRAb düzeyleri daha yüksekti. Sigara içimi, TİO gelişimi için anlamlı bir risk faktörü olarak belirlendi. En sık uygulanan tedavi damardan verilen metilprednizolon olurken; bunu tiroidektomi, orbital radyoterapi, radyoaktif iyot tedavisi ve orbital dekompresyon cerrahisi izledi.

Sonuç: GH hastalarında, başvuru sırasında asemptomatik olsalar bile takip süresince TİO gelişme riski bulunmaktadır. Özellikle sigara içen veya yüksek TRAb düzeylerine sahip hastalarda düzenli oftalmolojik değerlendirme önerilmektedir. KAS, hastalık aktivitesinin değerlendirilmesinde ve tedavi kararlarının yönlendirilmesinde değerli bir araç olmaya devam etmektedir.

Anahtar Kelimeler: Graves hastalığı, tiroid ilişkili oftalmopati, klinik aktivite skoru

Address for Correspondence: Mehmet Özbaş, MD, University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Ophthalmology, İstanbul, Türkiye
E-mail: dr.mehmetozbas@gmail.com **ORCID ID:** orcid.org/0000-0002-5679-3762

Cite as: Özbaş M, Ersoy Şenel SS. Evaluation of the prevalence and activity of thyroid ophthalmopathy in patients with thyroid disease (Graves' disease). Med J Bakirkoy. 2025;21(4):398-404

Received: 28.07.2025
Accepted: 02.09.2025
Publication Date: 18.12.2025

INTRODUCTION

Thyroid associated ophthalmopathy (TAO) is a significant autoimmune disorder that substantially impairs quality of life. Although rare, it is the most common inflammatory orbital disease and is associated with autoimmune thyroid dysfunction (1). This condition arises from an antibody response against a shared antigen present in both the thyroid gland and retro-orbital tissues (2). TAO almost always occurs in conjunction with circulating thyroid-stimulating hormone receptor antibodies (TRAb) (3).

The incidence of TAO is approximately 1.9 cases per 10,000 people annually (4). Although TAO is most commonly associated with hyperthyroidism secondary to Graves' disease (GD), about 10% of TAO patients are euthyroid or hypothyroid (5). The overall prevalence of TAO among patients with GD can be as high as 50% (6).

Although TAO is mild and non-progressive in most patients, close monitoring of high-risk individuals is crucial to ensure timely and appropriate treatment based on disease severity and activity. Moderate-to-severe forms, which necessitate aggressive therapy, constitute only 5-6% of all cases (7).

Risk factors identified for TAO include smoking, female sex, advanced age, genetic predisposition, wide lateral orbital wall angle, elevated TRAb levels, high pre-treatment triiodothyronine and thyroxine levels, uncontrolled hypo- or hyperthyroidism, and radioactive iodine (RAI) therapy (8).

Reports in the literature indicate that GD and associated TAO occur more frequently in women than in men. The prevalence of TAO increases with age, particularly between 40 and 60 years, and peaks during the fifth and sixth decades of life (9-11).

TAO is generally diagnosed clinically. However, in atypical or unilateral cases, orbital imaging plays an important role in the diagnosis, differential diagnosis, and clinical or surgical follow-up (12). TAO is diagnosed when at least two of the following three findings are present: thyroid dysfunction of autoimmune origin, one or more ocular signs, or radiological evidence of fusiform enlargement of the bellies of the extraocular muscles, sparing the tendinous insertions (13).

To assess TAO activity and to monitor treatment response, the clinical activity score (CAS), which reflects inflammatory changes, is commonly used (14).

The management of TAO is determined by disease severity. Mild cases typically require only symptomatic treatment, whereas moderate-to-severe TAO may necessitate multiple medical, surgical, or combined interventions. Close monitoring and appropriately timed treatments are essential; early initiation of medical therapy during the active phase of the disease is critical (14).

General management strategies for TAO encompass correcting hyperthyroidism, monitoring and treating hypothyroidism, and encouraging smoking cessation when appropriate (15).

Upon diagnosis, treatment should promptly target the active inflammatory phase of the disease to reduce severity, especially as chronic or fibrotic phases tend to be more resistant to therapy (13).

This study examined the demographic characteristics of GD patients, the presence of comorbidities (diabetes mellitus and hypertension), smoking status, the prevalence and activity of TAO, and the treatment modalities applied.

METHODS

This retrospective observational study included 371 patients diagnosed with GD and followed at the endocrinology clinic between January 2019 and September 2023, who were subsequently referred to the Ophthalmology Clinic of University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital. The study was conducted in accordance with the Declaration of Helsinki, and approval by the University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (approval no: 2023-21-26, date: 06.11.2023) and informed consent from all patients were obtained.

Patients' medical records were retrospectively reviewed. Only those with a minimum follow-up duration of six months were included. The mean follow-up period was 20.07±17.05 months (range: 6-57 months). Recorded data included the duration of ophthalmologic follow-up, current thyroid treatment, presence of comorbidities (diabetes mellitus and hypertension), TRAb levels, smoking status, ophthalmic examination findings, presence of TAO, and, when TAO was present, the treatment modalities applied.

TRAb levels were measured using a standardized immunoassay analyzer with a measurement range of 0.3-40 IU/L and a cut-off value of 1.75 IU/L. Values above this threshold were considered positive.

Assessment of TAO activity was performed according to the European Group on Graves' Orbitopathy guidelines, using the CAS. CAS is a seven-parameter scoring system that evaluates inflammatory activity in the eye. The parameters include spontaneous retrobulbar pain, pain on eye movement, eyelid erythema, conjunctival hyperemia, eyelid edema, conjunctival edema (chemosis), and inflammation of the caruncle or plica. The CAS is scored from 0 to 7 based

on the presence of these inflammatory signs (Table 1). Patients with a CAS score of 3 or higher were classified as having active TAO, those with scores of 1 or 2 as having inactive TAO, and patients with a CAS score of 0 as having no disease activation.

An experienced ophthalmologist performed the ophthalmologic examinations. Each patient underwent a comprehensive ophthalmic evaluation, including clinical assessment of CAS parameters, measurement of visual acuity, assessment of intraocular pressure, anterior segment examination with slit-lamp biomicroscopy, and fundus examination.

Thyroid function status at presentation (hypothyroid, hyperthyroid, or euthyroid) and smoking history were obtained from patients' medical records. Patients were categorized into three groups based on smoking status: current smokers, former smokers, and non-smokers.

Initially, 400 GD patients were screened for the study. However, patients with incomplete examination data or follow-up periods shorter than six months were excluded. Additionally, individuals with orbital diseases other than TAO were not included. Consequently, 371 patients with sufficient data and follow-up duration were enrolled in the study.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics 25.0 (IBM Corp., Armonk, NY, USA). The distribution of continuous variables was assessed using the Shapiro-Wilk test. Since TRAb levels were not normally distributed, the Mann-Whitney U test was used for group comparisons. A p-value of <0.05 was considered statistically significant.

Table 1. Clinical activity score criteria

Clinical activity score criteria*	Description	Score if present
Spontaneous retrobulbar pain	Pain behind the eye at rest	1
Pain on eye movement	Pain caused by moving the eye	1
Eyelid erythema	Redness of the eyelids	1
Conjunctival injection (redness)	Redness of the conjunctiva	1
Eyelid edema	Swelling of the eyelids	1
Chemosis (conjunctival edema)	Swelling of the conjunctiva	1
Inflammation of caruncle or plica	Redness or swelling of caruncle or plica	1

*: Clinical activity score criteria, used to assess inflammatory activity in thyroid eye disease, are based on the guidelines of the European Group on Graves' orbitopathy. Each criterion is scored as 1 if present, with a total possible score ranging from 0 to 7. A clinical activity score ≥3 indicates active disease

RESULTS

The majority of the 371 Graves disease patients included in the study were female, with a mean age of 47 years. General data on patients' smoking status, thyroid function, and accompanying systemic diseases are summarized in Table 2.

Of the 371 patients with GD included in the study, 65 (17.5%) with a CAS ≥3 constituted the active TAO group. Among the remaining patients, 146 (39.3%) with a CAS score of 1 or 2 were classified as the inactive TAO group, while 160 patients (43.2%) with a CAS score of 0 were classified as having no clinical activity. The mean TRAb levels were highest in the active TAO group, followed by the inactive TAO group, and lowest in patients without clinical activity. Furthermore, TRAb levels in the active TAO group were significantly higher than in the other groups (Table 3).

The demographic and clinical characteristics of the 65 patients diagnosed with active TAO—including age, sex, smoking status, thyroid function at presentation, systemic

Table 2. General demographic and clinical characteristics of the entire cohort (n*=371)

Variable	Value
Female, n (%)	289 (77.9%)
Male, n (%)	82 (22.1%)
Age, mean±SD (range)	47.01±11.05 years (22-84 years)
Smoking status	
Current smoker, n (%)	158 (42.6%)
Former smoker, n (%)	36 (9.7%)
Never smoker, n (%)	177 (47.7%)
Thyroid status at referral	
Hyperthyroid, n (%)	170 (45.8%)
Euthyroid, n (%)	162 (43.7%)
Hypothyroid, n (%)	39 (10.5%)
Systemic comorbidities	
HT, n (%)	16 (4.3%)
DM, n (%)	37 (10.0%)
Both HT and DM, n (%)	8 (2.2%)
Mean TRAb level, IU/L	10.63±11.45 (median: 4.37, range: 0.3-40.0)
Mean follow-up duration, months	20.70±17.05 (median: 12.0, range: 6-57)

*: n indicates the number of patients; percentages are calculated based on the total cohort (n=371), unless otherwise specified
HT: Hypertension, DM: Diabetes mellitus, SD: Standard deviation, TRAb: Thyroid-stimulating hormone receptor antibody

comorbidities, and TRAb levels—are summarized in Table 4. In this group, 3 patients had previously undergone thyroidectomy, 4 had received RAI therapy, and the remaining 58 patients were receiving antithyroid medication.

The frequencies of the clinical findings comprising the CAS criteria in patients diagnosed with active TAO are presented in Table 5.

The distribution of symptomatic, medical, surgical, and adjuvant treatments applied to patients with TAO is presented in Table 6.

Table 3. TRAb levels and clinical activity distribution according to clinical activity score -based classification in the study cohort

Disease activity group	Mean TRAb (IU/L*)	Median TRAb (IU/L)	Min-max TRAb (IU/L)	Number of patients (n)	Percentage (%)
Active thyroid associated ophthalmopathy (CAS≥3)	14.20**±14.20	8.36	0.3-40.0	65	17.5
İnactive thyroid associated ophthalmopathy (CAS 1-2)	8.72±9.70	5.11	0.3-40.0	146	39.3
No clinical activity (CAS=0)	6.84±8.39	3.95	0.3-40.0	160	43.2
Total cohort	10.63±11.45	4.37	0.3-40.0	371	100

*: IU/L: International units per liter, **: TRAb levels were significantly higher in the active TAO group compared to the inactive TAO and no clinical activity groups (Mann-Whitney U test, p=0.0017; significance level p<0.05 was considered)
TRAb: Thyroid-stimulating hormone receptor antibody, CAS: Clinical activity score, TAO: Thyroid associated ophthalmopathy

Table 4. Demographic and clinical features of the active thyroid associated ophthalmopathy patients (n*=65)

Variable	Value
Female, n (%)	42 (64.6%)
Male, n (%)	23 (35.4%)
Age, mean±SD (range)	48.8±10.8 years (22-67 years)
Smoking status	
Current smoker, n (%)	35 (53.8%)
Former smoker, n (%)	6 (9.2%)
Never smoker, n (%)	24 (36.9%)
Thyroid status at referral	
Hyperthyroid, n (%)	39 (60.0%)
Euthyroid, n (%)	18 (27.7%)
Hypothyroid, n (%)	8 (12.3%)
Systemic comorbidities	
HT, n (%)	2 (3.1%)
DM, n (%)	5 (7.7%)
Both HT and DM, n (%)	2 (3.1%)
Mean TRAb level, IU/L	14.20±14.20 (median: 8.36, range: 0.3-40.0)
Mean follow-up duration, months	26.57±17.90 (median: 19.0, range: 6-57)

*: Indicates the number of patients; percentages are calculated based on the total cohort (n=65), unless otherwise specified
HT: Hypertension, DM: Diabetes mellitus, SD: Standard deviation, TRAb: Thyroid-stimulating hormone receptor antibody

Table 5. Number and frequency of symptoms according to clinical activity score criteria in active thyroid associated ophthalmopathy patients

Clinical activity score criterion	Number of patients (n*)	Frequency (%)
Spontaneous retrobulbar pain	34	52.3%
Pain on eye movement	22	33.8%
Eyelid edema (swelling)	52	80.0%
Eyelid erythema (redness)	10	15.4%
Conjunctival injection (redness)	47	72.3%
Chemosis (conjunctival swelling)	36	55.4%
Caruncle or plica inflammation	23	35.4%

Since patients may exhibit multiple symptoms simultaneously, the total number of symptoms may exceed the number of patients. *: Number of patients in whom the symptom was observed

Table 6. Eye treatment approaches in active thyroid associated ophthalmopathy patients (n*=65)

Treatment	n* (%)
Symptomatic/lubricant treatment	65 (100%)
Intravenous methylprednisolone	40 (61.5%)
Thyroidectomy	9 (13.8%)
Orbital radiotherapy	6 (9.2%)
Radioactive iodine	4 (6.2%)
Orbital decompression surgery	1 (1.5%)
Only symptomatic treatment**	5 (7.7%)

*: Number of patients, **: Due to mild clinical findings, patient preferences, or the presence of systemic contraindications, symptomatic treatment was administered

DISCUSSION

This study retrospectively evaluated the prevalence, clinical features, and treatment approaches of TAO in patients with GD. According to our findings, TAO developed in 211 of 371 patients diagnosed with GD (56.9%). Among these patients with TAO, 146 (69.2%) were classified as having inactive TAO and 65 (30.8%) as having active TAO based on the CAS. Although the prevalence of TAO in our study appears higher than the 25-50% range reported in the literature (6,16,17), this can be explained by our cohort comprising patients referred to a tertiary care center. Therefore, the obtained rate can be considered acceptable within the study context. The rate of active TAO was within the previously reported range of 15-30% (17,18). These findings indicate that a significant proportion of patients with GD develop thyroid eye disease.

Approximately 60% of patients with active TAO in our study were in the hyperthyroid phase. However, a substantial proportion were euthyroid (28%), while a smaller proportion were hypothyroid (12%). This aligns with existing literature showing that TAO is not limited to the thyrotoxic phase but can also develop during euthyroid or hypothyroid states (19). In clinical practice, normal thyroid function does not exclude the risk of TAO, underscoring the need for vigilance, particularly in euthyroid patients.

Female sex has been reported in the literature as a risk factor for TAO (10). Similarly, in our study, the majority of patients who developed orbital involvement were female (64.6%).

We observed that TRAb levels increased with clinical activity in TAO patients. The mean TRAb level in the active TAO group was significantly higher than in the inactive and no-clinical-activity groups (p=0.0017) (Table 3). Similarly, the literature reports a significant association between elevated TRAb levels and active TAO. TRAb serves as a specific biomarker for TAO and is a valuable tool for the accurate management of this complex disease. Its measurement is important and clinically useful for the diagnosis, differential diagnosis, and monitoring of TAO and GD (20,21). Circulating TRAb have been correlated with clinical activity and severity of TAO (22). These data support TRAb as a reliable indicator of disease activity and suggest that it can be used alongside clinical assessment to guide treatment decisions.

According to the clinical findings comprising the CAS criteria (Table 5), the most frequently observed signs among active patients were eyelid edema (80%), conjunctival injection (72.3%), and chemosis (55.4%). These findings represent the main components of orbital inflammation and play a significant role in CAS scoring (23). In addition, the high prevalence of symptoms, such as spontaneous retrobulbar pain (52.3%) and pain on eye movement (33.8%), suggests that inflammation may adversely affect patients' quality of life. Inflammation of the caruncle or plica (35.4%) and eyelid erythema (15.4%) were other ocular signs observed in our patients and are also included in the CAS criteria. Our findings are consistent with the existing literature and reflect the clinical manifestations of the inflammatory phase of TAO (24,25).

Among the 65 patients with active TAO in our study, 53.8% (n=35) were current smokers, 9.2% (n=6) were former smokers, and 36.9% (n=24) had never smoked. This finding aligns with the literature, which consistently suggests that smoking increases the risk of TAO. Smoking has been identified as an independent risk factor for both the development and progression of TAO (26). Previous research has shown that smoking may exacerbate inflammation by stimulating orbital fibroblasts and activating hypoxia-inducible factors. Based on these findings, smoking cessation counseling should be considered a key component in the management of TAO (27).

Some of our patients also presented with systemic comorbidities such as diabetes mellitus and hypertension. Although the relationship between these comorbidities and TAO activity could not be analyzed in this study, their presence remains clinically relevant for systemic evaluation and potential treatment planning for patients.

All 65 patients diagnosed with active TAO received symptomatic treatment consisting of artificial tears and gel for ocular surface relief. Regarding systemic therapies (Table 6), intravenous methylprednisolone was the most commonly administered treatment (61.5%), supporting corticosteroids as the primary treatment modality for active TAO (19,28,29). Additionally, based on clinical and systemic factors, the following treatment approaches were administered: thyroidectomy in 9 patients, orbital radiotherapy in 6 patients, and RAI therapy in 4 patients. One patient underwent orbital decompression surgery due to marked proptosis, signs of orbital compression, and resistance to medical treatment.

Among five patients with active TAO, only symptomatic treatment was provided. This was attributed to mild clinical findings, patient preferences, or systemic contraindications. According to the literature, supportive therapy combined with close monitoring is considered appropriate for patients with active TAO and mild symptoms (20).

This therapeutic diversity highlights the need for individualized management of TAO based on disease activity, severity, and patient characteristics and demonstrates that clinical practice is shaped accordingly (30).

Except for the patient who underwent decompression surgery, ophthalmologic assessments during follow-up—including visual acuity, intraocular pressure, anterior segment examinations, and fundus examinations—showed no significant changes among the remaining patients with active orbitopathy. Overall, their ophthalmologic findings remained stable throughout the follow-up period.

Study Limitations

The primary limitation of our study is the absence of data regarding disease duration since the initial diagnosis of GD, which precluded assessment of its impact on ocular involvement. Additionally, the inability to evaluate the relationship between systemic comorbidities (hypertension and diabetes mellitus) and disease activity constitutes an additional limitation.

CONCLUSION

In conclusion, this study highlights the clinical spectrum of TAO in patients with GD and underscores the necessity of individualized treatment approaches. Our findings demonstrate that active TAO affects a significant proportion of patients and can occur not only during the hyperthyroid phase but also during the euthyroid and hypothyroid phases. The observed correlation between increasing TRAb levels and disease activity supports the use of this biomarker as an adjunct to clinical assessment. Furthermore, smoking was identified as an important risk factor, and individualized treatment strategies were found to be effective in achieving clinical stabilization. Early recognition of inflammatory signs and implementation of appropriate treatment strategies through a multidisciplinary approach are crucial for preventing serious TAO-related complications in patients with GD.

ETHICS

Ethics Committee Approval: This study approval by the University of Health Sciences Türkiye, Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (approval no: 2023-21-26, date: 06.11.2023).

Informed Consent: Informed consent from all patients were obtained.

Acknowledgments

We sincerely thank Dr. Özgür Örüm, MD, for his valuable contributions to the conduct of this study.

FOOTNOTES

Authorship Contributions

Surgical and Medical Practices: M.Ö., S.S.E.Ş., Concept: M.Ö., Design: M.Ö., Data Collection or Processing: M.Ö., S.S.E.Ş., Analysis or Interpretation: M.Ö., S.S.E.Ş., Literature Search: M.Ö., S.S.E.Ş., Writing: M.Ö.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declare that this study received no financial support.

REFERENCES

1. Szelog J, Swanson H, Sniegowski MC, Lyon DB. Thyroid eye disease. Mo Med. 2022;119:343-50.
2. Li Z, Cestari DM, Fortin E. Thyroid eye disease: what is new to know? Curr Opin Ophthalmol. 2018;29:528-34.
3. Kahaly GJ, Bartalena L, Hegedüs L, Leenhardt L, Poppe K, Pearce SH. 2018 European Thyroid Association guideline for the management of Graves' hyperthyroidism. Eur Thyroid J. 2018;7:167-86.
4. Smith TJ, Hegedüs L. Graves' disease. N Engl J Med. 2016;375:1552-65.
5. Smith TJ, Janssen J. Insulin-like Growth factor-I receptor and thyroid-associated ophthalmopathy. Endocr Rev. 2019;40:236-67.
6. Chin YH, Ng CH, Lee MH, Koh JWH, Kiew J, Yang SP, et al. Prevalence of thyroid eye disease in Graves' disease: a meta-analysis and systematic review. Clin Endocrinol (Oxf). 2020;93:363-74.
7. Bartalena L, Gallo D, Tanda ML, Kahaly GJ. Thyroid eye disease: epidemiology, natural history, and risk factors. Ophthalmic Plast Reconstr Surg. 2023;39:2-8.
8. Lombardi A, Menconi F, Greenberg D, Concepcion E, Leo M, Rocchi R, et al. Dissecting the genetic susceptibility to Graves' disease in a cohort of patients of Italian origin. Front Endocrinol (Lausanne). 2016;7:21.
9. Bartley GB. The epidemiologic characteristics and clinical course of ophthalmopathy associated with autoimmune thyroid disease in Olmsted County, Minnesota. Trans Am Ophthalmol Soc. 1994;92:477-588.
10. Laurberg P, Berman DC, Bülow Pedersen I, Andersen S, Carlé A. Incidence and clinical presentation of moderate to severe graves' orbitopathy in a Danish population before and after iodine fortification of salt. J Clin Endocrinol Metab. 2012;97:2325-32.
11. Tanda ML, Piantanida E, Liparulo L, Veronesi G, Lai A, Sassi L, et al. Prevalence and natural history of Graves' orbitopathy in a large series of patients with newly diagnosed graves' hyperthyroidism seen at a single center. J Clin Endocrinol Metab. 2013;98:1443-9.
12. Gonçalves AC, Gebrim EM, Monteiro ML. Imaging studies for diagnosing Graves' orbitopathy and dysthyroid optic neuropathy. Clinics (Sao Paulo). 2012;67:1327-34.
13. Hoang TD, Stocker DJ, Chou EL, Burch HB. 2022 update on clinical management of graves disease and thyroid eye disease. Endocrinol Metab Clin North Am. 2022;51:287-304.

14. Savku E, Gündüz K. Diagnosis, follow-up and treatment results in thyroid ophthalmopathy. Turk J Ophthalmol. 2015;45:156-63.
15. Khong JJ, Finch S, De Silva C, Rylander S, Craig JE, Selva D, et al. Risk factors for Graves' orbitopathy; the australian thyroid-associated orbitopathy research (ATOR) study. J Clin Endocrinol Metab. 2016;101:2711-20.
16. Hiromatsu Y, Eguchi H, Tani J, Kasaoka M, Teshima Y. Graves' ophthalmopathy: epidemiology and natural history. Intern Med. 2014;53:353-60.
17. Piantanida E, Tanda ML, Lai A, Sassi L, Bartalena L. Prevalence and natural history of Graves' orbitopathy in the XXI century. J Endocrinol Invest. 2013;36:444-9.
18. Subramaniam DL, Yadalla D, Rajagopalan J. Are severe forms of thyroid eye disease common in the Indian population? Clinical characteristics of 136 patients from a tertiary eye care centre. Indian J Endocrinol Metab. 2023;27:56-61.
19. Bartalena L, Kahaly GJ, Baldeschi L, Dayan CM, Eckstein A, Marcocci C, et al. The 2021 European Group on Graves' orbitopathy (EUGOGO) clinical practice guidelines for the medical management of Graves' orbitopathy. Eur J Endocrinol. 2021;185:G43-67.
20. Sarić-Matutinović M, Diana T, Nedeljković-Beleslin B, Ćirić J, Žarković M, Perović-Blagojević I, et al. Sensitivity of three thyrotropin receptor antibody assays in thyroid-associated orbitopathy. J Med Biochem. 2022;41:211-20.
21. George A, Diana T, Längericht J, Kahaly GJ. Stimulatory thyrotropin receptor antibodies are a biomarker for Graves' orbitopathy. Front Endocrinol (Lausanne). 2021;11:629925.
22. Vannucchi G, Campi I, Bonomi M, Covelli D, Dazzi D, Currò N, et al. Rituximab treatment in patients with active Graves' orbitopathy: effects on proinflammatory and humoral immune reactions. Clin Exp Immunol. 2010;161:436-43.
23. Mourits MP, Prummel MF, Wiersinga WM, Koornneef L. Clinical activity score as a guide in the management of patients with Graves' ophthalmopathy. Clin Endocrinol (Oxf). 1997;47:9-14.
24. Shah SS, Patel BC. Thyroid eye disease. [Updated 2023 May 22]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK582134/
25. Scarabosio A, Surico PL, Singh RB, Tereshenko V, Musa M, D'Esposito F, et al. Thyroid eye disease: advancements in orbital and ocular pathology management. J Pers Med. 2024;14:776.
26. Stan MN, Bahn RS. Risk factors for development or deterioration of Graves' ophthalmopathy. Thyroid. 2010;20:777-83.
27. Pfeilschifter J, Ziegler R. Smoking and endocrine ophthalmopathy: impact of smoking severity and current vs lifetime cigarette consumption. Clin Endocrinol (Oxf). 1996;45:477-81.
28. Marcocci C, Marinò M. Treatment of mild, moderate-to-severe and very severe Graves' orbitopathy. Best Pract Res Clin Endocrinol Metab. 2012;26:325-37.
29. Längericht J, Krämer I, Kahaly GJ. Glucocorticoids in Graves' orbitopathy: mechanisms of action and clinical application. Ther Adv Endocrinol Metab. 2020;11:2042018820958335.
30. Bartalena L, Tanda ML. Current concepts regarding Graves' orbitopathy. J Intern Med. 2022;292:692-716.