INSIGHTS-JOURNAL OF
HEALTH AND REHABILITATION

INSIGHTS-JHR
INSIGHTS-JOURNAL OF HEALTH AND REHABILITATION

SILENT THYROID, RARE BUT REAL. OCULAR MANIFESTATION OF EUTHYROID GRAVES' EYE DISEASE, PERSPECTIVE OF OCULOPLASTIC CENTER

Original Research

Nuzhat Rahil[1], Bilal Khan[2]*, Muhammad Idris[3], Ramin Ali[4], Arib Malik[5], Muhammad Israr[6]

[1]Assistant Professor and Head, Department of Ophthalmology, Medical Teaching Institute, Lady Reading Hospital, Peshawar, Pakistan.
[2]Assistant Professor of Ophthalmology, Khyber Teaching Hospital, Peshawar, Pakistan.
[3]Associate Professor of Ophthalmology, Lady Reading Hospital, Peshawar, Pakistan.
[4]Student, MSc Public Health, Berlin, Germany.
[5]MBBS Student (Fourth Year), Khyber Medical College, Peshawar, Pakistan.
[6]Vitreo-retinal Fellow, Ophthalmology, Khyber Teaching Hospital, Peshawar, Pakistan.
Corresponding Author: Bilal Khan, Assistant Professor of Ophthalmology, Khyber Teaching Hospital, Peshawar, Pakistan, drbilalokz@gmail.com
Acknowledgement: The authors acknowledge the support of the Oculoplastic Unit, Lady Reading Hospital, Peshawar.

Conflict of Interest: None
Grant Support & Financial Support: None

ABSTRACT

Background: Euthyroid Graves' disease (EGD) is a rare manifestation of thyroid-associated ophthalmopathy (TAO) occurring in patients with normal thyroid function. While TAO is well-documented in hyperthyroid patients, the characteristics and progression of EGD remain under-researched due to its low prevalence. Delays in diagnosis are common as patients lack systemic thyroid symptoms, and its clinical presentation often overlaps with other orbital pathologies. Early recognition of EGD is critical to preventing vision-threatening complications and reducing morbidity.

Objective: To determine the clinical signs and demographic distribution of EGD in patients attending a tertiary oculoplastic service.

Methods: A cross-sectional study was conducted at the Oculoplastic Center of Medical Teaching Institute, Lady Reading Hospital, Peshawar, from January 2019 to December 2020. All consecutive patients diagnosed with EGD based on clinical and radiological findings and normal thyroid function tests were included. Data on demographics and clinical features were collected and analyzed using SPSS version 25. Frequencies and percentages were used for categorical variables, and mean ± standard deviation was calculated for continuous variables such as age. Chi-square and t-tests were applied where relevant, with a p-value of <0.05 considered statistically significant.

Results: Out of 48 patients enrolled, 31 (63.3%) were female and 17 (36.7%) male. The majority, 30 patients (61.2%), were over 51 years old. Eyelid retraction was the most common sign, seen in 21 females (42.9%) and 10 males (20.4%). Eyelid swelling was noted in 13 females (26.5%) and 9 males (18.4%). Proptosis was more prevalent in males. In the >51 age group, 18 patients (38.7%) presented with eyelid retraction, followed by 12 (24.5%) with eyelid swelling. Optic neuropathy was identified in 4 cases (8.2%).

Conclusion: Upper eyelid retraction was the most frequent clinical sign in EGD, particularly in older females. Serious complications like optic neuropathy and myopathy underscore the importance of early identification and multidisciplinary management in euthyroid patients presenting with orbital symptoms.

Keywords: Aged; Clinical Features; Euthyroid Graves' Disease; Female; Optic Neuropathy; Thyroid-Associated Ophthalmopathy; Thyroid Function Tests.

INSIGHTS-JOURNAL OF
HEALTH AND REHABILITATION

INTRODUCTION

Thyroid-associated ophthalmopathy (TAO), a debilitating autoimmune condition most commonly seen in hyperthyroid individuals, can also present in patients with normal thyroid function, a phenomenon referred to as euthyroid Graves' disease (EGD) or euthyroid Graves' ophthalmopathy (EGO). This variant, although rare, represents a diagnostic and therapeutic challenge due to its atypical clinical course and the absence of overt thyroid dysfunction. The reported prevalence of EGD varies widely, ranging from 0.7% to 21%, which is largely attributed to under-recognition and the lack of standardized diagnostic criteria (1). In classic Graves' disease, TAO is often linked to elevated levels of thyroid-stimulating immunoglobulins (TSI), which stimulate the thyroid-stimulating hormone receptor (TSHR) expressed on orbital fibroblasts, leading to inflammatory and fibrotic changes in periorbital tissues (2). However, this mechanism becomes less straightforward in patients with normal thyroid function and negative serologic tests, further complicating clinical assessment (3). A significant diagnostic dilemma arises when patients present with the ocular features of TAO—such as eyelid retraction, proptosis, diplopia, lid lag, and extraocular muscle involvement—yet lack biochemical evidence of thyroid dysfunction or circulating TSHR autoantibodies (4). Only a minority of patients with Graves' orbitopathy exhibit the classical signs of thyroid hormone imbalance, and this subgroup falls under the category of EGO, where the pathophysiology remains poorly understood (5). The heterogeneity of clinical presentation in these patients has raised questions about the underlying immunologic triggers, with some researchers proposing localized autoimmune activity confined to orbital tissues, independent of systemic thyroid involvement. Furthermore, no consensus exists on the diagnostic criteria for EGD, contributing to delays in diagnosis and timely management (6,7).

Clinical progression in EGD appears to be highly variable and unpredictable. Studies suggest that the course of TAO in euthyroid individuals is not significantly influenced by the restoration of thyroid function or adjustment of antithyroid medication, such as methimazole, indicating that traditional therapeutic strategies may not be applicable to this subgroup (8,9). Although the hallmark ocular features are shared with hyperthyroid TAO, the disease may follow a milder or more asymmetric course in euthyroid or hypothyroid patients (10,11). Nevertheless, the delayed recognition and underdiagnosis of this condition can result in advanced disease at presentation, particularly in regions where access to specialized oculoplastic care is limited. Given the scarcity of regional data and the clinical burden posed by delayed diagnosis, this study was undertaken to identify and document the clinical presentations of euthyroid Graves' disease in patients presenting to a tertiary oculoplastic service. By delineating these patterns, the study aims to enhance early recognition and inform better management strategies for this often-overlooked manifestation of thyroid eye disease.

METHODS

A retrospective study was conducted at the tertiary oculoplastic service of Lady Reading Hospital, Peshawar, from January 2019 to December 2020. The study enrolled consecutive patients diagnosed with euthyroid Graves' disease (EGD), selected based on multidisciplinary clinical assessment involving ophthalmologic examination, thyroid function testing, and orbital imaging. Inclusion criteria were patients presenting with clinical signs of thyroid-associated ophthalmopathy (TAO), normal thyroid function tests—defined as serum thyroxine (T4), triiodothyronine (T3), and thyroid-stimulating hormone (TSH) levels within reference ranges—and no current or prior history of hyperthyroidism, hypothyroidism, or treatment with thyroid-modifying agents. Patients who failed to meet these criteria were excluded from the study. Diagnosis of EGD was established through a combination of clinical ophthalmic features—including eyelid retraction, lid swelling, proptosis, diplopia, and signs of optic neuropathy—and radiological findings. Orbital imaging modalities used included contrast-enhanced computed tomography (CT), T2-weighted short tau inversion recovery (STIR) magnetic resonance imaging (MRI), and ultrasonography, depending on clinical indication and availability. Imaging findings supportive of EGD included extraocular muscle thickening, inflammatory fat stranding, and evidence of orbital congestion. Laboratory testing for thyroid-specific antibodies—such as thyroid-stimulating hormone receptor antibodies (TRAb), thyroid-binding inhibitory immunoglobulin (TBII), long-acting thyroid stimulators (LATS), thyroid peroxidase antibodies (TPOAb), and thyroglobulin antibodies (TgAb)—was performed when available. In cases where thyroid antibodies were negative, diagnosis was supported by a consistent clinical and imaging profile in the absence of systemic thyroid dysfunction or prior antithyroid treatment, in accordance with established diagnostic criteria for EGD (8).

INSIGHTS-JHR
INSIGHTS-JOURNAL OF HEALTH AND REHABILITATION

A total of 49 patients met the study criteria. Data extracted included demographic details such as age and gender, as well as clinical findings. Exophthalmos was quantified using a Hertel's exophthalmometer, with >3 mm displacement considered significant. Eyelid changes, relative afferent pupillary defect (RAPD) indicating optic nerve involvement, and extraocular motility restriction were systematically recorded. Written informed consent was obtained from all participants or their guardians. The study was conducted in accordance with the ethical standards of the Declaration of Helsinki and was approved by the Institutional Review Board of Lady Reading Hospital. Statistical analysis was performed using SPSS software, version 25. Descriptive statistics were used to summarize demographic and clinical characteristics. Continuous variables were expressed as means ± standard deviation, and categorical variables as frequencies and percentages. Between-group comparisons were conducted using the chi-square test or Fisher's exact test where appropriate for categorical variables, and the one-sample t-test for continuous variables. A p-value of less than 0.05 was considered statistically significant for all analyses.

RESULTS

A total of 48 patients diagnosed with euthyroid Graves' disease were included in the study. Of these, 31 (63.3%) were female and 17 (36.7%) were male. The majority of patients, 30 (61.2%), belonged to the age group of 51 years and above, followed by 11 patients (22.2%) in the 41–50 year age group. The remaining patients were distributed across the younger age brackets, though their frequencies were comparatively lower. Among the clinical manifestations, eyelid retraction emerged as the most frequently observed sign, present in 21 (42.9%) females and 10 (20.4%) males. Eyelid swelling was the second most common feature, seen in 13 (26.5%) females, while proptosis was most frequently observed in males, reported in 7 (14.3%) cases. In terms of age-specific presentation, patients aged over 51 years showed a notably higher frequency of eyelid retraction in 18 cases (38.7%), followed by eyelid swelling in 12 cases (24.5%). Statistical analysis revealed that none of the associations between clinical signs and age groups reached statistical significance. The p-values for eyelid swelling, eyelid retraction, proptosis, optic nerve dysfunction assessed by relative afferent pupillary defect (RAPD), and restrictive extraocular myopathy were 0.945, 0.673, 0.109, 0.558, and 0.833 respectively, indicating no significant correlation between age and specific clinical signs.

Visual documentation of selected patients was also obtained. One of the commonest presentations was a 27-year-old female exhibiting isolated left eyelid retraction. Another illustrative case was a 65-year-old male who presented with advanced disease, including pronounced eyelid retraction, upper and lower lid retraction, periorbital edema, conjunctival chemosis, and axial proptosis measuring 2 mm. In addition to the primary signs reported, several less common but clinically relevant features associated with thyroid-associated ophthalmopathy were also observed among the study population. Conjunctival chemosis was noted in 6 patients (12.5%), predominantly in those with more advanced disease presentations. Diplopia was reported in 4 individuals (8.3%), with 3 cases occurring in males above the age of 50. Lid lag on downgaze was observed in 5 patients (10.4%), mostly among females. These findings, although less frequent than eyelid retraction or swelling, underscore the variable and occasionally severe presentation of euthyroid Graves' ophthalmopathy and contribute further to the characterization of the disease spectrum in the studied cohort.

Table 1: Demographic Characteristics

Variable	n (%)
Total Patients	48 (100%)
Females	31 (63.3%)
Males	17 (36.7%)
Age ≥ 51 years	30 (61.2%)
Age 41–50 years	11 (22.2%)

Table 2: Clinical Signs by Gender

Clinical Sign	Females (n=31)	Males (n=17)
Eyelid Retraction	21 (42.9%)	10 (20.4%)
Eyelid Swelling	13 (26.5%)	
Proptosis		7 (14.3%)

INSIGHTS-JHR
INSIGHTS-JOURNAL OF HEALTH AND REHABILITATION

Table 3: Clinical Signs by Age Group (>51 years)

Clinical Sign	Age ≥ 51 Years (n=30)
Eyelid Retraction	18 (38.7%)
Eyelid Swelling	12 (24.5%)

Table 4: Statistical Significance of Clinical Signs by Age

Clinical Sign	p-value
Eyelid Swelling	0.945
Eyelid Retraction	0.673
Proptosis	0.109
Optic Nerve Dysfunction (RAPD)	0.558
Restrictive Extraocular Myopathy	0.833

Table 5: Additional Clinical Features in EGD Patients

Clinical Feature	Number of Patients (n=48)	Percentage (%)
Conjunctival Chemosis	6	12.5%
Diplopia	4	8.3%
Lid Lag	5	10.4%

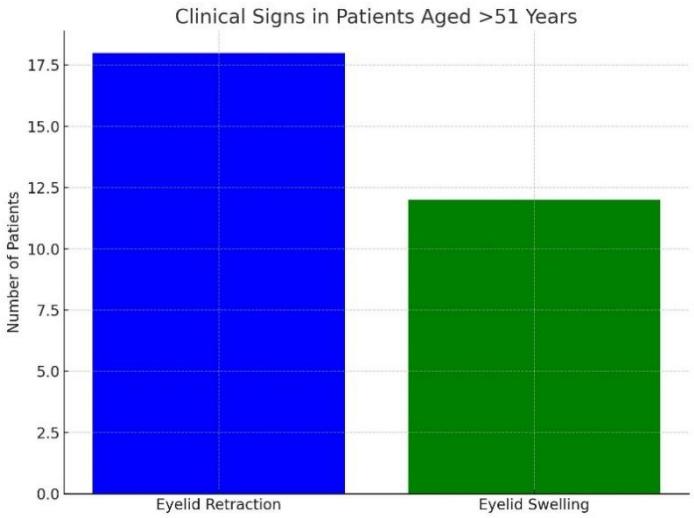

Figure 1 Clinical Signs in Patients Aged >51 Years

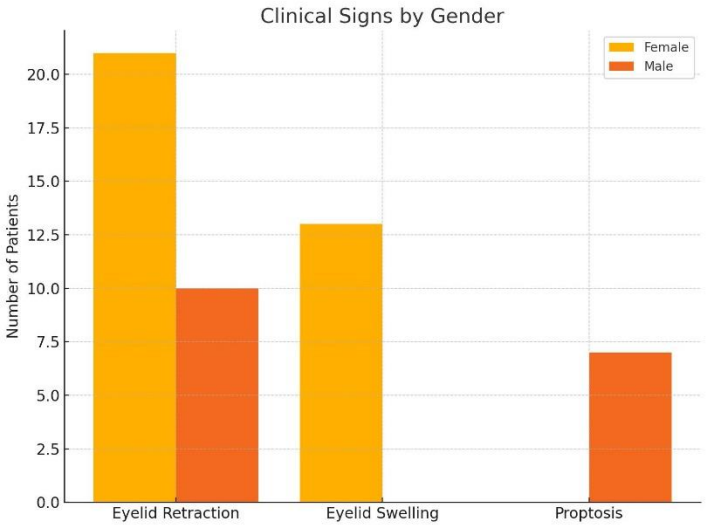

Figure 2 Clinical Signs by Gender

DISCUSSION

Thyroid-associated ophthalmopathy (TAO) presents a wide clinical spectrum and, although frequently linked with hyperthyroidism, it also manifests in individuals with normal or reduced thyroid function. In the current study, a higher frequency of euthyroid Graves' disease (EGD) was observed among patients above 50 years of age, which is consistent with previous research indicating age as a significant risk factor for thyroid disorders and related orbitopathy (12,13). TAO can occur in euthyroid, hypothyroid, or hyperthyroid states, and approximately 5% of TAO patients present with euthyroidism or hypothyroidism at the time of diagnosis, often with low anti-TSH receptor antibody titers (14). The distinct ocular features generally allow a straightforward diagnosis of TAO; however, in the absence of thyroid dysfunction or clinical suspicion, the condition may be underrecognized, leading to diagnostic and therapeutic delays, increased economic burden, and unnecessary investigations. This reinforces the clinical value of identifying and characterizing EGD specifically through its ophthalmic features. The findings from this study further emphasized eyelid retraction as the most prevalent

INSIGHTS-JHR
INSIGHTS-JOURNAL OF HEALTH AND REHABILITATION

clinical sign of EGD, particularly in females and in patients over 50 years of age. This aligns with global observations that women are more commonly affected by TAO, although men tend to exhibit more severe forms (15,16). Interestingly, although a milder asymmetric ophthalmopathy has been reported in euthyroid men compared to women (17), this study found no statistically significant gender-based differences in symptom severity, suggesting that gender-related differences may not be as clinically meaningful in all populations. Furthermore, the predominance of older individuals in this cohort is consistent with previous comparisons that noted similar mean ages of onset between euthyroid and dysthyroid groups (18).

Eyelid retraction, eyelid edema, proptosis, and extraocular muscle involvement were commonly reported signs in this cohort, corroborating international data that identify these as hallmark features of TAO (19). These manifestations, particularly eyelid retraction and periocular inflammation, are indicative of the active phase of the disease, a period during which prompt recognition is crucial for effective management and visual prognosis (20,21). The presence of optic nerve dysfunction, assessed by relative afferent pupillary defect (RAPD), was found in 8.2% of patients. Although less common, this finding is of significant concern due to its association with compressive optic neuropathy, often caused by medial rectus enlargement, and its unpredictable response to conventional treatment (22,23). The occurrence of optic neuropathy in EGD highlights the potential severity of the disease, even in the absence of overt thyroid dysfunction, and underscores the need for thorough ophthalmic and radiologic evaluations. An important strength of this study lies in its exclusive focus on euthyroid patients with TAO, a subgroup that remains underrepresented in existing literature despite its clinical relevance. By documenting the spectrum of ocular presentations in this population, the study adds to the understanding of EGD as a distinct clinical entity. However, several limitations must be acknowledged. The retrospective design may have introduced selection bias, and the reliance on available clinical and imaging records may have limited the assessment of more subtle findings. In addition, antibody testing was not uniformly available, which may have affected the ability to correlate serologic markers with clinical severity. Despite these limitations, the findings contribute to the growing recognition that EGD can mimic the full clinical spectrum of dysthyroid orbitopathy, necessitating long-term monitoring and a high index of suspicion in patients with suggestive ocular signs. Importantly, the possibility that patients with EGD may eventually develop thyroid dysfunction over time emphasizes the need for prolonged follow-up and interdisciplinary collaboration between endocrinology and ophthalmology services (24). Future research should consider prospective multicenter studies with standardized imaging, serologic evaluation, and long-term follow-up to better define the natural history, risk factors, and optimal management strategies for EGD.

CONCLUSION

Euthyroid Graves' disease most commonly presents with upper eyelid retraction and may progress to serious complications such as optic neuropathy, restrictive myopathy, and proptosis. The findings of this study emphasize that older adults, particularly females, are more frequently affected. Given the potential for delayed diagnosis due to normal thyroid function, it is crucial to recognize the ophthalmic signs early and monitor patients closely. Timely identification and management of sight-threatening complications require a multidisciplinary approach involving oculoplastic, strabismus, and neuro-ophthalmology services. Regular evaluation of thyroid status, even in the absence of biochemical abnormalities, remains essential to ensure comprehensive care and improved clinical outcomes in patients with this condition.

INSIGHTS-JHR
INSIGHTS-JOURNAL OF HEALTH AND REHABILITATION

AUTHOR CONTRIBUTION

Author	Contribution
Nuzhat Rahil	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Bilal Khan*	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published
Muhammad Idris	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published
Ramin Ali	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Arib Malik	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Muhammad Israr	Substantial Contribution to study design and Data Analysis Has given Final Approval of the version to be published

REFERENCES

1. Diana T, Ponto KA, Kahaly GJ. Thyrotropin receptor antibodies and Graves' orbitopathy. J Endocrinol Invest. 2021 Apr;44(4):703-712.
2. Moeen Z, Aliuddin AM, Gray Wlazlo T, Majid H, Kolli S. An Interesting Case of Euthyroid Graves' Ophthalmopathy, With Negative Thyroid-Stimulating Hormone Receptor Antibodies. Cureus. 2021 Oct 24;13(10): e19015.
3. Li Y, Teng D, Ba J, et al. Efficacy and safety of long-term universal salt iodization on thyroid disorders: epidemiological evidence from 31 provinces of mainland China. *Thyroid*. 2020;30(4):568-579.
4. Eshraghi B, Dehghan A, Javadi N, Fazel M. Nonspecific orbital inflammation and thyroid eye disease, a rare comorbidity: report of two cases and review of literature. BMC Ophthalmol. 2021 Jun 5;21(1):251.
5. Pan Y, Chen Y, Zhang J, et al. Doxycycline vs Placebo at 12 Weeks in Patients with Mild Thyroid-Associated Ophthalmopathy: A Randomized Clinical Trial. *JAMA Ophthalmol.* Published online September 29, 2022.
6. Macovei ML, Azis Ű, Gheorghe AG, Burcea M. A systematic review of euthyroid Graves' disease (Review). Exp Ther Med. 2021 ;22(5):1346.
7. Muñoz-Ortiz J, Sierra-Cote MC, Zapata-Bravo E, Valenzuela-Vallejo L, Marin-Noriega MA, Uribe-Reina P, Terreros-Dorado JP, Gómez-Suarez M, Arteaga-Rivera K, de-la-Torre A. Prevalence of hyperthyroidism, hypothyroidism, and euthyroidism in thyroid eye disease: A systematic review of the literature. *Syst Rev.* 2020;9(201)
8. Macovei ML, Azis Ű, Gheorghe AG, Burcea M. A systematic review of euthyroid Graves' disease (Review). *Exp Ther Med*. 2021;22(5):1346.
9. Hodgson NM, Rajaii F. Current understanding of the progression and management of thyroid associated orbitopathy: A systematic review. *Ophthalmol Ther.* 2020; 9:21□33.
10. Sears CM, Wang Y, Bailey LA, Turbin R, Subramanian PS, Douglas R, Cockerham K, Kossler AL. Early efficacy of teprotumumab for the treatment of dysthyroid optic neuropathy: A multicenter study. Am J Ophthalmol Case Rep. 2021; 23:101111.

11. Hirokawa T, Mimura M, Tonari M, Sato Y, Fujita Y, Matsuo J, Oku H, Sugasawa J, Ikeda T. Hirokawa T, et al Compressive optic neuropathy (CON) in Graves' disease caused by hypertrophy of levator and superior rectus muscles: A case report. Medicine (Baltimore). 2021 Apr 9;100(14): e25062.
12. 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(4):G43-g67.
13. Neag EJ, Smith TJ. 2021 update on thyroid-associated ophthalmopathy. J Endocrinol Invest. 2022;45(2):235-59.
14. 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(2):287-304.
15. Panagiotou G, Perros P. Asymmetric Graves' Orbitopathy. Front Endocrinol (Lausanne). 2020;11:611845.
16. Moledina M, Damato EM, Lee V. The changing landscape of thyroid eye disease: current clinical advances and future outlook. Eye (Lond). 2024;38(8):1425-37.
17. Duarte AF, Xavier NF, Sales Sanz M, Cruz AAV. Efficiency and Safety of Tocilizumab for the Treatment of Thyroid Eye Disease: A Systematic Review. Ophthalmic Plast Reconstr Surg. 2024;40(4):367-73.
18. Smith TJ, Hegedüs L, Lesser I, Perros P, Dorris K, Kinrade M, et al. How patients experience thyroid eye disease. Front Endocrinol (Lausanne). 2023;14:1283374.
19. Burch HB, Perros P, Bednarczuk T, Cooper DS, Dolman PJ, Leung AM, et al. Management of Thyroid Eye Disease: A Consensus Statement by the American Thyroid Association and the European Thyroid Association. Thyroid. 2022;32(12):1439-70.
20. Ing EB, Madjedi K, Hurwitz JJ, Nijhawan N, Oestreicher J, Torun N. Nomenclature: thyroid-associated orbitopathy, Graves ophthalmopathy, or thyroid eye disease? Can J Ophthalmol. 2021;56(1):e22-e4.
21. Szelog J, Swanson H, Sniegowski MC, Lyon DB. Thyroid Eye Disease. Mo Med. 2022;119(4):343-50.
22. Wagner LH, Bradley EA, Tooley AA, Ren Y, Rachmasari KN, Stan MN. Thyroid eye disease or Graves' orbitopathy: What name to use, and why it matters. Front Endocrinol (Lausanne). 2022;13:1083886.
23. Bartalena L, Gallo D, Tanda ML, Kahaly GJ. Thyroid Eye Disease: Epidemiology, Natural History, and Risk Factors. Ophthalmic Plast Reconstr Surg. 2023;39(6s):S2-s8.
24. González-García A, Sales-Sanz M. Treatment of Graves' ophthalmopathy. Med Clin (Barc). 2021;156(4):180-6.