How to Cite:
Al-Mutairi, N. S. A., Alharthi, M. M. H., Saleh, S., Aldossri, H. A. Z., Alqahtani, M. N. A., Alotaibi, F. Z. H., Almutairi, M. A., Alotaibi, A. S. M., & Alruqi, M. K. (2020). Euthyroid graves' disease: Clinical characteristics, pathophysiological mechanisms, diagnostic challenges, and contemporary management approaches. *International Journal of Health Sciences*, *4*(S1), 560–577. https://doi.org/10.53730/ijhs.v4nS1.15986

Euthyroid graves' disease: Clinical characteristics, pathophysiological mechanisms, diagnostic challenges, and contemporary management approaches

Nader Saad Awad Al-Mutairi
National Guard Health Affairs

Mashan Mashal Hubaylis Alharthi
National Guard Health Affairs

Shaie Saleh
National Guard Health Affairs

Hzam Alkorbi Zid Aldossri
National Guard Health Affairs

Mohammad Naseer Ali Alqahtani
National Guard Health Affairs

Faisal Zabin Hashar Alotaibi
National Guard Health Affairs

Muteb Abdullah Almutairi
National Guard Health Affairs

Abdullah Saleh Mohammed Alotaibi
National Guard Health Affairs

Mohammed Khalaf Alruqi
National Guard Health Affairs

***Abstract*---Background:** Euthyroid Graves' disease (EGD) is an uncommon subtype of thyroid-associated ophthalmopathy characterized by orbital autoimmune inflammation occurring in the absence of clinical or biochemical thyroid dysfunction. Although it shares several immunopathological mechanisms with Graves' disease, EGD presents unique diagnostic and therapeutic challenges because

ocular manifestations frequently precede thyroid abnormalities and conventional thyroid autoantibodies may be absent. Early recognition is therefore essential to prevent disease progression and preserve visual function. **Aim:** This review aimed to summarize the current evidence regarding the epidemiology, risk factors, pathogenesis, clinical characteristics, diagnosis, and management considerations of euthyroid Graves' disease. **Methods:** A comprehensive narrative review of published literature was conducted, focusing on clinical studies, systematic reviews, observational investigations, and experimental research evaluating the immunological mechanisms, diagnostic biomarkers, imaging characteristics, clinical manifestations, and long-term outcomes of patients with EGD. **Results:** Available evidence indicates that EGD accounts for approximately 0.9–15.4% of Graves' ophthalmopathy cases and generally presents with milder, asymmetric, or unilateral orbital involvement. Orbital fibroblast activation, T-cell-mediated inflammation, and TSH receptor autoimmunity are central pathogenic mechanisms. Thyroid-stimulating antibodies demonstrate greater diagnostic sensitivity than conventional antibody assays, while orbital CT and MRI provide valuable diagnostic confirmation. Although most patients remain euthyroid initially, approximately 8–25% subsequently develop thyroid dysfunction during long-term follow-up. Early diagnosis and multidisciplinary management improve clinical outcomes and reduce the risk of vision-threatening complications. **Conclusion:** EGD represents a distinct autoimmune orbital disorder requiring comprehensive clinical evaluation, advanced serological testing, appropriate orbital imaging, and prolonged endocrinological surveillance. Improved understanding of its pathogenesis and biomarkers may facilitate earlier diagnosis and more individualized therapeutic strategies.

***Keywords*---**Euthyroid Graves' disease, thyroid-associated ophthalmopathy, Graves' orbitopathy, thyroid-stimulating antibodies, thyrotropin receptor antibodies, orbital fibroblasts, autoimmune disease, orbital imaging.

Introduction

Thyroid-associated ophthalmopathy (TAO), also referred to as thyroid eye disease (TED), represents the most common autoimmune inflammatory disorder affecting the orbit and is closely associated with autoimmune thyroid diseases, particularly Graves' disease and, less frequently, Hashimoto thyroiditis [1]. The condition is characterized by immune-mediated inflammation of the orbital connective tissues and extraocular muscles, leading to progressive orbital remodeling, expansion of adipose tissue, fibrosis, and varying degrees of ocular dysfunction. Clinical manifestations range from mild ocular discomfort and eyelid retraction to proptosis, restrictive extraocular myopathy, diplopia, exposure keratopathy, compressive optic neuropathy, and, in severe cases, permanent visual impairment. Although the disease frequently follows a self-limiting course, its

functional, cosmetic, and psychosocial consequences can substantially impair patients' quality of life and necessitate multidisciplinary management involving endocrinologists, ophthalmologists, radiologists, and orbital surgeons [1]. The occurrence of thyroid-associated ophthalmopathy is strongly linked to abnormalities in thyroid autoimmunity, with hyperthyroidism secondary to Graves' disease representing the predominant clinical association. Nevertheless, the disorder may also develop in patients with hypothyroidism or in individuals who remain euthyroid throughout the disease course. A systematic review conducted by Muñoz-Ortiz et al. demonstrated that approximately 86.2% of patients with thyroid-associated ophthalmopathy present with hyperthyroidism, whereas 10.36% exhibit hypothyroidism and only 7.9% remain euthyroid [2]. These epidemiological findings emphasize the close relationship between orbital inflammation and thyroid dysfunction while simultaneously highlighting the existence of a clinically important subgroup of patients in whom ophthalmopathy develops independently of overt thyroid disease.

The temporal relationship between thyroid dysfunction and orbital manifestations is highly variable and contributes significantly to the diagnostic complexity of thyroid-associated ophthalmopathy. Although thyroid dysfunction commonly precedes the onset of ocular manifestations, ophthalmic involvement may develop before biochemical or clinical evidence of thyroid disease becomes apparent. Previous investigations have reported that ophthalmopathy precedes thyroid dysfunction in approximately 19.6% of affected individuals, whereas nearly 80% of patients with Graves' disease develop ophthalmologic manifestations within 18 months following the diagnosis of thyroid dysfunction [3]. These observations indicate that orbital disease and thyroid abnormalities do not necessarily evolve simultaneously and underscore the importance of maintaining a high index of clinical suspicion when evaluating patients presenting with unexplained inflammatory orbital disease. Among the various clinical phenotypes of thyroid-associated ophthalmopathy, euthyroid Graves' disease (EGD) represents an uncommon yet clinically significant entity. EGD is defined as autoimmune infiltrative orbitopathy occurring in individuals who demonstrate no current or previous clinical or biochemical evidence of thyroid dysfunction and who have not received antithyroid therapy [4]. Unlike classical Graves' ophthalmopathy, patients with EGD present with characteristic orbital manifestations despite maintaining normal thyroid hormone concentrations and the absence of clinically detectable thyroid disease. The rarity of this condition presents considerable diagnostic challenges, frequently resulting in delayed recognition or misdiagnosis as other inflammatory, neoplastic, infectious, or idiopathic orbital disorders. Consequently, careful exclusion of alternative orbital pathologies is required before establishing the diagnosis of euthyroid Graves' disease.

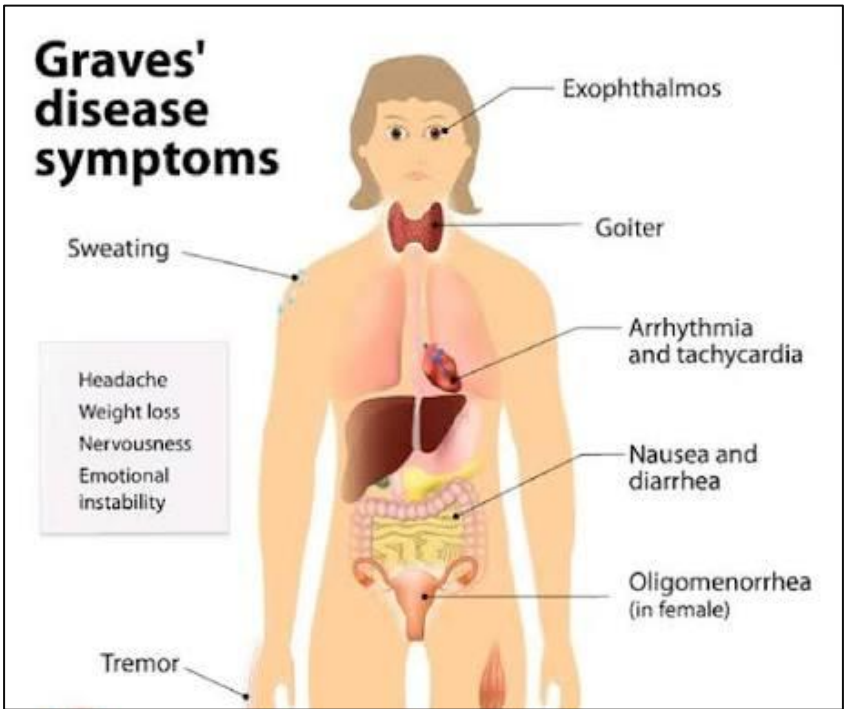

Figure 1. Graves Disease Symptoms

The limited prevalence of EGD has resulted in relatively few comprehensive investigations evaluating its epidemiology, clinical characteristics, natural history, immunopathogenesis, and therapeutic outcomes. Most of the available evidence originates from isolated case reports, small retrospective series, and narrative reviews rather than large prospective clinical studies [5]. Consequently, many aspects of the disease remain incompletely understood, including the precise mechanisms responsible for orbital inflammation in the absence of clinically apparent thyroid dysfunction, the optimal diagnostic criteria, predictors of disease progression, and the most effective long-term management strategies. This scarcity of high-quality evidence continues to pose challenges for clinicians managing affected patients and highlights the need for further multicenter investigations. An important clinical consideration in patients diagnosed with euthyroid Graves' disease is the possibility that orbital manifestations represent the earliest phase of evolving autoimmune thyroid disease rather than a permanently isolated orbital disorder. Current evidence suggests that euthyroid ophthalmopathy may precede the future development of thyroid dysfunction, indicating that the orbital autoimmune process can become clinically evident before detectable abnormalities in thyroid hormone production or thyroid gland function emerge [5]. Furthermore, some patients categorized as euthyroid may have experienced previous transient or subclinical thyroid abnormalities that remained undetected because of spontaneous resolution or lack of biochemical assessment during the earlier stages of disease [5]. These observations reinforce the concept that euthyroid Graves' disease exists within the broader clinical spectrum of autoimmune thyroid disorders rather than representing an entirely separate pathological entity. For these reasons, continuous biochemical

surveillance constitutes a fundamental component of patient management. Periodic assessment of thyroid function and thyroid autoantibodies is essential throughout follow-up, even in patients who initially demonstrate persistently normal thyroid hormone concentrations. Longitudinal studies have reported that overt dysthyroidism subsequently develops in approximately 8–25% of patients within 15–45 months after the initial presentation of euthyroid ophthalmopathy [5]. Nevertheless, considerable heterogeneity exists in disease progression, as illustrated by reports describing individuals who remained euthyroid despite prolonged observation extending over 12 years without developing any clinical or biochemical evidence of thyroid dysfunction [6]. These findings emphasize the unpredictable clinical course of euthyroid Graves' disease and support the necessity for individualized long-term monitoring, comprehensive endocrine evaluation, and coordinated multidisciplinary follow-up to facilitate early detection of thyroid abnormalities and optimize clinical outcomes [5,6].

Epidemiology and Risk Factors

Euthyroid Graves' disease (EGD) represents an uncommon clinical subtype within the spectrum of thyroid-associated ophthalmopathy (TAO), characterized by the presence of orbital inflammatory manifestations despite normal thyroid function and the absence of clinically apparent thyroid disease. Although Graves' orbitopathy (GO) is most frequently associated with hyperthyroidism, accumulating evidence indicates that orbital involvement may also occur in euthyroid individuals, thereby creating significant diagnostic and therapeutic challenges. The reported prevalence of Graves' orbitopathy in patients with normal thyroid function varies considerably across published studies, ranging from 0.9% to 15.4% [2]. This wide variation is likely attributable to differences in study populations, diagnostic criteria, duration of follow-up, laboratory methodologies, and geographical and ethnic factors. Furthermore, because euthyroid patients frequently remain undiagnosed or are initially misclassified as having idiopathic orbital inflammatory disorders, the true prevalence of EGD is likely underestimated. The demographic characteristics of euthyroid Graves' disease appear to resemble those observed in patients with conventional thyroid-associated ophthalmopathy. Comparative analyses have demonstrated that the average age at disease onset is approximately 53.3 years among euthyroid patients and 54.6 years among individuals with dysthyroid Graves' ophthalmopathy, suggesting that age does not substantially influence the clinical phenotype of orbital disease [7]. These findings support the concept that autoimmune orbital inflammation develops during a similar period of adult life regardless of thyroid functional status. Nevertheless, subtle differences in demographic characteristics have been reported, particularly regarding sex distribution and disease severity.

Although Graves' disease generally demonstrates a marked female predominance, the gender distribution appears less pronounced among patients with euthyroid Graves' disease. Comparative studies have suggested that the overall sex ratio is relatively similar between euthyroid and dysthyroid populations [7]. However, other investigations have identified lower female-to-male ratios of approximately 1.62 among euthyroid patients compared with 3.2 in classical Graves' disease, indicating a relatively greater frequency of orbital involvement among men who

remain euthyroid [7]. Interestingly, despite this increased representation of males within the euthyroid population, several studies have observed that male patients tend to develop milder and frequently asymmetric forms of thyroid-associated ophthalmopathy, characterized by unilateral or markedly unequal orbital involvement [8]. These observations suggest that sex-related biological factors may influence disease expression independently of thyroid hormone abnormalities and warrant further investigation into the immunological and genetic mechanisms underlying these differences. The pathogenesis of euthyroid Graves' disease is multifactorial and results from a complex interaction between genetic susceptibility, immune dysregulation, hormonal influences, and environmental exposures. Similar to classical Graves' ophthalmopathy, disease development is believed to require the convergence of multiple endogenous and exogenous risk factors that collectively initiate and perpetuate autoimmune inflammation within orbital tissues [2]. Endogenous factors include inherited genetic predisposition, advancing age, sex, and elevated concentrations of thyrotropin receptor antibodies (TRAb), whereas environmental contributors encompass iodine intake, oxidative stress, cigarette smoking, psychosocial stress, bacterial and viral infections, as well as exposure to certain medications capable of altering immune function [2]. The multifactorial nature of EGD explains the considerable variability in disease onset, severity, progression, and therapeutic response observed among affected individuals.

Among the recognized environmental risk factors, cigarette smoking remains the most consistently established and clinically significant determinant of disease development and progression. Smoking prevalence among patients with euthyroid Graves' disease closely parallels that reported in hyperthyroid and hypothyroid forms of thyroid-associated ophthalmopathy, emphasizing that tobacco exposure exerts its pathogenic effects independently of thyroid functional status [5]. Termote et al. reported that approximately 40% of patients with euthyroid Graves' disease were active smokers, highlighting the substantial contribution of tobacco use to disease occurrence [5]. Numerous investigations have demonstrated that cigarette smoking significantly increases both the likelihood of developing thyroid-associated ophthalmopathy and the severity of orbital inflammation. Smoking has been associated with accelerated disease progression, increased orbital tissue expansion, greater degrees of proptosis, higher incidence of restrictive extraocular myopathy leading to diplopia, and poorer visual outcomes [9]. Moreover, smoking adversely influences therapeutic efficacy, as smokers frequently exhibit delayed or diminished responses to immunosuppressive therapy, particularly in patients with moderate-to-severe active Graves' orbitopathy [9]. These observations underscore the importance of smoking cessation as a fundamental component of disease prevention and comprehensive patient management. Autoimmune mechanisms remain central to the pathogenesis of euthyroid Graves' disease, with thyrotropin receptor antibodies playing a pivotal role in both thyroid dysfunction and orbital inflammation. TRAb are well established as the principal pathogenic autoantibodies responsible for stimulating thyroid hormone production in Graves' hyperthyroidism [10]. However, their biological activity extends beyond the thyroid gland, as thyrotropin receptors are also expressed on orbital fibroblasts and preadipocytes. Activation of these receptors promotes inflammatory cytokine production, fibroblast proliferation, adipogenesis, glycosaminoglycan accumulation, and progressive expansion of orbital connective tissues.

Importantly, these pathogenic processes may occur even in the absence of overt thyroid dysfunction, providing a plausible explanation for the development of ophthalmopathy in euthyroid individuals.

Several studies have investigated the relationship between disease activity and circulating thyroid autoantibody concentrations in euthyroid patients. Gerding et al. evaluated untreated individuals with euthyroid ophthalmopathy and demonstrated a significant association between clinical disease activity, degree of proptosis, and serum concentrations of thyroid-stimulating antibodies (TSAb) and thyrotropin-binding inhibitory immunoglobulins (TBII) [11]. Elevated TSAb and TBII titers correlated positively with disease severity, suggesting that these immunological markers may serve as valuable indicators of orbital inflammatory activity even when thyroid hormone concentrations remain within normal limits. These findings support the concept that autoimmune activation rather than thyroid dysfunction itself constitutes the principal driver of orbital disease progression in euthyroid Graves' disease. Genetic susceptibility has also been implicated in the development of euthyroid Graves' disease, although the precise genetic architecture remains incompletely understood. Human leukocyte antigen (HLA) polymorphisms appear to contribute significantly to disease susceptibility by influencing antigen presentation and adaptive immune responses. Inoue et al. compared HLA typing among patients with euthyroid ophthalmopathy, Graves' ophthalmopathy, and Hashimoto thyroiditis-associated ophthalmopathy, demonstrating that euthyroid disease possesses a distinct genetic profile differing substantially from the other clinical subgroups [12]. Significant associations were identified with several HLA antigens, including HLA-B40 (w61), DR9, DQw3, HLA-B12, and Cw1, highlighting the genetic heterogeneity characteristic of euthyroid Graves' disease [12]. Among these markers, HLA-B12 exhibited the most striking difference, demonstrating an approximately 17-fold increase in frequency among euthyroid patients compared with the other study groups [12]. These observations suggest that unique immunogenetic pathways may predispose certain individuals to isolated orbital autoimmunity while protecting against clinically overt thyroid dysfunction.

Interestingly, despite evidence supporting a genetic contribution, other observations indicate that hereditary factors alone cannot fully explain disease development. Inoue et al. proposed that specific genetic mechanisms may actually protect susceptible individuals from developing persistent hyperthyroidism despite ongoing autoimmune orbital inflammation [12]. Furthermore, the relatively low prevalence of family history of diffuse goiter among patients with euthyroid Graves' disease suggests that traditional familial genetic risk factors associated with Graves' hyperthyroidism may play a comparatively limited role in isolated ophthalmopathy [12]. Nevertheless, additional investigations have continued to demonstrate evidence supporting genetic susceptibility. Ardley et al. reported that approximately 33% of euthyroid patients developed mild ocular manifestations associated with circulating autoantibodies directed against collagen XIII and calsequestrin-1 (CASQ1), both of which are expressed within extraocular muscle tissues [13]. The presence of these tissue-specific autoantibodies suggests that immune responses targeting orbital antigens may contribute to disease initiation independently of thyroid autoimmunity. Collectively, these findings indicate that euthyroid Graves' disease arises from a

multifaceted interaction between genetic predisposition, immune-mediated mechanisms, environmental exposures, and modifiable lifestyle factors, emphasizing the importance of individualized risk assessment and long-term clinical surveillance in affected patients.

Pathogenesis and Diagnosis of EGD

Euthyroid Graves' disease (EGD) shares several immunological and pathological characteristics with classical Graves' disease; however, the two conditions differ in their principal target organs and clinical manifestations. In EGD, the autoimmune response predominantly affects the orbital tissues while thyroid function remains clinically and biochemically normal, whereas Graves' disease primarily involves autoimmune stimulation of the thyroid gland leading to hyperthyroidism [2]. Despite these clinical differences, both disorders share the thyrotropin receptor (TSH-R) as a major autoantigen, highlighting the close immunopathological relationship between thyroid dysfunction and thyroid-associated ophthalmopathy. The selective orbital involvement observed in EGD suggests that local immunological mechanisms, tissue-specific susceptibility, and distinct molecular pathways contribute to disease development independently of overt thyroid abnormalities. The pathogenesis of EGD is driven by a complex interplay between immune cells, orbital fibroblasts, cytokines, and autoantibodies. Orbital fibroblasts serve as the principal effector cells in the disease process and play a central role in initiating and sustaining orbital inflammation. Autoimmune activation begins with the recruitment of activated T lymphocytes into the orbital connective tissue, where they interact with orbital fibroblasts expressing TSH-R and other surface receptors. This interaction stimulates fibroblast proliferation and promotes the production of large quantities of glycosaminoglycans, particularly hyaluronan, which possesses strong hydrophilic properties that lead to tissue edema and expansion of orbital contents [14]. In addition to extracellular matrix production, orbital fibroblasts can differentiate into adipocytes and myofibroblasts, thereby contributing to orbital fat expansion, fibrosis, and progressive remodeling of orbital tissues. These pathological changes ultimately produce the characteristic clinical manifestations of thyroid-associated ophthalmopathy, including proptosis, eyelid retraction, diplopia, and restricted ocular motility.

Several intracellular signaling pathways regulate fibroblast activation and disease progression in EGD. Activation of TSH-R stimulates both the phosphatidylinositol-3 kinase/protein kinase B (PI3K/Akt) signaling cascade and the adenylyl cyclase/cyclic adenosine monophosphate (cAMP) pathway, both of which promote fibroblast proliferation, adipogenesis, and glycosaminoglycan synthesis [14]. Furthermore, insulin-like growth factor-1 receptor (IGF-1R) signaling has emerged as another important contributor to orbital inflammation and tissue remodeling. The interaction between TSH-R and IGF-1R amplifies inflammatory responses within the orbit and enhances fibroblast activation, emphasizing the multifactorial molecular mechanisms responsible for disease progression. These signaling pathways have attracted considerable attention because they represent promising therapeutic targets for future biologic interventions. Immune-mediated inflammation within the orbit is further intensified through continuous interactions between activated T lymphocytes and

autoreactive B lymphocytes. Activated T cells release numerous pro-inflammatory cytokines that sustain chronic inflammation and recruit additional immune cells into orbital tissues [15]. This inflammatory microenvironment stimulates orbital fibroblasts to maintain extracellular matrix production while simultaneously promoting adipocyte differentiation and tissue remodeling. The cumulative consequences include enlargement of extraocular muscles, expansion of orbital adipose tissue, progressive orbital congestion, and fibrosis, all of which contribute to the characteristic clinical features of EGD. Experimental studies have further clarified the immunological basis of orbital involvement. Wakelkamp et al. demonstrated that expression of TSH receptor messenger RNA was significantly higher in orbital adipose and connective tissues obtained from patients with active untreated Graves' ophthalmopathy compared with patients exhibiting inactive disease [16]. These findings support the concept that increased local TSH-R expression enhances tissue susceptibility to autoimmune attack and contributes to disease activity. Moreover, the inflammatory environment in active orbital disease is characterized predominantly by T helper type 1 (Th1) cytokines, indicating that cellular immune responses dominate the early phase of disease development before humoral immunity becomes fully established [16]. As disease progresses, autoreactive B cells produce thyroid-specific autoantibodies that amplify inflammation and perpetuate orbital tissue damage.

Additional autoimmune mechanisms have also been proposed in the pathogenesis of EGD. Autoantigens derived from extraocular muscles, particularly calsequestrin, have been identified as potential targets of the autoimmune response. Calsequestrin has demonstrated promising diagnostic value as a sensitive and specific biomarker for thyroid-associated ophthalmopathy and may contribute directly to immune-mediated injury of extraocular muscles [17]. Recognition of these novel autoantigens has broadened current understanding of disease mechanisms and may facilitate the development of more accurate diagnostic tools and targeted therapeutic strategies. Diagnosing EGD remains particularly challenging because patients exhibit characteristic ophthalmopathy despite maintaining normal thyroid hormone concentrations and lacking a previous history of thyroid dysfunction. Consequently, diagnosis requires careful integration of clinical findings, laboratory investigations, and orbital imaging studies. Biochemical evaluation should demonstrate normal serum concentrations of thyroxine (T4), triiodothyronine (T3), and thyroid-stimulating hormone (TSH), while simultaneously excluding any previous thyroid disease or antithyroid treatment [18]. Since thyroid dysfunction may develop months or years after the onset of ophthalmopathy, long-term monitoring of thyroid function is considered an essential component of patient management. Imaging modalities play an important complementary role in confirming orbital involvement and assessing disease severity. Contrast-enhanced computed tomography (CT), T2-weighted short tau inversion recovery (STIR) magnetic resonance imaging (MRI), and orbital ultrasonography provide detailed visualization of extraocular muscle enlargement, orbital fat expansion, inflammatory edema, and other structural abnormalities characteristic of thyroid-associated ophthalmopathy [18]. These imaging techniques are valuable not only for establishing the diagnosis but also for evaluating disease activity, monitoring therapeutic response, and excluding alternative orbital pathologies.

Serological assessment significantly enhances diagnostic accuracy in patients suspected of having EGD. Detection of thyroid-specific autoantibodies, including thyrotropin receptor antibodies (TRAb), thyrotropin-binding inhibitory immunoglobulins (TBII), thyroid-stimulating antibodies (TSAb), thyroid peroxidase antibodies (TPOAb), thyroglobulin antibodies (TgAb), and long-acting thyroid stimulator assays, strongly supports the diagnosis despite preserved thyroid function [18]. Because both ophthalmopathy and thyroid-stimulating antibodies are highly specific indicators of Graves' disease, simultaneous measurement of TBII and TSAb is particularly valuable in atypical presentations, including unilateral disease or cases lacking prominent inflammatory manifestations [19]. Given the absence of thyroid dysfunction, EGD frequently resembles several other orbital disorders, making differential diagnosis an essential aspect of clinical evaluation. Alternative conditions requiring exclusion include idiopathic orbital inflammatory disease, sarcoidosis, amyloidosis, orbital cellulitis, vascular malformations, orbital neoplasms, lymphoma, systemic vasculitides, hydrocephalus, and drug-induced proptosis associated with agents such as lithium or corticosteroids [20]. Careful integration of clinical presentation, laboratory investigations, imaging findings, and immunological markers enables clinicians to establish an accurate diagnosis while minimizing diagnostic delay and facilitating timely therapeutic intervention.

Clinical Characteristics of EGD

Euthyroid Graves' disease (EGD) demonstrates a clinical course that closely resembles thyroid-associated ophthalmopathy (TAO) associated with Graves' disease, although it generally presents with milder manifestations and preserved thyroid function. The natural history of the disease follows the biphasic model described by Rundle, consisting of an initial active inflammatory phase followed by a chronic inactive stage. During the active phase, progressive autoimmune inflammation leads to orbital tissue edema, enlargement of extraocular muscles, and expansion of orbital adipose tissue. This inflammatory period usually persists for approximately 6–18 months before stabilizing into a chronic fibrotic phase characterized by minimal inflammatory activity but persistent structural abnormalities [21]. Understanding this temporal progression is essential because therapeutic interventions are generally most effective during the active inflammatory stage, whereas surgical rehabilitation is typically reserved for the stable chronic phase. The clinical manifestations of EGD largely parallel those observed in conventional Graves' ophthalmopathy, although disease severity is generally less pronounced. The most frequently encountered clinical findings include eyelid retraction, proptosis, restrictive strabismus resulting from extraocular muscle involvement, and, less commonly, dysthyroid optic neuropathy [15]. Ocular discomfort, diplopia, periorbital edema, conjunctival injection, and impaired ocular motility may also occur depending on disease activity and the extent of orbital inflammation. An unusual but clinically significant manifestation is blepharoptosis, which should prompt evaluation for concomitant myasthenia gravis because ptosis is uncommon in isolated thyroid-associated ophthalmopathy and may indicate the coexistence of another autoimmune neuromuscular disorder [22].

Several comparative clinical investigations have provided important insights into the distinctive characteristics of EGD. Komoto et al. performed a three-year comparative study evaluating patients with EGD and untreated Graves' ophthalmopathy and demonstrated that EGD occurred more frequently among male patients than previously recognized [23]. The investigators observed that proptosis, eyelid retraction, and enlargement of the extraocular muscles represented the predominant ophthalmic manifestations. Endocrinological evaluation revealed relatively higher thyrotropin concentrations in euthyroid patients despite preserved thyroid hormone levels. Thyroid-stimulating antibodies (TSAb) were detected in approximately 40% of patients, whereas thyrotropin receptor antibodies (TRAb), thyroid peroxidase antibodies (TPOAb), and thyroglobulin antibodies (TgAb) were identified in 35%, 25%, and 21% of cases, respectively [23]. These findings emphasize that although thyroid autoantibodies support the diagnosis, their absence does not exclude EGD. Further evidence regarding disease severity has been provided by Eckstein et al., who investigated the prevalence, clinical activity, disease severity, antibody profiles, and long-term outcomes among euthyroid, hypothyroid, and hyperthyroid Caucasian patients with Graves' ophthalmopathy during a 36-month follow-up period [24]. Disease severity was assessed using the NO SPECS classification, while inflammatory activity was evaluated using Mourits' Clinical Activity Score (CAS). Their findings demonstrated that cigarette smoking remained a major environmental risk factor across all thyroid function groups. Nevertheless, euthyroid patients generally experienced less severe ophthalmopathy, lower inflammatory activity scores, and significantly reduced soft-tissue inflammation compared with patients exhibiting thyroid dysfunction. A particularly distinctive characteristic of EGD was the markedly asymmetric presentation of orbital disease, frequently demonstrated by differences in proptosis exceeding 3 mm between the two eyes [24]. These observations reinforce the concept that asymmetrical orbital involvement should increase clinical suspicion for EGD, particularly in patients with otherwise normal thyroid function. The predominance of unilateral or markedly asymmetric disease has been consistently confirmed by subsequent investigations. Kavoussi et al. similarly reported a higher frequency of asymmetric ophthalmopathy among euthyroid patients [8]. Importantly, none of the euthyroid patients included in the study by Eckstein et al. developed severe visual loss or dysthyroid optic neuropathy during follow-up, suggesting a generally more favorable clinical course [24]. Endocrinological assessment further demonstrated that TRAb concentrations remained significantly lower among euthyroid patients throughout the six-month observation period. Suppressed thyroid-stimulating hormone together with detectable TRAb were identified as the strongest predictors of future development of euthyroid ophthalmopathy. However, the diagnosis remains challenging because thyroid dysfunction frequently develops after the onset of ocular manifestations, thereby creating considerable diagnostic uncertainty [25]. Approximately 18% of patients with Graves' disease develop thyroid dysfunction within one year after ophthalmopathy onset, whereas nearly one-quarter of euthyroid patients subsequently develop thyroid abnormalities within four years. Furthermore, TSAb measurements appear to possess greater diagnostic sensitivity than conventional antibody testing for identifying EGD [24].

Additional clinical observations have been reported in Asian populations. Jang et al. evaluated Korean patients with EGD and found unilateral orbital involvement

in approximately 79.2% of patients, emphasizing that asymmetric disease represents a hallmark feature of this condition [3]. Upper eyelid retraction constituted the predominant clinical sign, occurring in 91.7% of affected individuals [3]. Disease activity and severity were comparable to those described by Eckstein et al. [24], while the average duration of ophthalmic symptoms before diagnosis was approximately three months. Most patients maintained normal thyroid function throughout follow-up, although a small proportion eventually developed biochemical thyroid abnormalities. Although TRAb remained an important diagnostic biomarker, antibody concentrations were consistently lower than those observed in patients with hyperthyroid Graves' disease [3]. Interestingly, several patients developed classical ophthalmopathy despite negative TRAb results, highlighting the temporal variability of antibody production and emphasizing the importance of early antibody testing after symptom onset. Evidence also suggests that TSAb bioassays provide greater diagnostic specificity than conventional thyrotropin-binding inhibitory immunoglobulin (TBII) assays [26]. Clinical observations reported by Termote et al. further support the concept that EGD generally follows a milder clinical course characterized predominantly by unilateral orbital disease [5]. The investigators proposed that previous transient exposure to elevated thyroid hormone concentrations may contribute to the development of proptosis and extraocular muscle restriction even in patients who subsequently demonstrate normal thyroid function [5]. Preservation of euthyroidism appears to favor a more benign disease course with reduced inflammatory activity and slower progression [27]. Conversely, elevated TRAb concentrations have been associated with the later development of overt hyperthyroidism, particularly among patients with a previous history of thyroid hyperfunction [28]. Consequently, prolonged endocrinological surveillance remains essential because ophthalmopathy may represent the earliest clinical manifestation of Graves' disease, preceding biochemical thyroid dysfunction by several years.

The mechanisms responsible for maintaining normal thyroid function despite active orbital autoimmunity remain incompletely understood. Several hypotheses have been proposed, including relatively low concentrations or reduced biological activity of TSAb that are insufficient to induce thyroid hormone overproduction. Alternative mechanisms include the presence of endogenous suppressive pathways capable of neutralizing TSAb activity and structural differences in the antigenic epitopes of TSH receptors expressed in orbital tissues compared with those involved in classical hyperthyroid Graves' disease [29]. These immunological differences may explain why orbital inflammation develops independently of clinically apparent thyroid dysfunction. Despite preserved thyroid function at presentation, subtle endocrinological abnormalities frequently emerge during long-term follow-up. Patients may subsequently develop either thyrotoxicosis [30] or hypothyroidism [31]. Reported abnormalities include thyroid enlargement in approximately 24–40% of patients, suppressed TSH concentrations in 14–23%, diminished or absent TSH response following thyrotropin-releasing hormone stimulation in 40–63%, increased radioactive iodine uptake in approximately 20%, abnormal TSH suppression testing in 30–73%, positive TgAb in 11–67%, positive TBII in 31–36%, and positive TSAb in 43–87% of cases [29]. Importantly, several patients with clinically typical ophthalmopathy remain seronegative for conventional thyroid autoantibodies [26,32,33]. Watanabe et al. demonstrated

that highly sensitive TSAb bioassays identified positive antibody activity in 93% of such patients, emphasizing the superior diagnostic utility of these assays, particularly in seronegative disease [29]. Moreover, TSAb activity correlated directly with the severity of proptosis, further supporting its pathogenic role through activation of TSH receptors expressed within orbital tissues.

Although EGD generally follows a milder clinical course than classical Graves' ophthalmopathy, clinicians should remain vigilant for potentially vision-threatening complications. Exposure keratopathy resulting from severe proptosis [34] and dysthyroid optic neuropathy [35] may occasionally occur even during the initial stages of disease. Several case reports have documented bilateral euthyroid optic neuropathy associated with profound visual impairment despite aggressive intravenous corticosteroid therapy [36]. Conversely, unilateral optic neuropathy has also been described as the initial presentation of EGD, with substantial visual recovery achieved either following corticosteroid administration [35] or spontaneous clinical improvement during careful observation [37]. Conservative management may therefore be appropriate in selected patients exhibiting inactive disease with low Clinical Activity Scores, preserved thyroid function, and absence of thyroid autoantibodies, circumstances under which spontaneous remission appears more likely [37]. Orbital imaging provides valuable information regarding disease distribution and assists in confirming the diagnosis. Radiological studies characteristically demonstrate tendon-sparing enlargement of the extraocular muscles, particularly involving the lateral and medial rectus muscles [3]. Nevertheless, Dickinson and Perros reported that the inferior rectus muscle remains the muscle most frequently affected in thyroid-associated ophthalmopathy overall, followed sequentially by the medial, superior, and lateral rectus muscles [38]. Rare patterns of muscular involvement have also been documented, including isolated enlargement of the inferior oblique muscle in a patient presenting with unilateral blepharoptosis, orbital pain, and headache, illustrating the considerable clinical heterogeneity that may characterize EGD [39]. Collectively, these findings underscore the broad clinical spectrum of euthyroid Graves' disease and highlight the importance of comprehensive clinical, serological, and radiological evaluation to facilitate early diagnosis, monitor disease progression, and optimize long-term patient management.

Treatment

The management of euthyroid Graves' disease (EGD) is guided by disease severity according to the European Group on Graves' Orbitopathy (EUGOGO) classification and by the Clinical Activity Score (CAS), which helps determine the appropriate therapeutic approach [40]. Treatment during the active inflammatory phase primarily focuses on suppressing orbital inflammation and modulating the autoimmune response to prevent disease progression [41]. Overall, EGD generally has a favorable prognosis, and surgical intervention is required less frequently than in classical Graves' ophthalmopathy. Smoking cessation remains a critical component of management, as it reduces disease severity, improves treatment response, and slows disease progression [40–44]. Patients with mild ophthalmopathy are usually managed conservatively with regular clinical follow-up based on disease activity. Moderate-to-severe active disease is commonly treated with intravenous corticosteroids, often combined with orbital

radiotherapy, which effectively improves soft-tissue inflammation, eyelid swelling, and proptosis, although diplopia is less responsive. Glucocorticoid therapy has also demonstrated clinical benefit in TRAb-negative patients. Once the disease becomes inactive, rehabilitative procedures such as extraocular muscle surgery and blepharoplasty may be performed to correct persistent diplopia, strabismus, and eyelid abnormalities [23]. Sight-threatening optic neuropathy requires immediate treatment with high-dose intravenous corticosteroids, followed by orbital decompression surgery if the response is inadequate. Clinical improvement varies among patients, although recovery of visual acuity has been reported, particularly in unilateral disease [36,37]. Clinical evidence indicates that approximately half of EGD patients require active ophthalmic treatment, including local triamcinolone injections, orbital radiotherapy, glucocorticoids, or surgical intervention, while many patients experience spontaneous improvement without therapy [45]. Emerging biologic therapies have expanded treatment options for patients with steroid-resistant disease. Teprotumumab, an insulin-like growth factor-1 receptor (IGF-1R) inhibitor, has demonstrated significant improvements in proptosis, diplopia, Clinical Activity Score, and quality of life, with relatively few serious adverse effects, making it a promising alternative to surgery [46]. Rituximab, an anti-CD20 monoclonal antibody targeting B lymphocytes, reduces autoantibody production, suppresses orbital inflammation, and improves both disease activity and proptosis [47]. Optimal management requires a multidisciplinary approach involving endocrinologists, ophthalmologists, oculoplastic surgeons, strabismus specialists, and neuro-ophthalmologists, together with long-term thyroid function monitoring to detect delayed thyroid dysfunction and optimize patient outcomes [48].

Conclusion

Euthyroid Graves' disease is a rare but clinically important form of thyroid-associated ophthalmopathy in which orbital autoimmune inflammation develops despite normal thyroid function. Although its clinical manifestations resemble those of classical Graves' ophthalmopathy, EGD generally exhibits milder disease activity, greater asymmetry, and a higher frequency of unilateral orbital involvement. Current evidence demonstrates that immune-mediated activation of orbital fibroblasts, T lymphocytes, and thyroid-stimulating hormone receptor signaling constitutes the principal pathogenic mechanism underlying disease progression. Diagnosis requires careful integration of clinical examination, orbital imaging, and sensitive serological biomarkers, particularly thyroid-stimulating antibody assays, since conventional thyroid autoantibodies may be absent in a proportion of patients. Long-term endocrinological monitoring remains essential because thyroid dysfunction may emerge months or years after the initial presentation. Early recognition, appropriate differential diagnosis, and multidisciplinary collaboration between ophthalmologists and endocrinologists are fundamental for optimizing patient outcomes, preventing irreversible orbital damage, and preserving visual function. Continued research into the molecular mechanisms, predictive biomarkers, and targeted immunotherapies is expected to enhance diagnostic accuracy and support the development of more effective personalized treatment strategies for patients with euthyroid Graves' disease.

References

1. Wang Y and Smith TJ: Current concepts in the molecular pathogenesis of thyroid-associated ophthalmopathy. Invest Ophthalmol Vis Sci. 55:1735–1748. 2014.
2. 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 and de-la-Torre A: Prevalence of hyperthyroidism, hypothyroidism, and euthyroidism in thyroid eye disease: A systematic review of the literature. Syst Rev. 9(201)2020.
3. Jang SY, Lee SY, Lee EJ and Yoon JS: Clinical features of thyroid-associated ophthalmopathy in clinically euthyroid Korean patients. Eye (Lond). 26:1263–1269. 2012.
4. Boddu N, Jumani M, Wadhwa V, Bajaj G and Faas F: Not all orbitopathy is Graves': Discussion of cases and review of literature. Front Endocrinol (Lausanne). 8(184)2017.
5. Termote K, Decallonne B and Mombaerts I: The influence of prior hyperthyroidism on euthyroid graves' ophthalmopathy. J Ophthalmol. 2014(426898)2014.
6. Peter SA: Euthyroid Graves' disease. Report of a case observed over a 12-year period. Am J Med. 80:1197–1198. 1986.
7. Bhatnagar A, Tsirbas A, Douglas RS, Goldberg RA and Hoyama E: Graves' orbitopathy. Ophthalmology. 114:392.e1–e2. 2007.
8. Kavoussi SC, Giacometti JN, Javier Servat JJ and Levin F: The relationship between sex and symmetry in thyroid eye disease. Clin Ophthalmol. 8:1295–1300. 2014.
9. Bartalena L and Piantanida E: Cigarette smoking: Number one enemy for Graves ophthalmopathy. Pol Arch Med Wewn. 126:725–726. 2016.
10. Takasu N, Oshiro C, Akamine H, Komiya I, Nagata A, Sato Y, Yoshimura H and Ito K: Thyroid-stimulating antibody and TSH-binding inhibitor immunoglobulin in 277 Graves' patients and in 686 normal subjects. J Endocrinol Invest. 20:452–461. 1997.
11. Gerding MN, Van Der Meer JW, Broenink M, Bakker O, Wiersinga WM and Prummel MF: Association of thyrotrophin receptor antibodies with the clinical features of Graves' ophthalmopathy. Clin Endocrinol (Oxf). 52:267–271. 2000.
12. Inoue D, Sato K, Maeda M, Inoko H, Tsuji K, Mori T and Imura H: Genetic differences shown by HLA typing among Japanese patients with euthyroid Graves' ophthalmopathy, Graves' disease and Hashimoto's thyroiditis: Genetic characteristics of euthyroid Graves' ophthalmopathy. Clin Endocrinol (Oxf). 34:57–62. 1991.
13. Ardley M, McCorquodale T, Lahooti H, Champion B and Wall JR: Eye findings and immunological markers in probands and their euthyroid relatives from a single family with multiple cases of thyroid autoimmunity. Thyroid Res. 5(4)2012.
14. Khoo TK and Bahn RS: Pathogenesis of Graves' ophthalmopathy: The role of autoantibodies. Thyroid. 17:1013–1018. 2007.
15. Stan MN, Garrity JA and Bahn RS: The evaluation and treatment of Graves ophthalmopathy. Med Clin North Am. 96:311–328. 2012.

16. Wakelkamp IM, Bakker O, Baldeschi L, Wiersinga WM and Prummel MF: TSH-R expression and cytokine profile in orbital tissue of active vs inactive Graves' ophthalmopathy patients. Clin Endocrinol (Oxf). 58:280–287. 2003.
17. Gopinath B, Musselman R, Beard N, El-Kaissi S, Tani J, Adams CL and Wall JR: Antibodies targeting the calcium binding skeletal muscle protein calsequestrin are specific markers of ophthalmopathy and sensitive indicators of ocular myopathy in patients with Graves' disease. Clin Exp Immunol. 145:56–62. 2006.
18. Krishnan VM, Baba D, Kumar KR and Venkatesh P: Case report a case of unilateral euthyroid Graves' disease. Sch J App Med Sci. 3:2534–2536. 2015.
19. Kotwal A and Stan M: Thyrotropin receptor antibodies-an overview. Ophthal Plast Reconstr Surg. 34 (Suppl 1):S20–S27. 2018.
20. Bartley GB and Gorman CA: Diagnostic criteria for Graves' ophthalmopathy. Am J Ophthalmol. 119:792–795. 1995.
21. Bartley G: Rundle and His Curve. Arch Ophthalmol. 129:356–358. 2011.
22. Marinò M, Barbesino G, Pinchera A, Manetti L, Ricciardi R, Rossi B, Muratorio A, Braverman LE, Mariotti S and Chiovato L: Increased frequency of euthyroid ophthalmopathy in patients with Graves' disease associated with myasthenia gravis. Thyroid. 10:799–802. 2000.
23. Komoto N, Kozaki A, Yu F, Inoue R, Maeda T, Inoue T and Inoue Y: Clinical feature of euthyroid Graves' ophthalmopathy. Invest Ophthalmol Vis Sci. 49(5250)2008.
24. Eckstein AK, Lösch C, Glowacka D, Schott M, Mann K, Esser J and Morgenthaler NG: Euthyroid and primarily hypothyroid patients develop milder and significantly more asymmetrical Graves ophthalmopathy. Br J Ophthalmol. 93:1052–1056. 2009.
25. Wiersinga WM, Smit T, van der Gaag R and Koornneef L: Temporal relationship between onset of Graves' ophthalmopathy and onset of thyroidal Graves' disease. J Endocrinol Invest. 11:615–619. 1988.
26. Cakir M: Euthyroid Graves' ophthalmopathy with negative autoantibodies. J Natl Med Assoc. 97:1547–1549. 2005.
27. Hegedüs L, Bonnema SJ, Smith TJ and Brix TH: Treating the thyroid in the presence of Graves' ophthalmopathy. Best Pract Res Clin Endocrinol Metab. 26:313–324. 2012.
28. Khoo DH, Eng PH, Ho SC, Tai ES, Morgenthaler NG, Seah LL, Fong KS, Chee SP, Choo CT and Aw SE: Graves' ophthalmopathy in the absence of elevated free thyroxine and triiodothyronine levels: Prevalence, natural history, and thyrotropin receptor antibody levels. Thyroid. 10:1093–1100. 2000.
29. Watanabe M, Iwatani Y, Kashiwai T, Iijima T, Fujikado T and Amino N: Euthyroid Graves' disease showing no thyroid abnormalities except positive thyroid-sstimulating antibody (TSAb): Two case reports. J Intern Med. 238:379–384. 1995.
30. Tanaka K, Nomura T, Ohta Y, et al: A case of euthyroid Graves disease which developed into Graves disease with thyrotoxicosis after subacute thyroiditis. The Endocrinologist. 19:124–125. 2009.
31. Majumder A and Chatterjee S: Euthyroid Graves' ophthalmopathy patients remaining stable on more than 20 months follow up-a report of 9 patients. Hot Thyroidol. 2019.
32. Hotta A, Tanaka T, Kato H, Kakoi S, Shimizu Y, Hasegawa C, Hayakawa A, Yasuda S, Ogawa K, Ito S, et al: A case of euthyroid Graves' ophthalmopathy

in a patient sero-negative for TSH receptor autoantibody. Case Rep Endocrinol. 2018(1707959)2018.
33. Tabasum A, Khan I, Taylor P, Das G and Okosieme OE: Thyroid antibody-negative euthyroid Graves' ophthalmopathy. Endocrinol Diabetes Metab Case Rep. 2016(160008)2016.
34. Shah Y: Thyroid ophthalmopathy. J Assoc Physicians India. 59 (Suppl 1):S60–S65. 2011.
35. Arslan E, Yavaşoğlu I, Çildağ BM and Kocatürk T: Unilateral optic neuropathy as the initial manifestation of euthyroid Graves' disease. Intern Med. 48:1993–1994. 2009.
36. Lee YC, Chang FL and Tsai RK: Intravenous pulse corticosteroid therapy in euthyroid optic neuropathy: A case report. Neuro Ophthalmol. 36:143–145. 2012.
37. Kitaguchi Y, Ishihara K and Nishida K: Spontaneous resolution of euthyroid optic neuropathy. Can J Ophthalmol. 54:e188–e192. 2019.
38. Dickinson AJ and Perros P: Controversies in the clinical evaluation of active thyroid-associated orbitopathy: Use of a detailed protocol with comparative photographs for objective assessment. Clin Endocrinol (Oxf). 55:283–303. 2001.
39. Kakizaki H, Zako M and Iwaki M: Thyroid-associated inferior oblique myopathy. Ophthalmology. 114(2106)2007.
40. Bartalena L, Baldeschi L, Boboridis K, Eckstein A, Kahaly GJ, Marcocci C, Perros P, Salvi M and Wiersinga WM: European Group on Graves' Orbitopathy (EUGOGO). The 2016 European thyroid association/European group on Graves' orbitopathy guidelines for the management of Graves' orbitopathy. Eur Thyroid J. 5:9–26. 2016.
41. Wawhal M, Mogal V, Patil P, Ahire P and Yadav S: Euthyroid ophthalmopathy: A rare case report and a brief review of literature. Int J Sci Res. 4:529–532. 2015.
42. Ursu HI, Hortopan D, Podia-Igna C, Vizireanu A, Harsan T, Dumitriu L and Alexandrescu D: Late onset Graves' thyrotoxicosis in a patient with 18 years history of euthyroid Graves' ophthalmopathy. Acta Endo (Buc). 1:227–232. 2005.
43. Sarkar PK, Sarkar P, Acharjee U, Halder S, Sarkar S and Noatia C: Graves ophthalmopathy in a euthyroid patient-a rare case report. J Evol Med Dent Sci. 3:7150–7155. 2014.
44. Khan AA, Mahmoud Muammar AR and Kamal I: A case of unilateral exophthalmos due to thyroid orbitopathy in a clinically euthyroid patient.
45. Suzuki N, Noh JY, Kameda T, Yoshihara A, Ohye H, Suzuki M, Matsumoto M, Kunii Y, Iwaku K, Watanabe N, et al: Clinical course of thyroid function and thyroid associated-ophthalmopathy in patients with euthyroid Graves' disease. Clin Ophthalmol. 12:739–746. 2018.
46. Douglas RS, Kahaly GJ, Patel A, Sile S, Thompson EHZ, Perdok R, Fleming JC, Fowler BT, Marcocci C, Marinò M, et al: Teprotumumab for the treatment of active thyroid eye disease. N Engl J Med. 382:341–352. 2020
47. Stan MN, Garrity JA, Carranza Leon BG, Prabin T, Bradley EA and Bahn RS: Randomized controlled trial of rituximab in patients with Graves' orbitopathy. J Clin Endocrinol Metab. 100:432–441. 2015.

48. Hodgson NM and Rajaii F: Current understanding of the progression and management of thyroid associated orbitopathy: A systematic review. Ophthalmol Ther. 9:21–33. 2020.