

Update on thyroid eye disease: Regional variations in prevalence, diagnosis, and management

Caroline Y Yu, Rebecca L Ford¹, Sara T Wester², Erin M Shriver

Thyroid eye disease (TED) is a rare disease that can lead to decreased quality of life, permanent disfigurement, and vision loss. Clinically, TED presents with exophthalmos, periorbital edema, extraocular muscle dysfunction, and eyelid retraction, and can lead to vision-threatening complications such as exposure to keratopathy and dysthyroid optic neuropathy (DON). Over the last several years, significant advancements have been made in the understanding of its pathophysiology as well as optimal management. Ethnic variations in the prevalence, clinical presentation, and risk of vision-threatening complications of TED are summarized, and risk factors associated with TED are discussed. Additionally, significant advances have been made in the management of TED. The management of TED traditionally included anti-inflammatory medications, orbital radiation therapy, orbital surgical decompression, and biologic therapies. Most recently, targeted therapies such as teprotumumab, an insulin-like growth factor-1 receptor antagonist, have been studied in the context of TED, with promising initial data. In this review, updates in the understanding and management of TED are presented with a focus on the international variations in presentation and management.

Key words: Dysthyroid optic neuropathy, Graves' ophthalmopathy, oculoplastics, orbital inflammation, strabismus, teprotumumab, thyroid eye disease

Thyroid eye disease (TED), also known as Graves' ophthalmopathy, is a rare orbital inflammatory disease that can lead to visual disability, disfigurement, and in some cases permanent visual loss and can thus dramatically impact the quality of life. First described in the early 1800s,^[1] TED is estimated to affect between 155 and 250 people per 100,000 of the overall population.^[2,3] TED is more common among patients with Graves' disease (GD), which affects about 3% of women and 0.5% of men with a peak in incidence between 30 and 50 years of age.^[4] The prevalence of TED in GD is estimated to be as high as 25 to 58%.^[2-6] Less commonly, TED can also present in the setting of a euthyroid or hypothyroid status.^[3,4,6] Clinical manifestations of TED include exophthalmos, periorbital edema, extraocular muscle dysfunction, and eyelid retraction, and can lead to vision-threatening complications such as exposure to keratopathy and dysthyroid optic neuropathy (DON).^[3,4,6] It is well documented that TED can have a dramatic effect on a patient's quality of life due to a combination of impairment of visual function, emotional distress from perceived disfigurement, and pain.^[7,8] In fact, Ferlov-Schwensen *et al.*^[9] reported that adults with TED had a nearly threefold risk of death from suicide compared to the average Danish population even after adjusting for pre-existing somatic and psychiatric co-morbidities. Treatment options for TED traditionally included corticosteroids, orbital radiation, and surgical approaches, with a more recent

investigation of second-line immunosuppressive agents and emphasis on more targeted therapies such as rituximab, tocilizumab, and teprotumumab. The aim of this review is to discuss updates in the understanding of the pathophysiology and management of TED from an international perspective.

Methods

A comprehensive literature search was performed in preparation for this manuscript using PubMed, Google Scholars, and Web of Science. The literature search was performed using keywords including Thyroid Eye Disease, Graves' ophthalmopathy, Thyroid Eye Disease AND (global prevalence), Thyroid Eye Disease AND (risk factors), and Thyroid Eye Disease AND (treatment or management). All relevant original articles, review articles, case series, and case reports were reviewed. This search was not limited by year of publication; however, emphasis was given to articles published after January 1, 2000.

Prevalence of TED among different regional groups

Ethnicity likely plays an important role in TED; however, there are limited data comparing the prevalence of TED

Access this article online

Website:

www.ijo.in

DOI:

10.4103/ijo.IJO_3217_21

Quick Response Code:



Department of Ophthalmology and Visual Sciences, University of Iowa, Iowa City, IA, USA, ¹Department of Ophthalmology, Bristol Eye Hospital, University Hospitals Bristol NHS Foundation Trust, Bristol, UK, ²Department of Ophthalmology, Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami, FL, USA

Correspondence to: Dr. Erin M. Shriver, Department of Ophthalmology and Visual Sciences University of Iowa, Iowa City, IA, 52242, USA. E-mail: erin-shriver@uiowa.edu

Received: 31-Dec-2021

Revision: 20-Mar-2022

Accepted: 02-Jun-2022

Published: 30-Jun-2022

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

Cite this article as: Yu CY, Ford RL, Wester ST, Shriver EM. Update on thyroid eye disease: Regional variations in prevalence, diagnosis, and management. Indian J Ophthalmol 2022;70:2335-45.

among different ethnic groups. A meta-analysis by Chin *et al.*^[5] showed that there was no significant difference in the reported prevalence rate of TED among patients with GD of different ethnic groups within the United States; however, those rates varied as much as 21% between continents (Europe: 38%, Asia: 44%, North America: 27%, and Oceania: 58%). Within the Asian population, Lim *et al.*^[10] found no significant difference in the prevalence of TED in patients with GD between ethnically Indian, Malay, and Chinese patients in Malaysia (Indians: 40%, Malays: 35.1%; Chinese: 34%, $P = 0.928$). In contrast, in the United Kingdom, Tellez *et al.*^[11] found that patients of European descent with GD had a 42% prevalence rate of TED compared to a 7.7% prevalence rate in patients of Asian descent. Reddy *et al.*^[12] reported a TED prevalence of 28% among GD patients referred to one subspecialty clinic in northern India. There are limited data from Africa, with a few publications reporting an increasing rate of hyperthyroidism but a low incidence of sight-threatening complications.^[13-15]

Interestingly, although other studies have reported a female to male predominance with a ratio ranging from 3:1 to 14:1,^[2,3,5] this gender imbalance seems to be less pronounced in the Asian population. Three reports from the Indian subcontinent found approximately a 1:1,^[12] 1.12:1,^[16] and 1.5:1^[17] ratio between females and males, respectively, whereas a Malaysian study reported a female to male ratio of 1.5:1 in a subset of ethnically Indian patients.^[10] Cultural factors such as a lower rate of healthcare utilization among women in some regions may drive part of this reported difference in gender-based prevalence rates.^[18]

Pathophysiology of TED

Over the past decade, there has been significant progress in elucidating the pathophysiology of TED, in particular the interplay between the Thyroid stimulating hormone receptor (TSHR) and the insulin-like growth factor-1 receptor (IGF-1R).^[19-21] Initial research was focused principally on the role of the TSHR in TED.^[22] Although increased expression of the TSHR has been found on orbital fibroblasts of patients with active TED,^[23] a direct causal relationship between the TSHR increase and the pathophysiology was not clear. Further research disclosed that the IGF-1R colocalizes with TSHR in human orbital fibroblasts, forming a physical and functional signaling complex, and leads to the up-regulation of genes in the IGF/IGF-1R signaling pathway.^[20,21] IGF-1R expression is also increased on T-cells and B-cells in TED and involved in increased production of cytokines such as interleukin 16 (IL-16) and regulated on activation, normal T cell expressed and presumably secreted (RANTES), which are potent T-cell chemoattractants that are elevated in TED and involved in the inflammatory process that occurs in the orbit.^[20,24-27] This autoimmune cascade leads to the activation of orbital fibroblasts, which proliferate and differentiate into adipocytes and myocytes, as well as infiltration of the orbital tissue by T lymphocytes, mast cells, and B-cells [see Fig. 1].^[26] T cells have been shown to play an important role in both acute and chronic TED.^[28-31] In the early stage of disease, Th1-type cytokine secretion predominates, leading to a pro-inflammatory response with the secretion of glycosaminoglycans.^[28,29] Later in the disease, there is a predominance of Th2-type cytokines, which promote B-cell proliferation and maturation into plasma cells as well as fibrotic changes in the orbit.^[30,31] Ultimately,

these inflammatory cascades lead to soft tissue expansion and fibrosis of orbital soft tissue within the confined bony orbital cavity, leading to the classic clinical changes seen in TED.^[32] IGF-1R may also play an important role in chronic, non-inflammatory TED as well.^[33] Ugradar *et al.*^[33] found that patients with chronic TED and Clinical Activity Scores (CAS) of 1 or less had increased expression of both IGF-1R α and β in their orbital tissues compared with controls. Promising initial data from patients treated with teprotumumab (Horizon Therapeutics, Dublin, IRL), a human monoclonal antibody that binds to IGF-1R with high affinity and specificity, supports the idea that IGF-1R plays a central role in the pathogenesis of TED.^[22,34,35]

Natural history of TED

Early studies on the natural history of TED suggest that it follows a biphasic pattern, classically titled "Rundle's Curve."^[36] In Rundle's landmark 1945 paper, he plotted ophthalmometry readings of 18 TED patients from Australia over time, showing an initial active state of 18 months on average before transitioning to a more static, fibrotic state.^[37] Subsequent literature has suggested that the time range may vary as much as between 6 and 36 months but has supported the notion of an early inflammatory phase followed by a fibrotic phase.^[3,4,6,38] Treatment of TED is guided by the severity and activity of the disease, which can be assessed by rubrics such as the VISA^[39] and CAS,^[40] respectively. The 2021 European Group of Graves' Orbitopathy (EUGOGO) consensus statement defines moderate-to-severe TED as ≥ 2 mm of lid retraction, ≥ 3 mm of proptosis, and inconstant or constant diplopia.^[41]

It is important to recognize the sight-threatening disease, which is defined by the 2021 EUGOGO consensus statement as DON and severe corneal exposure; however, it also more rarely can include globe subluxation, choroidal folds, and postural visual obscuration.^[41,42] The 2021 EUGOGO guidelines cite a 3–5% rate of sight-threatening disease;^[41] however, the incidence of the sight-threatening disease has been reported to be as high as 19% in one South Indian cohort,^[43] highlighting the regional and ethnic variation in disease characteristics. Therefore, patients should be followed closely and counseled on measures to monitor signs and symptoms of DON and other causes of vision loss.

Diagnosis of TED: One size does not fit all

The diagnosis of TED can be somewhat subjective in nature as it is primarily based on clinical features, including proptosis, lid retraction, diplopia, and ocular surface health.^[39-41,44,45] Several rubrics have been devised for grading the degree of symptoms, inflammation, and severity of TED, including the CAS,^[40] NOSPECS (N-No signs or symptoms; O-only signs, no symptoms; S-soft tissue involvement; P-proptosis; E-extraocular muscle involvement; C-corneal involvement; S-sight loss),^[45] the VISA (vision, inflammation, strabismus, and appearance) system,^[39] and the EUGOGO classification.^[41] Interestingly, multiple publications have reported differences in the clinical signs and symptoms of TED based on ethnicity.^[10-17,46-48] For example, Asian patients tend to present with less-pronounced proptosis and diffuse extraocular muscle involvement,^[46-48] as well as a tendency to exhibit lower lid retraction rather than upper lid retraction.^[10] Asian patients may have an increased risk of DON compared to Caucasians due to anatomical differences

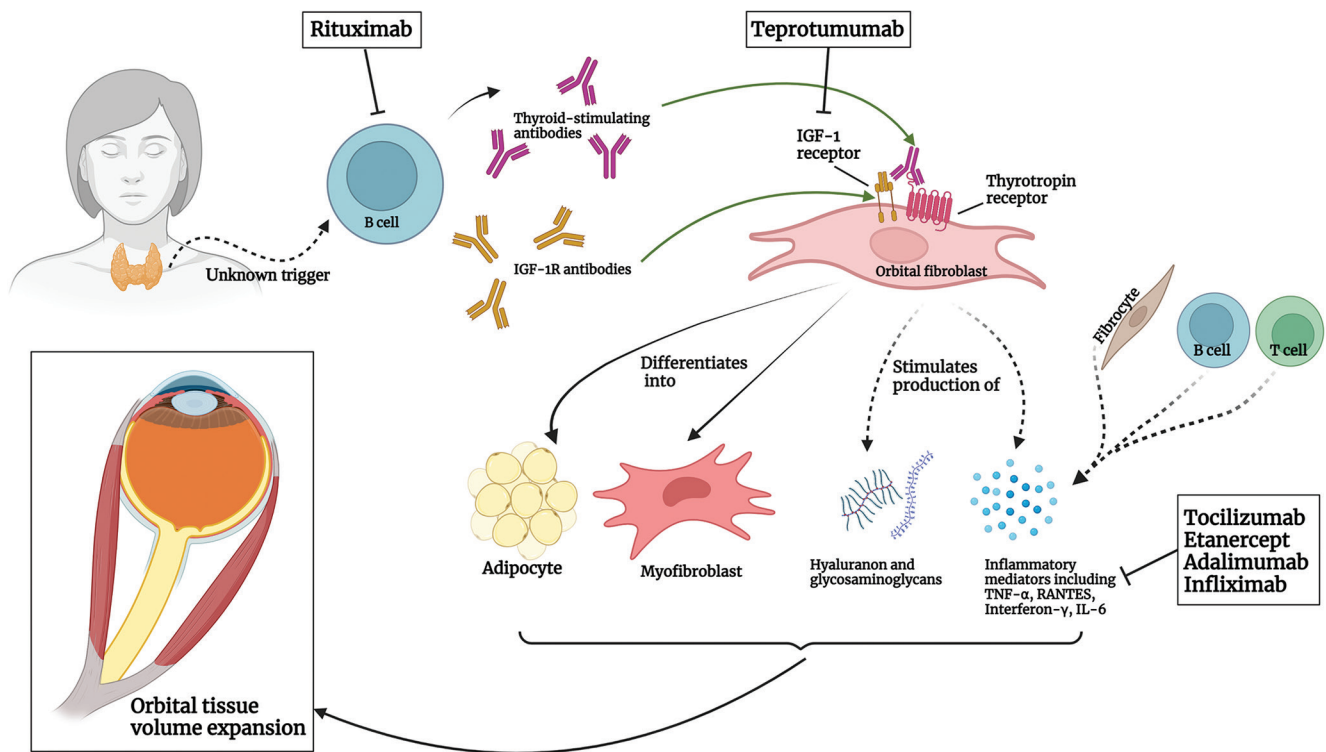


Figure 1: Simplified pathophysiology of thyroid eye disease (TED). Following an unknown trigger, there is a production of thyroid-stimulating antibodies and insulin-like growth factor-1 receptor (IGF-1R) antibodies. The downstream inflammatory cascade leads to the activation of orbital fibroblasts and stimulation of the production of inflammatory mediators, ultimately leading to soft tissue expansion of the orbit. Biologics including rituximab and teprotumumab are depicted at their hypothesized site of action. Figure created with BioRender.com

such as a shallower orbital depth and a more compact orbital apex.^[46] Although there are limited data on the prevalence of DON in the South Asian cohort, one South Indian study reported a 14.3% rate of DON in their retrospective chart review,^[43] which is significantly elevated compared to the frequently quoted prevalence of 3–5% as noted in the EUGOGO guidelines.^[41] Furthermore, a significantly higher proportion of Indian TED patients were hypothyroid or euthyroid (33.96% and 19.81%, respectively) compared to European and North American studies, which have been reported to represent 5% and 1%, respectively, of TED patients.^[3,17,49]

The varying clinical presentations of TED based on patient ethnicity or geographical location may affect clinicians' ability to diagnose TED, especially as commonly used TED diagnostic criteria and grading rubrics were devised based on Caucasian populations from North America^[39,44,45] and Europe.^[40,41] Although multiple rubrics exist, one survey-based study of oculoplastic surgeons in India showed that the VISA (45%) and EUGOGO (27%) severity scales were the most commonly used rubrics for grading disease severity in TED, whereas CAS (60%) and VISA (11%) were the most commonly used for grading disease activity.^[19] Lim *et al.*^[10] found that including lower lid retraction in the diagnostic criteria for TED, which included upper eyelid retraction, thyroid dysfunction, exophthalmos, optic nerve dysfunction, and extraocular muscle involvement, increased the prevalence rate of TED from 34.7% to 46.7% in their cohort of Malaysian, Chinese, and Indian patients, suggesting that there may be a need for diversifying the clinical diagnostic criteria for TED.

Risk factors for TED

Several risk factors have been found to be associated with a greater likelihood of developing severe disease, and it is important to identify modifiable risk factors for patients at risk of or diagnosed with TED. For all stages of TED, patients should be recommended to refrain from smoking. The association between smoking and TED is well documented, with multiple studies from North America, Europe, and Asia showing approximately 3.9 to 9.8 increased odds of developing TED in smokers as well as an increased rate of disease relapse after treatment with corticosteroids and radiotherapy.^[50-52] The mechanism by which smoking potentiates TED is unclear; however, multiple proposed mechanisms include hypoxia-induced adipogenesis, cytokine production, cyanide toxicity, and orbital venous congestion.^[53-55] Fortunately, smoking cessation has been shown to be effective at reversing these changes as ex-smokers displayed no increased risk of developing orbitopathy, diplopia, or proptosis compared to never smokers in one cohort study.^[56] Smoking prevalence has been shown to vary based on geographic region, with the highest prevalence at around 62% in East Asia and the Pacific and the lowest prevalence in sub-Saharan Africa at 28%, as well as based on gender, with males comprising more than 80% of all smokers worldwide.^[48,57] This may impact patterns of TED presentations. For example, in New Zealand, Angelo *et al.*^[58] observed an increased relative risk of TED in indigenous Maori people compared with other races but hypothesized that this could be explained by the much higher rate of smoking in this population group rather

than genetic factors and calculated that eliminating smoking could reduce the national incidence of TED by 28%. However, smoking is unlikely to be the only source of observed racial differences.^[48]

Another important modifiable risk factor is thyroid function. In addition to producing systemic symptoms such as tachycardia or fatigue, dysthyroidism has been reported to be associated with more severe TED.^[59,60] In one United States cohort, euthyroid patients had a significantly lower rate of orbital decompression (7% vs. 24%) and strabismus surgery (26% vs. 50%).^[59] Thyroid status is best managed in conjunction with endocrinologists and primary care physicians with anti-thyroid drugs such as methimazole (MMI) and propylthiouracil (PTU), radioactive iodine (RAI) treatment, and thyroidectomy. Although a discussion of the approach to managing systemic thyroid dysfunction is beyond the scope of this review, it is important that any ophthalmologist managing TED be well-versed on the risks/benefits of each treatment option. RAI has been shown to be an independent risk factor for the development of TED. Oral steroids at the time of RAI therapy are generally recommended in those with ophthalmopathy as they can mitigate the risk of exacerbating TED and a more individualized approach can be taken in those without pre-existing ophthalmopathy.^[61,62]

Dietary supplementation with selenium has been recommended by some experts; however, it remains controversial due to mixed results in the literature.^[41,63-66] A case-control study from Australia found that lower serum selenium concentrations were correlated with disease severity^[64] and an Italian study found that selenium supplementation in euthyroid patients with mild disease and disease duration of less than 18 months decreased eyelid retraction and improved CAS by 1.9 points at 6 months and 2.2 points at 12 months.^[63] However, positive results from selenium supplementation have not been reported in other populations. One possible reason for this is that selenium soil concentration varies significantly by region, with relatively high concentrations in parts of the United States,^[65] India,^[66] Ireland, Colombia, and Venezuela.^[67] Nevertheless, oral selenium supplementation in TED patients is recommended by most clinicians in Europe.^[41,68]

Similarly, vitamin D deficiency has been associated with an increased risk of a diagnosis of TED,^[65,69,70] as well as a number of other autoimmune diseases such as multiple sclerosis, rheumatoid arthritis, and systemic lupus erythematosus.^[71] Vitamin D has been shown to play an important role in immune modulation, including inhibiting B cell differentiation and suppressing T cell differentiation.^[71] Community and hospital-based studies set in India have both found a high prevalence of vitamin D deficiency in the general population;^[72] however, these values vary from 40 to 99% as there is no universal guideline to define cutoff values for vitamin D deficiency. In terms of vitamin D supplementation in TED, studies at this point remain observational^[65,69,70] and prospective clinical trials are needed to determine if vitamin D supplementation can improve global outcomes.

Diabetes is another important risk factor that has been shown to correlate with an increased risk of optic neuropathy.^[73-76] Multiple studies from across the globe, including India,^[73,74] the Netherlands,^[75] and the United States,^[76] have found that the prevalence of diabetes is higher

in patients with TED compared to the general population. Furthermore, patients with diabetes have a higher risk of developing DON and corneal decompensation, which may be exacerbated by underlying diabetes-related vasculopathy.^[73-76] Importantly, one study found that 6.67% of their cohort with TED were diagnosed with diabetes shortly after the ophthalmic presentation.^[73] Given the rising prevalence of diabetes globally, providers should consider screening patients with newly diagnosed TED for diabetes.^[73,76] More research is needed to understand if there is a correlation between glucose levels and TED severity as well as if diabetes affects the efficacy of various TED management strategies.

Obstructive sleep apnea (OSA) is another possible modifiable risk factor that has been identified. Several observational studies have reported a correlation between OSA and the severity of TED presentations, including DON.^[77,78] No studies to date have examined the effect of sleep apnea treatment on TED outcomes.

Finally, research is ongoing in elucidating other risk factors that may contribute to TED and the broader context of autoimmune disease. TED has been reported to develop as an immune reconstitution inflammatory syndrome (IRIS) in rare cases, including following highly active antiretroviral therapy (HAART) for human immunodeficiency virus (HIV)^[79] and alemtuzumab therapy.^[80] Other ongoing work suggests a possible connection between the gut microbiome and autoimmune conditions including Graves' and TED,^[81] opening potential new treatment avenues including antibiotic or probiotic modulation of gut flora, fecal transplants, and dietary modifications.

Treatment of active TED

Glucocorticoids

For patients with moderate-to-severe active TED, glucocorticoids have been the first-line option and can be administered orally, intravenously, or locally.^[41,82-87] Currently, the 2021 EUGOGO guidelines recommend a cumulative dose of up to 4.5 g of intravenous methylprednisolone weekly infusions [see Fig. 2].^[41] Although randomized clinical trials comparing glucocorticoids to placebo are lacking, glucocorticoids have been shown to be effective at treating DON,^[82] decreasing the risk of TED exacerbation following RAI therapy,^[61,62] and improving soft tissue changes such as eyelid retraction^[85] and subjective diplopia.^[83,84] The optimal route for delivery has been debated, and a survey of Indian oculoplastic physicians showed that 54% prefer giving a combination of intravenous and oral corticosteroids.^[19] Studies have shown a better response rate with intravenous vs. oral glucocorticoid administration (77% vs. 51%, respectively).^[86] Furthermore, intravenous glucocorticoids have been reported to have a lower rate of side effects compared to oral glucocorticoids,^[83,86] however, they are still associated with serious complications such as hyperglycemia and fatal liver failure.^[87,88] To minimize the risk of liver failure, it is recommended that the total cumulative dose of methylprednisolone not exceed 8 g.^[41] The 2021 EUGOGO guidelines have also recommended the use of mycophenolate in conjunction with glucocorticoids.^[41,89] The efficacy of glucocorticoids is limited by a high recurrence rate after treatment cessation^[89,90] as well as minimal effect on final proptosis measurements.^[83,86,87]

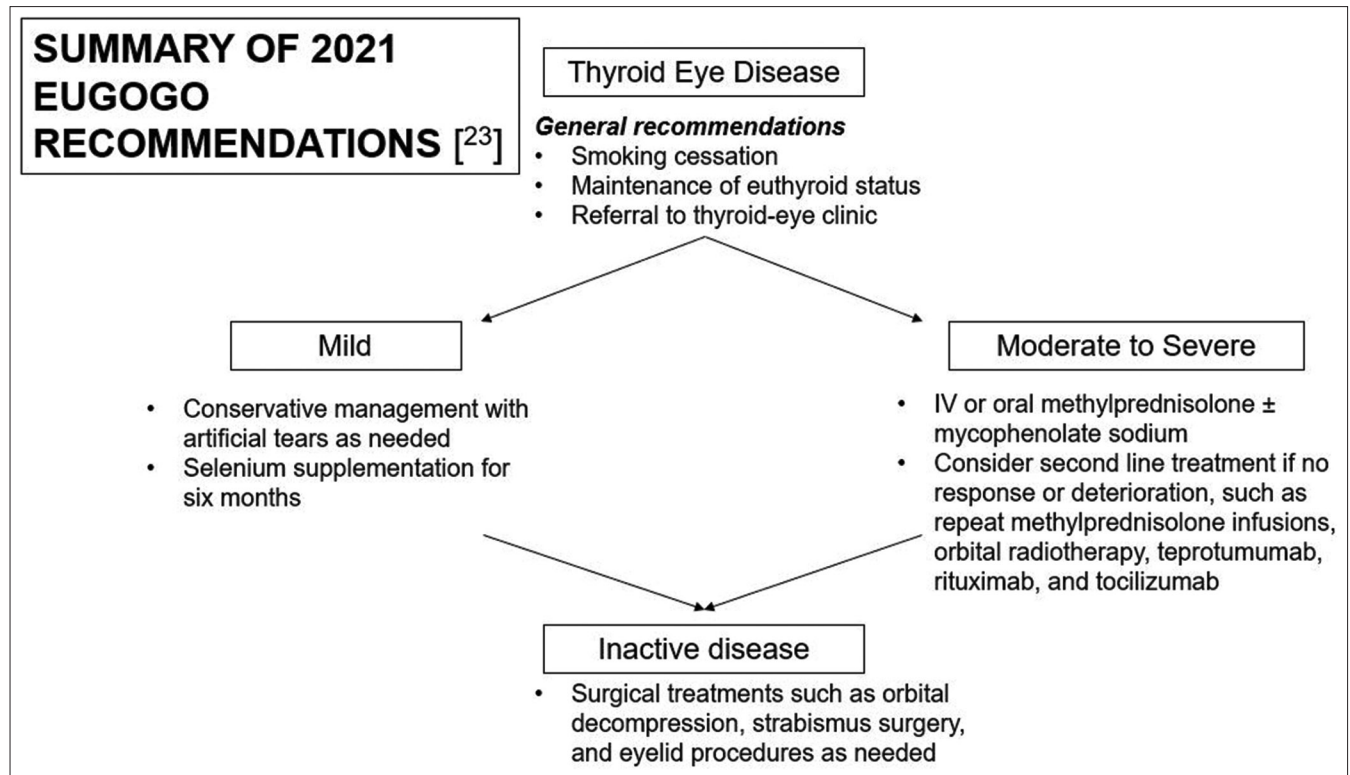


Figure 2: Adaptation of 2021 European Group on Graves' orbitopathy (EUGOGO) recommendations for the management of thyroid eye disease

Orbital radiation therapy

Orbital radiation therapy (ORT) is another therapeutic option for active TED, most often used in patients who have a clinical response to oral steroids.^[91,92] ORT has been studied as both a monotherapy^[93-95] as well as in conjunction with corticosteroids,^[96-100] with mixed findings on its efficacy. Some reports showed that ORT is effective both at improving extraocular motility as well as at reducing the need for surgical intervention and the cumulative amount of steroids needed.^[98-100] Furthermore, ORT may be effective at preventing the recurrence of DON after glucocorticoid cessation with a lower risk of requiring orbital decompression, strabismus repair, or eyelid surgery.^[96] However, other studies suggested that ORT has no significant effect on proptosis, rectus muscle size, and eyelid retraction.^[92,94,97] It is possible that further study may elucidate whether ORT is more efficacious in certain subgroups of patients, such as those with early ocular dysmotility. Furthermore, ORT can be cost-prohibitive, is associated with accelerated cataract formation and radiation retinopathy, and requires access to radiation delivery tools such as linear accelerator-derived external beams.^[100] Interestingly, 74% of Indian oculo-plastic physicians reported not utilizing ORT, with primary reasons cited being concern about lack of efficacy and/or safety as well as the prohibitive cost.^[19]

Biologics

Recently, there has been an effort to study the use of biological therapies in TED. Published data for the efficacy of several of these treatments is limited to case series at this time. Tocilizumab, an anti-interleukin-6 (IL-6) receptor monoclonal antibody, was shown in several publications to be effective in TED^[101-103] [see Fig. 3]. Perez-Moreiras *et al.*^[103] found that 93.3% of their Spanish patients had at least a 2-point improvement

in CAS score and 1.5 mm improvement in proptosis by week 16 of tocilizumab treatment; however, no randomized clinical trial data has been published on the efficacy of tocilizumab. Rituximab, an anti-CD20 agent that causes depletion of B lymphocytes, has been studied in TED with conflicting results in the two randomized studies published.^[104-106] TNF- α inhibitors, such as etanercept, adalimumab, and infliximab, have been studied in small cohort studies and found to have varying response rates, and better outcomes when used in patients with significant inflammation.^[107-111] Etanercept was shown to reduce CAS and lead to subjective improvement after 12 weeks of biweekly treatment but did not affect proptosis.^[107] Infliximab has been reported to be effective in several cases of severe sight-threatening TED^[109,111] as well as three cases of severe steroid and surgical resistant TED.^[110] Adalimumab was shown to have a greater effect on patients with higher baseline inflammation, suggesting that it may be more effective in patients with severe inflammation.^[108]

Targeted therapy

Teprotumumab, a monoclonal antibody antagonist to IGF-1R, was approved by the United States Food and Drug Administration (FDA) in January 2020 for TED. Recent phase 2 and phase 3 randomized, double-blind, placebo-controlled clinical trials in mostly Caucasian patients from the United States and Europe showed a significant reduction in proptosis, CAS, and diplopia, and an improvement in quality of life.^[34,35] In the pooled data from the 2 trials, 77% of teprotumumab-treated patients achieved a clinically significant proptosis response (defined as ≥ 2 mm), which was apparent as early as week 6 after teprotumumab initiation and was maintained up to 28 weeks.^[34,35,112] Furthermore, 70% of patients had improvement in diplopia (≥ 1 Bahn-Gorman

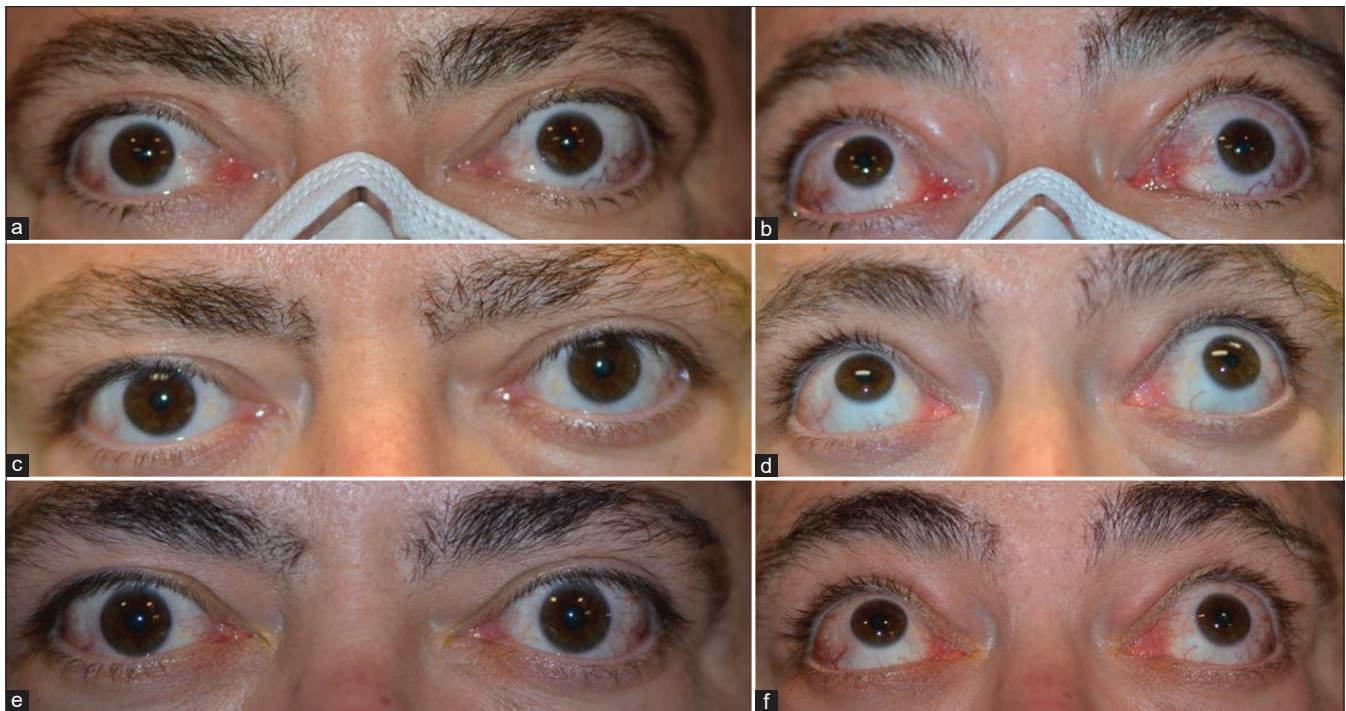


Figure 3: A 43-year-old Caucasian male patient with a 14-month history of thyroid eye disease treated with teprotumumab. (a, b) Primary and upgaze photographs after intravenous steroids and thyroidectomy showed eyelid retraction, upgaze restriction, and Clinical Activity Score (CAS) of 6. (c, d) After four infusions, he had improved eyelid retraction, motility, decrease in CAS to 3, and proptosis reduction of 3.5 and 2 mm. (e, f) 10 months after completion of eight infusions, there was a recurrence of eyelid retraction, decrease in motility, increase in CAS to 6, and overall proptosis reduction decreased to 2.5 and 0 mm

grade) and 53% of patients experienced diplopia resolution by week 24. Seventy-four percent of study patients treated with teprotumumab were clinical responders, defined as ≥ 2 mm and ≥ 2 -point CAS reduction, compared to 14% of controls. A meta-analysis comparing glucocorticoids and teprotumumab efficacy found that teprotumumab was associated with greater proptosis and diplopia response.^[113] In addition to acute, active TED, multiple publications have demonstrated its efficacy in chronic TED^[114-117] as well as in DON.^[118-123]

At this time, teprotumumab is primarily used in North America due to lack of approval in other countries and cost.^[124] It is administered via an intravenous route and is contraindicated in patients with inflammatory bowel disease or poorly controlled diabetes, pregnant or nursing patients, prepubertal children, and those on concomitant biologics.^[125] In addition, recent data have highlighted the potential risk of other adverse events, including hearing loss^[126-129] and cognitive decline^[130] as well as recurrence of TED symptoms in a subset of teprotumumab-responsive patients^[124] [see Fig. 4]. Further studies are needed to establish optimal dosing (ClinicalTrials.gov Identifier: NCT05002998), the durability of treatment effect (OPTIC-X), and efficacy in patients with chronic inactive disease (ClinicalTrials.gov Identifier: NCT05002998), as well as to gather more data from patients from different ethnic groups and geographic regions.

Surgery

Surgical treatments such as orbital decompression, strabismus surgery, and eyelid procedures are typically reserved for rehabilitation of the stable, inactive disease; however, urgent orbital decompression is often offered to active patients with

severe sight-threatening DON. There are many different approaches to orbital decompression, including external bony decompression of the medial wall, lateral wall, and/or orbital floor; endoscopic medial orbital wall decompression; and fat removal decompression.^[131-135] Traditionally, surgical rehabilitation is approached in a staged manner, typically with orbital decompression first, followed by strabismus repair, eyelid procedures in that order^[132] however, some authors have suggested that a one-stage repair can produce good patient outcomes with only 17% of patients requiring further surgery.^[136]

Education and support for TED patients

Early diagnosis of TED is critical to minimizing patient morbidity. Education on the modifiable risk factors and signs of TED is important for both patients and healthcare specialists.^[137-139] One model that has proven useful in aiding endocrinologists in the early diagnosis of TED is the Thyroid Eye Disease Amsterdam Declaration Implementation Group UK (TEAMeD) campaign in the UK.^[137] Furthermore, organizing healthcare teams into multi-disciplinary clinics is beneficial for both TED patients and physicians and has recently been recommended by the British Oculoplastics Surgery Society.^[138]

It is also critical that physicians provide psychosocial support for TED patients, such as TED, GD, and their treatments can have a massive impact on the quality of life of many patients.^[7-9] A number of validated tools, for example, GO-QOL and TED-QOL are available to monitor the quality of life in TED patients and identify those who are

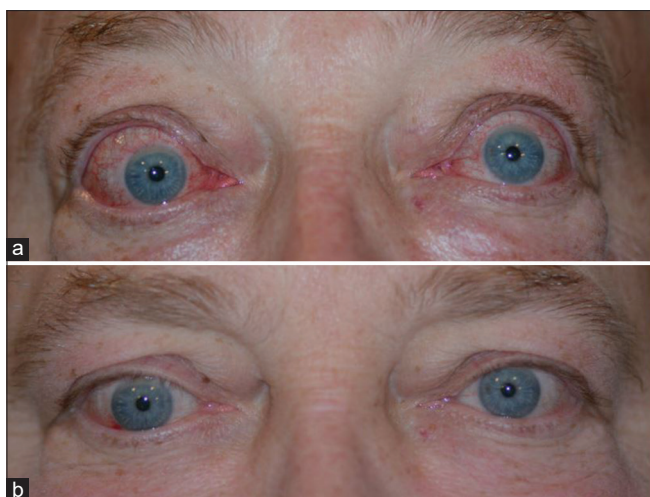


Figure 4: A 64-year-old Caucasian male patient with a 7-month history of thyroid eye disease (TED) before and after tocilizumab. (a) Initial visit after 2 months of oral prednisone presenting with a right hypotropia, restriction in upgaze and abduction bilaterally, eyelid retraction, conjunctival injection, and a Clinical Activity Score (CAS) of 4. (b) Sixteen weeks after initiation of tocilizumab with concurrent steroid taper, there was a persistent right hypotropia, improved extraocular motility and eyelid retraction, decrease in CAS to 2, and stable proptosis on the right and reduced proptosis by 2 mm on the left

struggling most.^[7,139,140] Healthcare professionals can support patients by helping them understand their condition^[137] and identifying those who may need professional psychological support or treatment. The internet has allowed patients with rare diseases to form peer support networks more readily, and people with TED may also benefit from patient-centered charities such as the Thyroid Eye Disease Charitable Trust.^[141]

Future directions and conclusions

In summary, TED is a rare and potentially sight-threatening disease. Management paradigms are primarily based on data from North American and European populations;^[41] however, it is important to recognize that TED may present differently in different ethnic populations,^[10-17,43,47-49] such as a potentially increased rate of sight-threatening complications in Southeastern Asian populations.^[43,46] Treatment for TED continues to evolve and major advances in the understanding of its pathophysiology have allowed for the development of targeted therapies such as teprotumumab.^[34,35,124] There are several ongoing trials for other targeted medications for the treatment of TED. These include Secukinumab, a human monoclonal anti-interleukin-17-A antibody (ClinicalTrials.gov Identifier: NCT04737330). Other preclinical studies are examining the possibility of small molecular TSHR antagonists for the treatment of TED as these may have the additional benefit of targeting IGF-1R-independent signaling pathways in TED as well as treating underlying GD.^[142,143] As our understanding of the underlying pathophysiology of TED is better elucidated, our treatment options have improved significantly, providing patients with the potential for less morbidity from this life-altering disease. More work is needed in more diverse populations to better understand the heterogeneity of this disease.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

- Bürgi H. Thyroid eye disease: A historical perspective. *Orbit* 2009;28:226-30.
- Abraham-Nordling M, Byström K, Törning O, Lantz M, Berg G, Calissendorff J, *et al.* Incidence of hyperthyroidism in Sweden. *Eur J Endocrinol* 2011;165:899-905.
- 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.
- Smith TJ, Hegedüs L. Graves' disease. *N Engl J Med* 2016;375:1552-65.
- 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* 2020;93:363-74.
- Bartalena L, Piantanida E, Gallo D, Lai A, Tanda ML. Epidemiology, natural history, risk factors, and prevention of Graves' orbitopathy. *Front Endocrinol* 2020;11:615993.doi: 10.3389/fendo. 2020.615993.
- Terwee CB, Gerding MN, Dekker FW, Prummel MF, Wiersinga WM. Development of a disease specific quality of life questionnaire for patients with Graves' ophthalmopathy: The GO-QOL. *Br J Ophthalmol* 1998;82:773-9.
- Cockerham KP, Padnick-Silver L, Stuert N, Francis-Sedlak M, Holt RJ. Quality of life in patients with chronic thyroid eye disease in the United States. *Ophthalmol Ther* 2021;10:975-87.
- Ferløv-Schwensen C, Brix TH, Hegedüs L. Death by suicide in Graves' disease and Graves' orbitopathy: A nationwide Danish register study. *Thyroid* 2017;27:1475-80.
- Lim SL, Lim AKE, Mumtaz M, Hussein E, Wan Bebakar WM, Khir AS. Prevalence, risk factors, and clinical features of thyroid-associated ophthalmopathy in multiethnic Malaysian patients with Graves' disease. *Thyroid* 2008;18:1297-301.
- Tellez M, Cooper J, Edmonds C. Graves' ophthalmopathy in relation to cigarette smoking and ethnic origin. *Clin Endocrinol* 1992;36:291-4.
- Reddy SV, Jain A, Yadav SB, Sharma K, Bhatia E. Prevalence of Graves' ophthalmopathy in patients with Graves' disease presenting to a referral centre in north India. *Indian J Med Res* 2014;139:99-104.
- Ogun OA, Adeleye JO. Severe ophthalmological complications of thyroid disease are rare in Ibadan, Southwestern Nigeria: Results of a pilot study. *Ophthalmol Eye Dis* 2016;8:5-9.
- Teshome T, Seyoum B. Graves' thyroid ophthalmopathy in Ethiopian patients. *Ethiopian Med J* 2001;39:1-8.
- Sarfo-Kantanka O, Kyei I, Sarfo FS, Ansah EO. Thyroid disorders in Central Ghana: The influence of 20 years of iodization. *J Thyroid Res* 2017;2017:2-8.
- Muralidhar A, Das S, Tiple S. Clinical profile of thyroid eye disease

- and factors predictive of disease severity. *Indian J Ophthalmol* 2020;68:1629-34.
17. Khurana AK, Sunder S, Ahluwalia BK, Malhotra KC, Gupta S. A clinico-investigative profile in Graves' ophthalmopathy. *Indian J Ophthalmol* 1992;40:56-8.
 18. Kapoor M, Agrawal D, Ravi S, Roy A, Subramanian SV, Guleria R. Missing female patients: An observational analysis of sex ratio among outpatients in a referral tertiary care public hospital in India. *BMJ Open* 2019;9:e026850.
 19. Pradhan A, Ganguly A, Naik MN, Nair AG, Desai S, Rath S. Thyroid eye disease survey: An anonymous web-based survey in the Indian subcontinent. *Indian J Ophthalmol* 2020;68:1609-14.
 20. Tsui S, Naik V, Hoa N, Hwang CJ, Afifyan NF, Sinha Hikim A, *et al.* Evidence for an association between thyroid-stimulating hormone and insulin-like growth factor 1 receptors: A tale of two antigens implicated in Graves' disease. *J Immunol* 2008;181:4397-405.
 21. Krieger CC, Place RF, Bevilacqua C, Marcus-Samuels B, Abel BS, Skarulis MC, *et al.* TSH/IGF-1 receptor cross talk in Graves' ophthalmopathy pathogenesis. *J Clin Endocrinol Metab* 2016;101:2340-7.
 22. Janssen JAMJL, Smith TJ. Lessons learned from targeting IGF-I receptor in thyroid-associated ophthalmopathy. *Cells* 2021;10:383. doi: 10.3390/cells10020383.
 23. Feliciello A, Porcellini A, Ciullo I, Bonavolontà G, Avvedimento EV, Fenzi G. Expression of thyrotropin-receptor mRNA in healthy and Graves' disease retro-orbital tissue. *Lancet* 1993;342:337-8.
 24. Hoa N, Tsui S, Afifyan NF, Sinha Hikim A, Li B, Douglas RS, *et al.* Nuclear targeting of IGF-1 receptor in orbital fibroblasts from Graves' disease: Apparent role of ADAM17. *PLoS One* 2012;7:e34173.
 25. Smith TJ, Hoa N. Immunoglobulins from patients with Graves' disease induce hyaluronan synthesis in their orbital fibroblasts through the self-antigen, insulin-like growth factor-I receptor. *J Clin Endocrinol Metab* 2004;89:5076-80.
 26. Pritchard J, Han R, Horst N, Cruikshank WW, Smith TJ. Immunoglobulin activation of T cell chemoattractant expression in fibroblasts from patients with Graves' disease is mediated through the insulin-like growth factor I receptor pathway. *J Immunol* 2003;170:6348-54.
 27. Weightman DR, Perros P, Sherif IH, Kendall-Taylor P. Autoantibodies to IGF-1 binding sites in thyroid associated ophthalmopathy. *Autoimmunity* 1993;16:251-7.
 28. Han R, Smith TJ. T helper type 1 and type 2 cytokines exert divergent influence on the induction of prostaglandin E2 and hyaluronan synthesis by interleukin-1beta in orbital fibroblasts: Implications for the pathogenesis of thyroid-associated ophthalmopathy. *Endocrinology* 2006;147:13.
 29. IMMJ Wakelkamp, Bakker O, Baldeschi L, Wiersinga WM, Prummel MF. TSH-R expression and cytokine profile in orbital tissue of active vs. inactive Graves' ophthalmopathy patients. *Clin Endocrinol* 2003;58:280-7.
 30. Xia N, Zhou S, Liang Y, Xiao C, Shen H, Pan H, *et al.* CD4+T cells and the Th1/Th2 imbalance are implicated in the pathogenesis of Graves' ophthalmopathy. *Int J Mol Med* 2006;17:911-6.
 31. Huang Y, Fang S, Li D, Zhou H, Li B, Fan X. The involvement of T cell pathogenesis in thyroid-associated ophthalmopathy. *Eye* 2019;33:176-82.
 32. Naik VM, Naik MN, Goldberg RA, Smith TJ, Douglas RS. Immunopathogenesis of thyroid eye disease: Emerging paradigms. *Surv Ophthalmol* 2010;55:215-26.
 33. Ugradar S, Shi L, Wang Y, Mester T, Yang H, Douglas RS. Teprotumumab for non-inflammatory thyroid eye disease (TED): Evidence for increased IGF-1R expression. *Eye* 2021;35:2607-12.
 34. Smith TJ, Kahaly GJ, Ezra DG, Fleming JC, Dailey RA, Tang RA, *et al.* Teprotumumab for thyroid-associated ophthalmopathy. *N Engl J Med* 2017;376:1748-61.
 35. Douglas RS, Kahaly GJ, Patel A, Sile S, Thompson EH, Perdok R, *et al.* Teprotumumab for the treatment of active thyroid eye disease. *N Engl J Med* 2020;382:341-52.
 36. Bartley GB. Rundle and his curve. *Arch Ophthalmol* 2011;129:356-8.
 37. Rundle FF, Wilson CW. Development and course of exophthalmos and ophthalmoplegia in Graves' disease with special reference to the effect of thyroidectomy. *Clin Sci* 1945;5:177-94.
 38. Patel P, Khandji J, Kazim M. Recurrent thyroid eye disease. *Ophthalmic Plast Reconstr Surg* 2015;31:445-8.
 39. Dolman PJ, Rootman J. VISA Classification for Graves orbitopathy. *Ophthalmic Plast Reconstr Surg* 2006;22:319-24.
 40. Mourits MP, Prummel MF, Wiersinga WM, Koornneef L. Clinical activity score as a guide in the management of patients with Graves' ophthalmopathy. *Clin Endocrinol* 1997;47:9-14.
 41. 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.
 42. Rose GE. Postural visual obscurations in patients with inactive thyroid eye disease; a variant of "hydraulic" disease. *Eye* 2006;20:1178-85.
 43. Gupta R, Thomas R, Almkhater F, Kiran A. Visual morbidity in thyroid eye disease in Asian Indian patients. *Indian J Ophthalmol* 2020;68:1622-7.
 44. Bartley GB, Gorman CA. Diagnostic criteria for Graves' ophthalmopathy. *Am J Ophthalmol* 1995;119:792-5.
 45. Werner SC. Modification of the classification of the eye changes of Graves' disease. *Am J Ophthalmol* 1977;83:725-7.
 46. J. Rootman. Aspects of current management of thyroid orbitopathy in Asians. *Asia Pac J Ophthalmol* 1998;10:2-6.
 47. Chung CL, Seah LL, Khoo DH. Ethnic differences in the clinical presentation of Graves' ophthalmopathy. *Best Pract Res Clin Endocrinol Metab* 2012;26:249-58.
 48. Woo KI, Kim YD, Lee SY. Prevalence and risk factors for thyroid eye disease among Korean dysthyroid patients. *Korean J Ophthalmol* 2013;27:397-404.
 49. Grover AK. Commentary: Thyroid eye disease-does the profile differ in India? *Indian J Ophthalmol* 2020;68:1635.
 50. Hegedüs L, Brix TH, Vestergaard P. Relationship between cigarette smoking and Graves' ophthalmopathy. *J Endocrinol Invest* 2004;27:265-71.
 51. Vestergaard P. Smoking and thyroid disorders—A meta-analysis. *Eur J Endocrinol* 2002;146:153-61.
 52. Stan MN, Bahn RS. Risk factors for development or deterioration of Graves' ophthalmopathy. *Thyroid* 2010;20:777-83.
 53. Chung CL, Lai OF, Chew CS, Peh YP, Fook-Chong SM, Seah LL, *et al.* Hypoxia increases adipogenesis and affects adipocytokine production in orbital fibroblasts—a possible explanation of the link between smoking and Graves' ophthalmopathy. *Int J Ophthalmol* 2014;7:403-7.
 54. Sadeghi-Tari A, Jamshidian-Tehrani M, Nabavi A, Sharif-Kashani S, Elhami E, Hassanpour N, *et al.* Effect of smoking on retrobulbar blood flow in thyroid eye disease. *Eye* 2016;30:1573-8.
 55. Erdogan MF. Thiocyanate overload and thyroid disease. *Biofactors* 2003;19:107-11.
 56. Pfeilschifter J, Ziegler R. Smoking and endocrine ophthalmopathy: Impact of smoking severity and current vs lifetime cigarette consumption. *Clin Endocrinol* 1996;45:477-81.
 57. Jha P, Ranson MK, Nguyen SN, Yach D. Estimates of global and regional smoking prevalence in 1995, by age and sex. *Am J Public Health* 2002;92:1002-6. doi: 10.2105/ajph.92.6.1002.
 58. Angelo L, Niederer R, Hart R. Thyroid eye disease in New Zealand: Interaction between ethnicity and smoking status. *N Z Med J* 2020;133:12-7.

59. Kim JM, LaBree L, Levin L, Feldon SE. The relation of Graves' ophthalmopathy to circulating thyroid hormone status. *Br J Ophthalmol* 2004;88:72-4.
60. Prummel MF, Wiersinga WM, Mounts MP, Koornneef L, Berghout A, van der Gaag R. Effect of abnormal thyroid function on the severity of Graves' ophthalmopathy. *Arch Intern Med* 1990;150:1098-101.
61. Vannucchi G, Covelli D, Campi I, Currò N, Dazzi D, Rodari M, *et al.* Prevention of orbitopathy by oral or intravenous steroid prophylaxis in short duration Graves' disease patients undergoing radioiodine ablation: A prospective randomized control trial study. *Thyroid* 2019;29:1828-33.
62. Ponto KA, Zang S, Kahaly GJ. The tale of radioiodine and Graves' orbitopathy. *Thyroid* 2010;20:785-93.
63. Marcocci C, Kahaly GJ, Krassas GE, Bartalena L, Prummel M, Stahl M, *et al.* Selenium and the course of mild Graves' orbitopathy. *N Engl J Med* 2011;364:1920-31.
64. Khong JJ, Goldstein RF, Sanders KM, Schneider H, Pope J, Burdon KP, *et al.* Serum selenium status in Graves' disease with and without orbitopathy: A case-control study. *Clin Endocrinol* 2014;80:905-10.
65. Sadaka A, Nguyen K, Malik A, Brito R, Berry S, Lee AG. Vitamin D and selenium in a thyroid eye disease population in Texas. *Neuroophthalmology* 2019;43:291-4.
66. Loomba R, Filippini T, Chawla R, Chaudhary R, Cilloni S, Datt C, *et al.* Exposure to a high selenium environment in Punjab, India: Effects on blood chemistry. *Sci Total Environ* 2020;716:135347. doi: 10.1016/j.scitotenv. 2019.135347.
67. Haug A, Graham RD, Christophersen OA, Lyons GH. How to use the world's scarce selenium resources efficiently to increase the selenium concentration in food. *Microb Ecol Health Dis* 2007;19:209-28.
68. Negro R, Hegedus L, Attanasio R, Papini E, Winther KH. A 2018 European thyroid association survey on the use of selenium supplementation in Graves' hyperthyroidism and Graves' orbitopathy. *Eur Thyroid J* 2019;9:99-105.
69. Yasuda T, Okamoto Y, Hamada N. Serum vitamin D levels are decreased and associated with thyroid volume in female patients with newly onset Graves' disease. *Endocrine* 2012;42:739-41.
70. Heisel CJ, Riddering AL, Andrews CA, Kahana A. Serum vitamin D deficiency is an independent risk factor for thyroid eye disease. *Ophthalmic Plast Reconstr Surg* 2020;36:17-20.
71. Aranow C. Vitamin D and the immune system. *J Investig Med* 2011;59:881-6.
72. Aparna P, Muthathal S, Nongkynrih B, Gupta SK. Vitamin D deficiency in India. *J Family Med Prim Care* 2018;7:324-30.
73. Ramamurthy LB, Rangarajan V, Srirao N, Malini B, Bansal R, Yuvarajan K. Severity of thyroid eye disease and type-2 diabetes mellitus: Is there a correlation? *Indian J Ophthalmol* 2020;68:1127-31.
74. Rath S, Pattnaik M, Tripathy D, Mohapatra S, Panigrahy B, Ali MH. Sight-threatening thyroid eye disease: Role of diabetes mellitus and interaction with other risk factors. *Ophthalmic Plast Reconstr Surg* 2021;37:352-60.
75. Kalman R, Mouritz MP. Diabetes mellitus: A risk factor in patients with Graves' orbitopathy. *Br J Ophthalmol* 1999;83:463-5.
76. Patel VK, Padnick-Silver L, D'Souza S, Bhattacharya RK, Francis-Sedlak M, Holt RJ. Characteristics of diabetic and nondiabetic patients with thyroid eye disease in the United States: A claims-based analysis. *Endocr Pract* 2022;28:159-64.
77. Godfrey KJ, Schmuter G, Hu B, Tooley AA, Dunbar KE, Basner RC, *et al.* Prospective correlation of risk of obstructive sleep apnea with severe clinical features of thyroid eye disease. *Ophthalmic Plast Reconstr Surg* 2021;37:558-61.
78. Habib LA, Godfrey KJ, Mathews P, De Rojas J, Kazim M. Association of risk of obstructive sleep apnea with thyroid eye disease: Compressive Optic neuropathy. *Ophthalmic Plast Reconstr Surg* 2019;35:232-4.
79. Edmunds MR, Mellington F, Ford RL, Torlinska B, Manavi K, Boelaert K. Clinical challenges of thyroid eye disease in HIV-positive patients on highly active antiretroviral therapy. *J Clin Endocrinol Metab* 2015;100:779-87.
80. Roos JCP, Moran C, Chatterjee VK, Jones J, Coles A, Murthy R. Immune reconstitution after alemtuzumab therapy for multiple sclerosis triggering Graves' orbitopathy: A case series. *Eye* 2019;33:223-9.
81. Covelli D, Ludgate M. The thyroid, the eyes and the gut: A possible connection. *J Endocrinol Invest* 2017;40:567-76.
82. Currò N, Covelli D, Vannucchi G, Campi I, Pirola G, Simonetta S, *et al.* Therapeutic outcomes of high-dose intravenous steroids in the treatment of dysthyroid optic neuropathy. *Thyroid* 2014;24:897-05.
83. Marcocci C, Bartalena L, Tanda ML, Manetti L, Dell'Unto E, Rocchi R, *et al.* Comparison of the effectiveness and tolerability of intravenous or oral glucocorticoids associated with orbital radiotherapy in the management of severe Graves' ophthalmopathy: Results of a prospective, single-blind, randomized study. *J Clin Endocrinol Metab* 2001;86:3562-7.
84. Ohtsuka K, Sato A, Kawaguchi S, Hashimoto M, Suzuki Y. Effect of steroid pulse therapy with and without orbital radiotherapy on Graves' ophthalmopathy. *Am J Ophthalmol* 2003;135:285-90.
85. Lee SJ, Rim TH, Jang SY, Kim CY, Shin DY, Lee EJ, *et al.* Treatment of upper eyelid retraction related to thyroid-associated ophthalmopathy using subconjunctival triamcinolone injections. *Graefes Arch Clin Exp Ophthalmol* 2013;251:261-70.
86. Kahaly GJ, Pitz S, Hommel G, Dittmar M. Randomized, single blind trial of intravenous versus oral steroid monotherapy in Graves' orbitopathy. *J Clin Endocrinol Metab* 2005;90:5234-40.
87. Bartalena L, Krassas GE, Wiersinga W, Marcocci C, Salvi M, Daumerie C, *et al.* Efficacy and safety of three different cumulative doses of intravenous methylprednisolone for moderate to severe and active Graves' orbitopathy. *J Clin Endocrinol Metab* 2012;97:4454-63.
88. Marino M. Acute and severe liver damage associated with intravenous glucocorticoid pulse therapy in patients with Graves' ophthalmopathy. *Thyroid* 2004;14:403-6.
89. Kahaly GJ, Riedl M, König J, Pitz S, Ponto K, Diana T, *et al.* Mycophenolate plus methylprednisolone versus methylprednisolone alone in active, moderate-to-severe Graves' orbitopathy (MINGO): A randomised, observer-masked, multicentre trial. *Lancet Diabetes Endocrinol* 2018;6:287-98.
90. Bartalena L, Marcocci C, Pinchera A. Treating severe Graves' ophthalmopathy. *Baillieres Clin Endocrinol Metab* 1997;11:521-36.
91. Kazim M, Garrity JA. Orbital radiation therapy for thyroid eye disease. *J Neuroophthalmol* 2012;32:172-6.
92. Bradley EA, Gower EW, Bradley DJ, Meyer DR, Cahill KV, Custer PL, *et al.* Orbital radiation for graves ophthalmopathy: A report by the American Academy of Ophthalmology. *Ophthalmology* 2008;115:398-409.
93. Shams PN, Ma R, Pickles T, Rootman J, Dolman PJ. Reduced risk of compressive optic neuropathy using orbital radiotherapy in patients with active thyroid eye disease. *Am J Ophthalmol* 2014;157:1299-305.
94. Mourits MP, van Kempen-Harteveld ML, García MB, Koppeschaar HP, Tick L, Terwee CB. Radiotherapy for Graves' orbitopathy: Randomised placebo-controlled study. *Lancet* 2000;355:1505-9.
95. Kazim M, Trokel S, Moore S. Treatment of acute Graves orbitopathy. *Ophthalmology* 1991;98:1443-8.
96. Gold KG, Scofield S, Isaacson SR, Stewart MW, Kazim M. Orbital radiotherapy combined with corticosteroid treatment for thyroid eye disease-compressive optic neuropathy. *Ophthalmic Plast Reconstr Surg* 2018;34:172-7.
97. Sisti E, Menconi F, Leo M, Profilo MA, Mautone T, Mazzi B, *et al.* Long-term outcome of Graves' orbitopathy following high-dose intravenous glucocorticoids and orbital radiotherapy. *J Endocrinol*

- Invest 2015;38:661-8.
98. Limone PP, Bianco L, Mellano M, Garino F, Giannoccaro F, Rossi A, *et al.* Is concomitant treatment with steroids and radiotherapy more favorable than sequential treatment in moderate-to-severe graves orbitopathy? *Radiol Med* 2021;126:334-42.
 99. Gorman CA, Garrity JA, Fatourehchi V, Bahn RS, Petersen IA, Stafford SL, *et al.* A prospective, randomized, double-blind, placebo-controlled study of orbital radiotherapy for Graves' ophthalmopathy. *Ophthalmology* 2020;127:S160-71.
 100. Marquez SD, Lum BL, McDougall IR, Katkuri S, Levin PS, MacManus M, *et al.* Long-term results of irradiation for patients with progressive Graves' ophthalmopathy. *Int J Radiat Oncol Biol Phys* 2001;51:766-74.
 101. Russell DJ, Wagner LH, Seiff SR. Tocilizumab as a steroid sparing agent for the treatment of Graves' orbitopathy. *Am J Ophthalmol Case Rep* 2017;7:146-8.
 102. Copperman T, Idowu OO, Kersten RC, Vagefi MR. Subcutaneous tocilizumab for thyroid eye disease: Simplified dosing and delivery. *Ophthalmic Plast Reconstr Surg* 2019;35:e64-6.
 103. Perez-Moreiras JV, Gomez-Reino JJ, Maneiro JR, Perez-Pampin E, Romo Lopez A, Rodríguez Alvarez FM, *et al.* Efficacy of tocilizumab in patients with moderate-to-severe corticosteroid-resistant graves orbitopathy: A randomized clinical trial. *Am J Ophthalmol* 2018;195:181-90.
 104. Salvi M, Vannucchi G, Currò N, Campi I, Covelli D, Dazzi D, *et al.* Efficacy of B-cell targeted therapy with rituximab in patients with active moderate to severe Graves' orbitopathy: A randomized controlled study. *J Clin Endocrinol Metab* 2015;100:422-31.
 105. Stan MN, Garrity JA, Carranza Leon BG, Prabin T, Bradley EA, Bahn RS. Randomized controlled trial of rituximab in patients with Graves' orbitopathy. *J Clin Endocrinol Metab* 2015;100:432-1.
 106. Vannucchi G, Campi I, Covelli D, Currò N, Lazzaroni E, Palomba A, *et al.* Efficacy profile and safety of very low-dose rituximab in patients with Graves' orbitopathy. *Thyroid* 2021;31:821-8.
 107. Paridaens D, van den Bosch WA, van der Loos TL, Krenning EP, van Hagen PM. The effect of etanercept on Graves' ophthalmopathy: A pilot study. *Eye* 2005;19:1286-9.
 108. Ayabe R, Rootman DB, Hwang CJ, Ben-Artzi A, Goldberg R. Adalimumab as steroid-sparing treatment of inflammatory-stage thyroid eye disease. *Ophthalmic Plast Reconstr Surg* 2014;30:415-9.
 109. Durrani OM, Reuser TQ, Murray PI. Infliximab: A novel treatment for sight-threatening thyroid associated ophthalmopathy. *Orbit* 2005;24:117-9.
 110. Strianese D. Efficacy and safety of immunosuppressive agents for thyroid eye disease. *Ophthalmic Plast Reconstr Surg* 2018;34 (4S Suppl 1):S56-9.
 111. Komorowski J, Jankiewicz-Wika J, Siejka A, Lawnicka H, Kłysik A, Goś R, *et al.* Monoclonal anti-TNF α antibody (infliximab) in the treatment of patient with thyroid associated ophthalmopathy. *Klin Oczna* 2007;109:457-60.
 112. Kahaly GJ, Douglas RS, Holt RJ, Sile S, Smith TJ. Teprotumumab for patients with active thyroid eye disease: A pooled data analysis, subgroup analyses, and off-treatment follow-up results from two randomised, double-masked, placebo-controlled, multicentre trials. *Lancet Diabetes Endocrinol* 2021;9:360-72.
 113. Douglas RS, Dailey R, Subramanian PS, Barbesino G, Ugradar S, Batten R, *et al.* Proptosis and diplopia response with teprotumumab and placebo vs the recommended treatment regimen with intravenous methylprednisolone in moderate to severe thyroid eye disease: A meta-analysis and matching-adjusted indirect comparison. *JAMA Ophthalmol* 2022;e216284. doi: 10.1001/jamaophthalmol. 2021.6284.
 114. Ozzello DJ, Kikkawa DO, Korn BS. Early experience with teprotumumab for chronic thyroid eye disease. *Am J Ophthalmol Case Rep* 2020;19:100744. doi: 10.1016/j.ajoc. 2020.100744.
 115. Ozzello DJ, Dallalzadeh LO, Liu CY. Teprotumumab for chronic thyroid eye disease. *Orbit* 2021;1-8. doi: 10.1080/01676830.2021.1933081.
 116. Ugradar S, Kang J, Kossler AL, Zimmerman E, Braun J, Harrison AR, *et al.* Teprotumumab for the treatment of chronic thyroid eye. *Eye* 2021. doi: 10.1038/s41433-021-01593-z.
 117. Yu CY, Simmons BA, Pham CM, Shriver EM. The role of teprotumumab in chronic, clinically active thyroid eye disease. *Eye* 2021. doi: 10.1038/s41433-021-01904-4.
 118. Hwang CJ, Nichols EE, Chon BH, Perry JD. Bilateral dysthyroid compressive optic neuropathy responsive to teprotumumab. *Eur J Ophthalmol* 2022;32:NP46-9.
 119. Sears CM, Azad AD, Dosiou C, Kossler AL. Teprotumumab for dysthyroid optic neuropathy: early response to therapy. *Ophthalmic Plast Reconstr Surg* 2021;37:S157-60.
 120. Sears CM, Wang Y, Bailey LA, Turbin R, Subramanian PS, Douglas R, *et al.* Early efficacy of teprotumumab for the treatment of dysthyroid optic neuropathy: A multicenter study. *Am J Ophthalmol Case Rep* 2021;23:101111. doi: 10.1016/j.ajoc. 2021.101111.
 121. Slentz DH, Smith TJ, Kim DS, Joseph SS. Teprotumumab for optic neuropathy in thyroid eye disease. *JAMA Ophthalmol* 2021;139:244-7.
 122. Lopez MJ, Herring JL, Thomas C, Bertram BA, Thomas DA. Visual recovery of dysthyroid optic neuropathy with teprotumumab. *J Neuroophthalmol* 2022;42:e491-3.
 123. Chiou CA, Reshef ER, Freitag SK. Teprotumumab for the treatment of mild compressive optic neuropathy in thyroid eye disease: A report of two cases. *Am J Ophthalmol Case Rep* 2021;22:101075. doi: 10.1016/j.ajoc. 2021.101075.
 124. Douglas RS, Kahaly GJ, Ugradar S, Elflein H, Ponto KA, Fowler BT, *et al.* Teprotumumab efficacy, safety, and durability in longer-duration thyroid eye disease and re-treatment: OPTIC-X study. *Ophthalmology* 2022;129:438-49.
 125. Douglas RS, Wang Y, Dailey RA, Harris GJ, Wester ST, Schiffman JS, *et al.* Teprotumumab in clinical practice: Recommendations and considerations from the OPTIC trial investigators. *J Neuroophthalmol* 2021;41:461-8.
 126. Chern A, Dagi Glass LR, Gudis DA. Thyroid eye disease, teprotumumab, and hearing loss: An evolving role for otolaryngologists. *Otolaryngol Head Neck Surg* 2021;165:757-8.
 127. Yu CY, Correa T, Simmons BA, Hansen MR, Shriver EM. Audiology findings in patients with teprotumumab associated otologic symptoms. *Am J Ophthalmol Case Rep* 2021;24:101202. doi: 10.1016/j.ajoc. 2021.101202.
 128. Belinsky I, Creighton FX Jr, Mahoney N, Petris CK, Callahan AB, Campbell AA, *et al.* Teprotumumab and hearing loss: Case series and proposal for audiologic monitoring. *Ophthalmic Plast Reconstr Surg* 2022;38:73-8.
 129. Highland J, Gordon S, Reddy D, Patel N. Ototoxicity and teprotumumab. *Ann Otol Rhinol Laryngol* 2021;34894211042740. doi: 10.1177/00034894211042740.
 130. Hoang TD, Nguyen NT, Chou E, Shakir MK. Rapidly progressive cognitive decline associated with teprotumumab in thyroid eye disease. *BMJ. Case. Rep* 2021;14:e242153.
 131. European Group on Graves' Orbitopathy (EUGOGO), Mourits MP, Bijl H, Altea MA, Baldeschi L, Boboridis K, *et al.* Outcome of orbital decompression for disfiguring proptosis in patients with Graves' orbitopathy using various surgical procedures. *Br J Ophthalmol* 2009;93:1518-23.
 132. Fichter N, Guthoff RF, Schittkowski MP. Orbital decompression in thyroid eye disease. *ISRN Ophthalmol* 2012;2012:739236. doi: 10.5402/2012/739236.

133. Bernardini FP, Nerad J, Fay A, Zambelli A, Cruz AA. The revised direct transconjunctival approach to the orbital floor. *Ophthalmic Plast Reconstr Surg* 2017;33:93-100.
134. Metson R, Samaha M. Reduction of diplopia following endoscopic orbital decompression: The orbital sling technique. *Laryngoscope* 2002;112:1753-7.
135. Trokel S, Kazim M, Moore S. Orbital fat removal. Decompression for Graves orbitopathy. *Ophthalmology* 1993;100:674-82.
136. Bernardini FP, Skippen B, Zambelli A, Riesco B, Devoto MH. Simultaneous aesthetic eyelid surgery and orbital decompression for rehabilitation of thyroid eye disease: The one-stage approach. *Aesthet Surg J* 2018;38:1052-61.
137. Thyroid Eye Disease Amsterdam Declaration Implementation Group UK (TEAMeD). The British Thyroid Foundation; c2019]. Available from: <https://www.btf-thyroid.org/teamed-page>. [Last accessed on 2021 Dec 21].
138. Lee V, Avari P, Williams B, Perros P, Dayan C, British Oculoplastic Surgery Society (BOPSS) and TEAMeD. A survey of current practices by the British Oculoplastic Surgery Society (BOPSS) and recommendations for delivering a sustainable multidisciplinary approach to thyroid eye disease in the United Kingdom. *Eye (Lond)* 2020;34:1662-71.
139. Mitchell AL, Hickey J, Vaidya B, Mason R, Ajjan R, Zammit N, *et al.* Raising awareness of Graves' orbitopathy with early warning cards. *Clin Endocrinol* 2017;87:853-9.
140. Fayers T, Dolman PJ. Validity and reliability of the TED-QOL: A new three-item questionnaire to assess quality of life in thyroid eye disease. *Br J Ophthalmol* 2011;95:1670-4.
141. Information and Support for Thyroid Eye Disease [Online]. Thyroid Eye Disease Charitable Trust. Available from: <http://tedct.org.uk/>. [Last accessed on 2021 Dec 29].
142. Neumann S, Krieger CC, Gershengorn MC. Targeting TSH and IGF-1 receptors to treat thyroid eye disease. *Eur Thyroid J* 2020;9(Suppl 1):59-65.
143. Marcinkowski P, Hoyer I, Specker E, Furkert J, Rutz C, Neuenschwander M, *et al.* A new highly thyrotropin receptor-selective small-molecule antagonist with potential for the treatment of Graves' orbitopathy. *Thyroid* 2019;29:111-23.