

Thyroid eye disease:

Primary care recognition and referral



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Background

Thyroid eye disease (TED) is a potentially sight-threatening autoimmune condition affecting up to half of patients with Graves' disease. It presents with variable ocular symptoms such as lid retraction, proptosis, diplopia and discomfort, which can significantly impair vision and quality of life. Early detection is crucial, as prompt management can prevent progression and visual loss.

Objective

This article provides general practitioners (GPs) with a framework to recognise, assess and initiate management of TED, and it outlines appropriate referral pathways to specialist care.

Discussion

GPs play an essential part in screening patients with thyroid disease for TED and identifying early warning signs. Initial measures include smoking cessation, restoration of euthyroid status and use of lubricants. Urgent referral is warranted for sight-threatening or rapidly progressive disease, while coordinated multidisciplinary management with endocrinologists and ophthalmologists supports optimal outcomes. Early recognition and referral by GPs can significantly improve visual and quality-of-life outcomes.

THYROID EYE DISEASE (TED), also known as Graves' orbitopathy, affects 25–50% of patients with Graves' hyperthyroidism.^{1,2} Meanwhile, up to 10% of patients with TED are associated with euthyroid or hypothyroid status.¹

The onset of TED is typically within 2 years of diagnosis of Graves' disease (GD).³ Patients with TED often notice facial changes characterised by eyelid retraction and proptosis, which give a staring appearance. Reduced eye movement and ocular misalignment can cause debilitating diplopia and blurred vision that affects reading, driving and ability to work. Periocular inflammation and congestion can lead to photosensitivity, tearing, eyelid swelling, eye pain and redness.⁴ The consequences of TED changes, ranging from mild to severe, significantly affect quality of life and mental health for those affected by the condition. In 3–5% of TED cases, dysthyroid optic neuropathy (DON) – presenting with progressive vision loss, colour vision reduction, relative afferent pupillary defect and visual field defects – is a threat to sight.^{5,6}

Smoking is the most significant modifiable risk factor for development and progression of TED.⁷ Although TED occurs more commonly in females, males are more likely to have more severe eye disease.⁸ Having high titres of thyrotropin receptor autoantibody (TRAb) also increases the relative risk for

developing TED.⁹ Given the wide range of manifestations of TED, potentially sight-threatening nature and impact on quality of life, it is vital to regularly assess for signs of TED and refer appropriately to endocrinology and ophthalmology units.

This article aims to provide general practitioners (GPs) with a guide to early recognition of TED and assessment for clinical signs and severity. We aim to provide an update on treatment strategies for mild, moderate-to-severe and sight-threatening forms of TED and recommend referral pathways for thyroid eye specialist care.

TED pathophysiology

TRAbs, which stimulate the thyroid gland in overproducing triiodothyronine (T₃) and thyroxine (T₄) in GD, cross-react with thyrotropin receptor (TSHR) and insulin growth factor receptor 1 (IGF1R) on orbital fibroblasts. This antigen–antibody recognition results in T cell activation and recruitment of lymphocytes and macrophages into the orbital connective tissues and orbital fat with increased pro-inflammatory cytokine production.¹⁰ Orbital fibroblasts are unique in that on activation, they produce hydrophilic glycosaminoglycans, namely hyaluronan, within extra-ocular muscles, which imbibes water, causing intense muscle swelling.¹¹ In addition, orbital fibroblasts

differentiate into adipocytes. Adipogenesis accelerates because of increased stimulation of TSHR, which leads to orbital adipose tissue volume expansion. The combination of glycosaminoglycan accumulation, oedematous expansion of extraocular muscles, adipogenesis and increased secretion of inflammatory cytokines within the orbit results in periorbital oedema, proptosis and oculomotility disturbance.^{10,12} Radiographically, inferior rectus is most commonly involved in patients with TED (61.8%), followed by medial rectus, superior rectus and lateral rectus.¹³

Clinical presentation and differentials

TED presents differently depending on the phase of disease. The initial active phase of TED is characterised by orbital inflammatory changes. This is followed by an inactive phase, usually occurring after 12–18 months.¹⁴ The inactive phase of TED is normally associated with some improvement in patient symptoms, but proptosis and extraocular muscle dysfunction can persist in up to 50% of patients.¹⁵ During the inflammatory phase, patients may complain of watery and gritty eyes, with photosensitivity, redness, eye pain and blurred vision,⁴ which mimics dry eye syndrome. Therefore, it is important to consider TED as a differential diagnosis in patients with persistent ocular surface symptoms, especially in the presence of other thyroid and eye signs (Figure 1). In addition, oedematous eyelids are often observed worse in the morning, which could be mistaken as 'hayfever' or seasonal allergic conjunctivitis. The increased volume of orbital tissues manifests as proptosis and eyelid retraction, while involvement of extraocular muscles often presents with double vision and reduced ocular motility, especially in upgaze and in abduction (Figure 2). When peri-orbital inflammation subsides, patients are often left with persistent exophthalmos, eyelid retraction and strabismus that may require surgical correction.¹⁶ Importantly, other differentials causing these symptoms should be excluded, particularly with unilateral presentations or in patients with euthyroid status. Differential diagnoses vital to exclude are orbital myositis, idiopathic orbital inflammation, specific orbital



Figure 1. Active phase of thyroid eye disease manifests with bilateral eyelid erythema, periocular oedema, conjunctival injection, proptosis and lid retraction. In the absence of retrobulbar pain, the clinical activity score in this case is 3 out of 7.



Figure 2. Extra-ocular muscle involvement with strabismus, shown as right hypotropia (right eye is depressed when compared with left eye). The clinical activity score is 2 out of 7 for lateral conjunctival chemosis and conjunctival redness in the right eye.

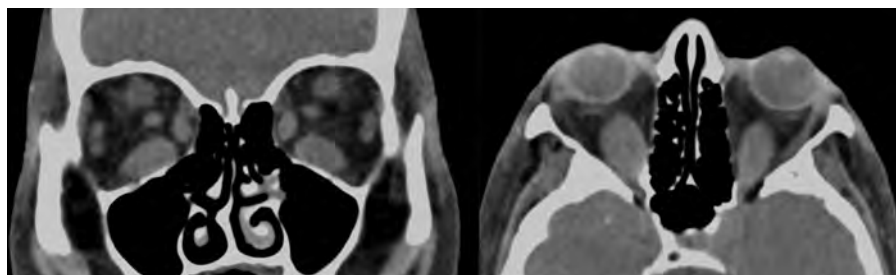


Figure 3. Coronal and axial non-contrast computed tomography scan of a patient with thyroid eye disease, showing marked bilateral inferior rectus muscle enlargement and, to a lesser degree, medial rectus enlargement.

inflammation such as sarcoidosis, orbital tumour, lymphoproliferative disease, vascular malformation, carotid-cavernous fistula (CCF) and myasthenia gravis. Further investigations recommended for diagnostic workup include preliminary blood investigations and radio-imaging with computed tomography (CT) or magnetic resonance imaging (MRI) of the orbit and brain (Figure 3).

Screening and grading of TED

All patients with GD should be alerted to the risk of TED so that patients are educated about TED early warning signs, which can be easily missed. TED can be screened for in patients with GD by focusing on key symptoms of TED: swelling of the upper eyelids and new lower eyelids 'bags' or festoons; redness in the eyes; changes in appearance where the eyes are more wide open; spontaneous pressure-like pain behind the eye, or pain increasing with eye movement; and changes in vision, such as

blurred vision or double vision. The 7-point clinical activity score (CAS) initially developed by Mourits et al is widely used in assessing extent of TED inflammation.¹⁷ It has since been developed into a 10-point scoring system that assesses for changes over time. The CAS is a useful initial tool in distinguishing between the active and inactive phases of TED. The 10-point CAS is shown in Table 1.¹⁸ It encompasses signs and symptoms, as well as impaired function in points 8–10. A CAS score of ≥ 3 indicates active disease.

The severity of TED is characterised by the functional and cosmetic consequences of the disease. The European Group on Graves' orbitopathy (EUGOGO) classification system of severity classes TED as mild, moderate-to-severe or sight threatening (Table 2).¹⁸ Sight-threatening TED is often characterised by the presence of at least one of the following: relative afferent pupillary defect, reduced visual acuity or colour vision, visual field deficits and optic disc swelling or pallor.

Table 1. Clinical activity score (CAS)¹⁸

	Itemised activity score	Clinical activity score
1	Retro-orbital pain	1
2	Pain on eye movement	1
3	Eyelid erythema	1
4	Conjunctival hyperaemia	1
5	Eyelid oedema	1
6	Conjunctival chemosis	1
7	Swelling of caruncle or plica	1
Following 1–3 months		
8	Increased proptosis of ≥ 2 mm	1
9	Reduced motility in any direction of gaze $\geq 8^\circ$	1
10	Decreased visual acuity of ≥ 1 line on Snellen chart	1
	Sum of maximum score	Initial out of 7 Subsequent out of 10
	Active thyroid eye disease definition	≥ 3 of first 7 ≥ 4 of 10

Adapted from Bartalena L, Kahaly GJ, Baldeschi L, et al; EUGOGO. The 2021 European Group on Graves' orbitopathy (EUGOGO) clinical practice guidelines for the medical management of Graves' orbitopathy. *Eur J Endocrinol* 2021;185(4):G43–67. doi: 10.1530/EJE-21-0479, licensed under CC BY 4.0 (<https://creativecommons.org/licenses/by/4.0>).

Table 2. Severity grading of thyroid eye disease¹⁸

Mild	Minor impact on daily life, insufficient to warrant immunosuppressive or surgical treatment. Includes ≥ 1 of: • minor lid reaction < 2 mm • mild soft tissue involvement • proptosis < 3 mm above normal for race and sex • no or intermittent diplopia • corneal exposure responsive to lubricants.
Moderate-to-severe	Moderate impact on daily life, sufficient to warrant immunosuppressive or surgical treatment. Includes ≥ 2 of: • lid retraction ≥ 2 mm • moderate-to-severe soft tissue involvement • proptosis ≥ 3 mm above normal for race and sex • diplopia (Gorman score 2–3, inconstant and constant).
Sight threatening	Dysthyroid optic neuropathy and/or corneal breakdown.

Adapted from Bartalena L, Kahaly GJ, Baldeschi L, et al; EUGOGO. The 2021 European Group on Graves' orbitopathy (EUGOGO) clinical practice guidelines for the medical management of Graves' orbitopathy. *Eur J Endocrinol* 2021;185(4):G43–67. doi: 10.1530/EJE-21-0479, licensed under CC BY 4.0 (<https://creativecommons.org/licenses/by/4.0>).

Initial investigation and diagnosis of TED

To ensure good outcomes for patients with TED, the role of the GP includes early diagnosis of thyroid disease, restoration and maintenance of euthyroid levels, regular patient review assessment for TED, patient education, and timely referral for endocrinology and ophthalmology management. Once a diagnosis of GD is established, all patients should be screened for TED at each visit, approximately every 3 months. While the majority of patients will experience mild TED, 20–30% develop moderate-to-severe disease and 3–5% develop DON or permanently lose vision in sight-threatening disease.⁶ Patient factors that may increase risk of DON include a history of diabetes, obstructive sleep apnoea, higher CAS at presentation, raised TRAb ≥ 5.0 IU/L, older age at diagnosis and smoking.^{7,19} Although restoring thyroid hormone levels to a normal range is vital in the treatment of GD and prevents progression of TED, their titres do not always correlate with TED activity or severity.²⁰ Therefore, although thyroid hormone levels may be normalised, TED should be continuously screened for throughout the course of the disease. Thyroid-stimulating immunoglobulin (TSI) assay, however, has been shown to correlate with disease severity.²¹ Radio-imaging with MRI or CT orbit is recommended at baseline to assess the degree of extra-ocular muscle enlargement, inflammation and orbital fat expansion. To share the load of screening patients with GD for TED, a chronic disease care plan may be developed, with ophthalmologists as a part of the care team. Their role involves conducting full eye examinations, fluorescein examinations for signs of corneal exposure, assessment for proptosis and assessment of disease activity, as well as screening for general eye health.

When to refer to an ophthalmologist?

Early referral to an ophthalmologist is indicated in:¹⁶

- diagnostic uncertainty
- ocular symptoms in the presence of GD, for assessment of TED
- unilateral or atypical presentation where other orbital pathologies (orbital myositis,

tumour, vascular malformation, CCF, myasthenia gravis) are possibilities, as the patient may need orbital biopsy for diagnostic confirmation

- CAS 3 or greater for consideration of medical treatment
- significant symptoms affecting daily life and visual functions
- stable-phase disease requiring surgical correction (proptosis, strabismus or lid malposition)

Urgent referral is indicated for:

- suspected DON
- corneal breakdown due to exposure
- rapidly progressive proptosis or globe subluxation.

Which general measures can be recommended in general practice?

Recommendations for all patients with TED include:^{16,22}

- smoking cessation
- restoration of euthyroid status (suggest co-management with endocrinologist)
- use of lubricating eye drops for dry eyes; ointment at night
- dark sunglasses for photophobia relief
- head elevation when sleeping to reduce oedema
- patching of one eye for diplopia, if any
- selenium supplementation (100 mcg twice daily for 6 months) in active cases
- correction of vitamin D deficiency with vitamin D supplement, if any
- if present, treatment of hypercholesterolaemia with a statin.

Although mild disease may be controlled with non-invasive interventions, early ophthalmologist review is crucial for moderate-to-severe disease. Approximately 1 in 20 patients with TED who have a moderate-to-severe active phase of disease will require medical treatment, including intravenous glucocorticoids, radiotherapy and biologics.²³ Medical therapy is based on the patient's symptoms, severity, comorbidities, duration of disease and preference.

Drivers with TED and diplopia should be informed of their responsibility to notify the driver licensing authority, with input from ophthalmologists in assessing visual acuity and formal visual fields. Generally, drivers with diplopia are not fit to drive; however, a conditional license may be considered if

diplopia is managed with corrective lenses or an occluder (after a 3-month non-driving period for adaptation).²⁴ Medical practitioners in South Australia and the Northern Territory have a mandatory reporting obligation. Meanwhile, mandatory reporting obligations in the Australian Capital Territory only apply if the driver holds a heavy vehicle license.²⁵

What are ophthalmologist-led treatments for TED?

Intravenous methylprednisolone

Intravenous methylprednisolone (IVMP) currently remains a first-line therapy in Australia, following the EUGOGO protocol (500 mg weekly for 6 weeks, then 250 mg weekly for 6 weeks) until biologics become more accessible. IVMP improves disease activity and quality of life with fewer side effects when compared with oral steroids.¹⁸ However, IVMP is not known to significantly improve severity of proptosis or oculomotility deficits. Contraindications include uncontrolled diabetes, severe hypertension, hepatitis and heart failure.²⁶

Teprotumumab

This novel human monoclonal antibody targets IGF1R activity on orbital fibroblasts.²⁷ Teprotumumab was approved by the Food and Drug Administration in 2020 and by the Therapeutic Goods Administration in

March 2025. Teprotumumab is indicated for the treatment of active, moderate-to-severe TED. Given as 3-weekly infusions for 6 months (eight doses), teprotumumab has been shown to reduce CAS to 0 in 62% of patients in phase 2 and 3 clinical trials, and reduce proptosis by ≥ 2 mm in 75% of treated individuals.^{27,28} In clinical practice, it has significantly reduced the rate of orbital decompression to 4.1%, compared with 25% in patients treated with corticosteroids and/or orbital radiation.²⁹ Hearing monitoring is required before and while having treatment. It is recommended that patients on teprotumumab are treated by specialists experienced in the treatment of TED.

Steroid-sparing therapies: Rituximab, tocilizumab and orbital radiotherapy

Rituximab depletes B cells via binding to CD20 ligands. A well-tolerated second-line therapy for poor responders to IVMP or those with subsequent disease recurrence, it reduces activity scores without adverse effects up to 1 year post infusion.^{30,31}

Tocilizumab (TCZ), an IL-6 receptor antagonist, has shown efficacy in moderate-to-severe, corticosteroid-resistance TED. A recent systematic review showed good control of inflammation with TCZ, with at least a 3-point CAS improvement in all studies with statistical analysis.³² However, a randomised controlled trial comparing TCZ



Figure 4. Proptosis, before decompression surgery.



Figure 5. Post decompression.

with placebo showed minimal improvement in proptosis.³³ This second-line therapy is well tolerated and lacks major adverse effects. It is contraindicated in those with diverticular disease, where TCZ increases risk of gastrointestinal perforation.³⁴

Orbital radiotherapy is often used alongside IVMP to improve inflammation control. This modality is especially useful in patients with predominantly myopathic subtype. Orbital radiation works by reducing inflammation through inactivation of orbital lymphocytes and fibroblasts.³⁵ This is particularly evident in DON, where 92% of cases responded to combination therapy, compared with 65% with IVMP alone.³⁶ It carries a risk of radiation retinopathy and therefore is contraindicated in patients with diabetic retinopathy and in patients aged under 35 years because of risk of head and neck malignancy.^{18,37}

When is surgical treatment appropriate?

Surgical management of TED is generally indicated once TED reaches the stable phase. Corrective surgery for TED is a multi-stage process to address orbit, extra-ocular muscle and eyelid sequelae in this order. Surgery also has a role in the acute setting of sight-threatening TED, indicated for the reversal of DON and severe exposure keratopathy. Urgent orbital decompression is recommended for DON not responding to medical treatment and for severe proptosis with globe subluxation and exposure keratopathy.¹⁶ Expedient eyelid recession may be considered for severe lagophthalmos from eyelid retraction. When TED has reached a stable, inactive phase, surgical management may be considered for correction of proptosis, strabismus and eyelid retraction. Orbital decompression aims to remove bony walls and orbital fat and is very effective in correcting proptosis (Figures 4 and 5). Following orbital decompression, strabismus surgery is next considered for correction of diplopia, usually when hypotropia or esotropia remains large.⁹ However, it is vital post orbital decompression to allow the postoperative swelling to settle prior to strabismus surgery being considered. Finally, lid surgeries such as eyelid recession repair and upper and lower lid blepharoplasty can be considered to address functional and cosmetic concerns.¹⁶

Conclusion

TED can present with non-specific symptoms such as dry, watery or gritty eyes and lid oedema, making it important to maintain a high index of suspicion, particularly in those with known or suspected thyroid disease. GPs play an essential part in diagnosing and treating thyroid disease, as well as screening for and diagnosing TED. They are also crucial in initiating first-line management strategies including smoking cessation, lubricating eye drops and monitoring of thyroid function. Just as importantly, timely referral to ophthalmologists and endocrinologists ensures coordinated care and access to specialist therapies. By recognising TED early and implementing these measures, GPs can significantly improve visual outcomes and quality of life in patients with TED.

Key points

- It is important to screen for TED symptoms in all patients with GD at each clinical visit.
- Recommendation of smoking cessation is a significant modifiable risk factor for TED.
- Thyroid hormone levels may not always correlate to activity or severity of TED.
- Simple, non-invasive measures are usually sufficient in managing mild cases of TED.
- Ensuring regular patient follow-up is crucial for monitoring of thyroid function, assessing for disease progression and supporting patients' mental health.

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