MOTORE SANITÀ
Cure the Future

RICERCA ED INNOVAZIONE
SCIENTIFICA CHE SPINGONO
ALL'INNOVAZIONE ORGANIZZATIVA

L'esempio della

Thyroid Eye Disease

REGIONE EMILIA-ROMAGNA

BOLOGNA
Starhotels Excelsior - Viale Pietramellara, 51

1 LUGLIO 2025
dalle 9.30 alle 13.30

Iscriviti su **www.motoresanita.it**

TED: impatto epidemiologico, clinico e socio-assistenziale

Il punto di vista dell'endocrinologo

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Although commonly associated with Graves' disease (GD), TED is a distinct disease that may cause irreversible damage[1-3]

TED more commonly affects women than men[4,5]

TED is a serious, progressive, and debilitating autoimmune disease[4,5]

Age-adjusted US incidence[4]:
Women: 16 cases per 100,000 per person per year (PPPY)
Men: 3 cases per 100,000 PPPY

Peaks of incidence among women occur between the ages of 40-44 and 60-64.
Peaks of incidence among men occur between ages of 45-49 and 65-69[4]

Marcocci, C., Smith, T.J. (2016). Graves' Ophthalmopathy. In: Vitti, P., Hegedus, L. (eds) Thyroid Diseases. Endocrinology. Springer, Cham.

1. Eckstein AK, et al. Br J Ophthalmol. 2009;93(8):1052-1056. 2. Bothun ED, et al. Clin Ophthalmol. 2009;3:543-551. 3. Barrio-Barrio J, et al. J Ophthalmol. 2015;2015:249125. 4. Bartley GB. Trans Am Ophthalmol Soc. 1994;92:477-588. 5. Perros P, et al. Clin Endocrinol (Oxf). 1993;38(4):367-372.

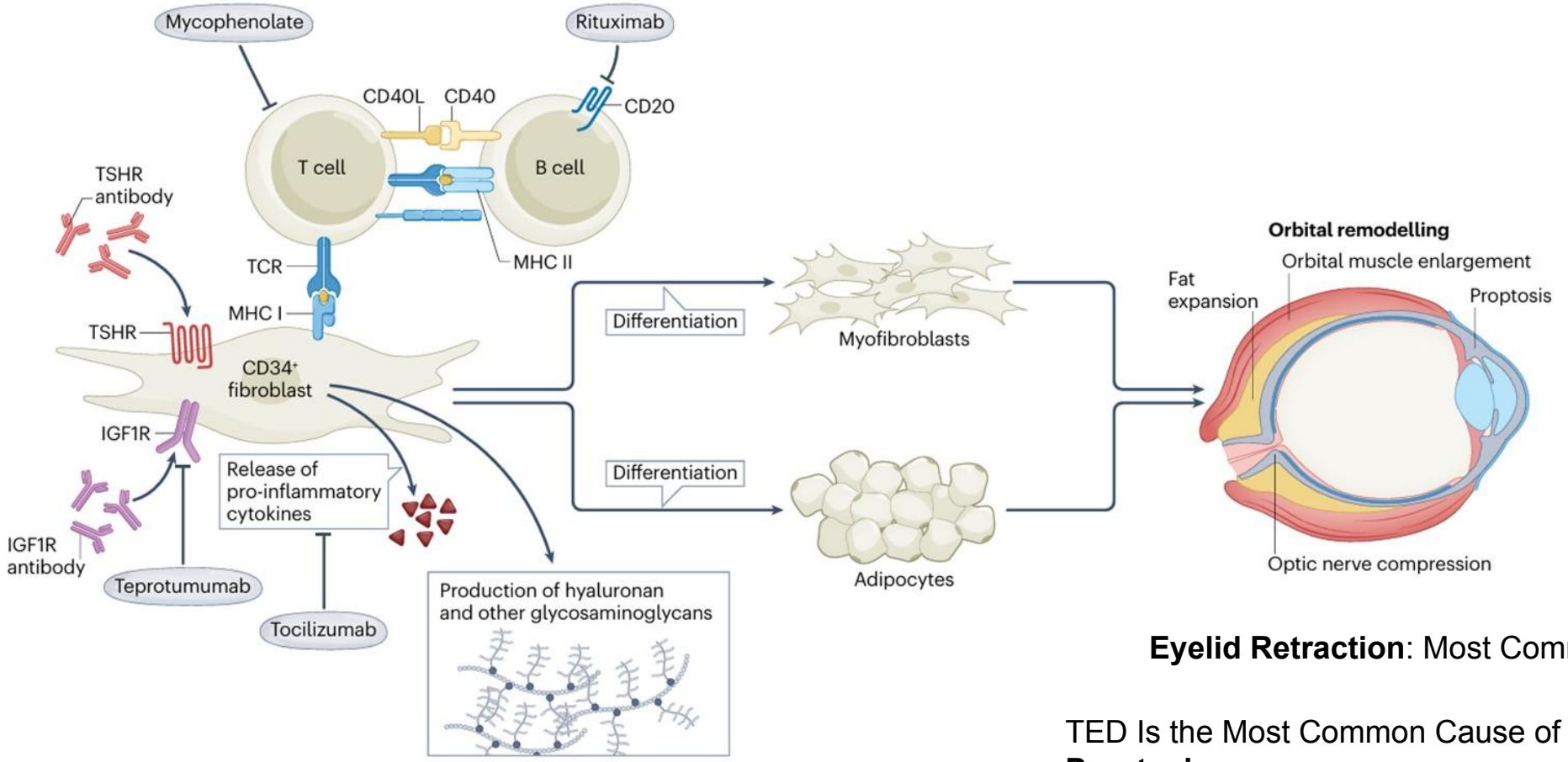
Etiology and Risk Factors for Developing TED

- TED is often associated with **hyperthyroidism** but may also occur in patients with euthyroidism or hypothyroidism
- Up to 30-40% of Graves disease patients may develop signs and symptoms of TED
- Approximately 37% of the overall TED population are in the acute stage of TED

- Risk factors associated with developing TED:
    - **Smoking** increases the risk of developing TED by 2- to 8-fold
    - The odds of developing TED increase by 17%, for each **decade increase**
    - The risk of developing new onset or worsening of preexisting TED are ~20% after **radioactive iodine** treatment
    - TED is approximately 4 times more commonly in **women** than men

Bartley GB. Trans Am Ophthalmol Soc. 1994;92:477-588. 2. Eckstein AK, et al. Br J Ophthalmol. 2009;93(8):1052-1056. 3. Bartalena L, et al. J Endocrinol Invest. 2014;37(8):691-700. 4. Perros P, et al. Br J Ophthalmol 2015; 99(11): 1531-5. 5. Ponto KA, et al. Thyroid : official journal of the American Thyroid Association 2015; 25(8): 942-8. 6. Bartley GB, et al. Ophthalmology 1996; 103(6): 958-62. 7. Prummel MF, et al. JAMA. 1993;269(4):479-482. 8. Manji N, et al. J Clin Endocrinol Metab. 2006;91(12):4873-4880. 9. Khong JJ, et al. J Clin Endocrinol Metab. 2016;101(7):2711-2720. 10. Ponto KA, et al. Thyroid. 2010;20(7):785-793. 9. Perros P, et al. Clin Endocrinol (Oxf). 1993;38(4):367-372. 11. Stein JD, et al. JAMA Ophthalmol. 2015;133(3):290-296.

TED: Mechanism of disease



Eyelid Retraction: Most Common Presenting Sign of TED

TED Is the Most Common Cause of **Proptosis**

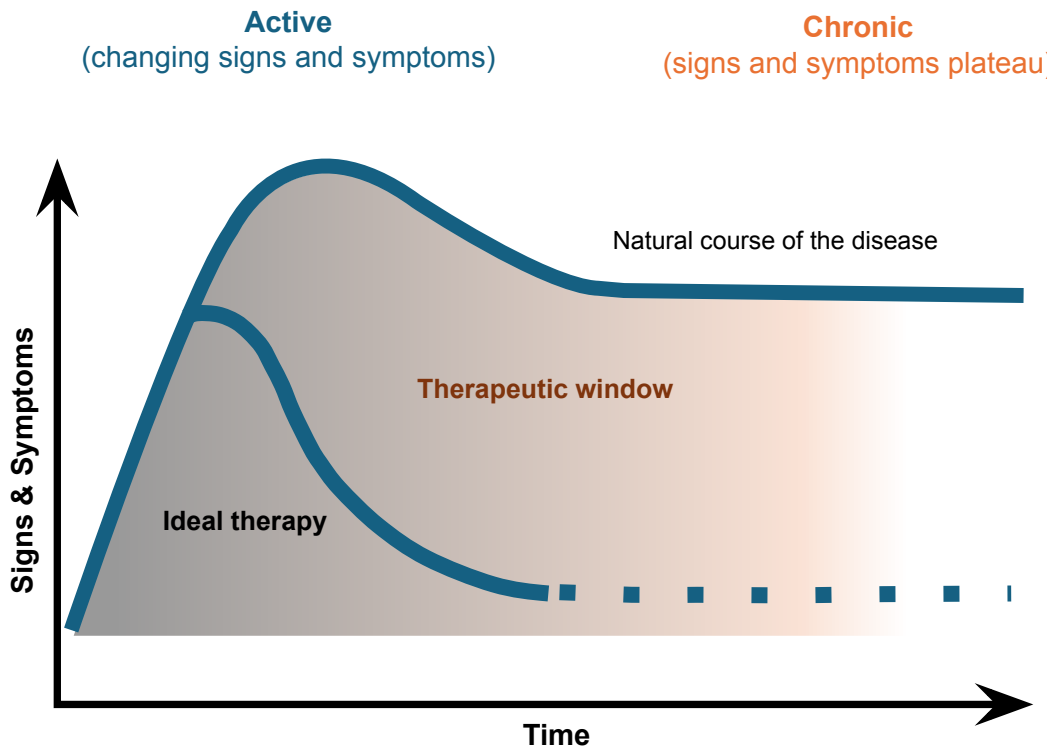
Strabismus in TED is a Result of the Expansion of the Extraocular Muscles

Compressive Optic Neuropathy (CON) Can Result in Irreversible Vision Loss

Lanzolla, Nat Reviews 2025

Natural History of TED

Natural History of TED[1-4]



Active
- Characterized by inflammation including periorbital chemosis, orbital congestion, and tissue expansion associated with eyelid retraction, proptosis, and diplopia for a variable period up to 3 years[5-7]
- Signs and symptoms worsen over time[1]

Chronic
- Inflammation will subside but the changes may remain and result in permanent damage to the eyes and damage to the muscles (**strabismus**), which result in **diplopia**[5]
- Clinical manifestations reach a plateau above normal and patient may require intervention[1]

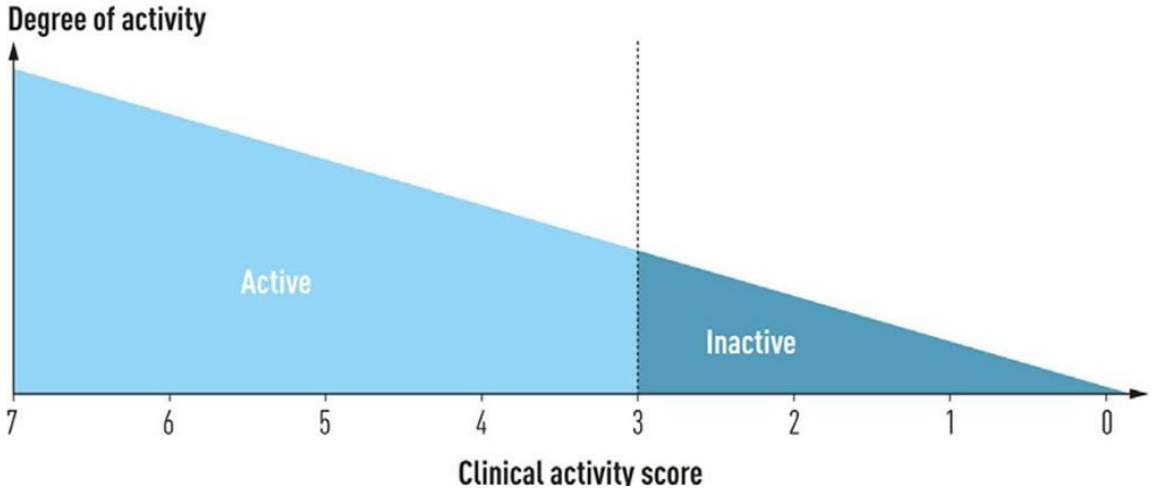
Therapeutic Window
- Initiating therapy early has been shown to be effective, but the therapeutic window may continue beyond the acute stage into chronic disease

1. Wang Y, et al. Ther Clin Risk Manag. 2019;15:1305-1318. 2. Tsui S, et al. J Immunol. 2008;181:4397-4405. 3. Pritchard J, et al. J Immunol. 2003;170:6348-6354. 4. Smith TJ, et al. J Clin Endocrinol Metab. 2004;89:5076-5080. 5. Bhatti MT, et al. J Neuroophthalmol. 2014;34(2):186-197. 6. Bothun ED, et al. Clin Ophthalmol. 2009;3:543-551. 7. Bartalena L, et al. Endocr Rev. 2000;21(2):168-199.

Diagnosis of TED

Items for the clinical activity score
(1pt/each)

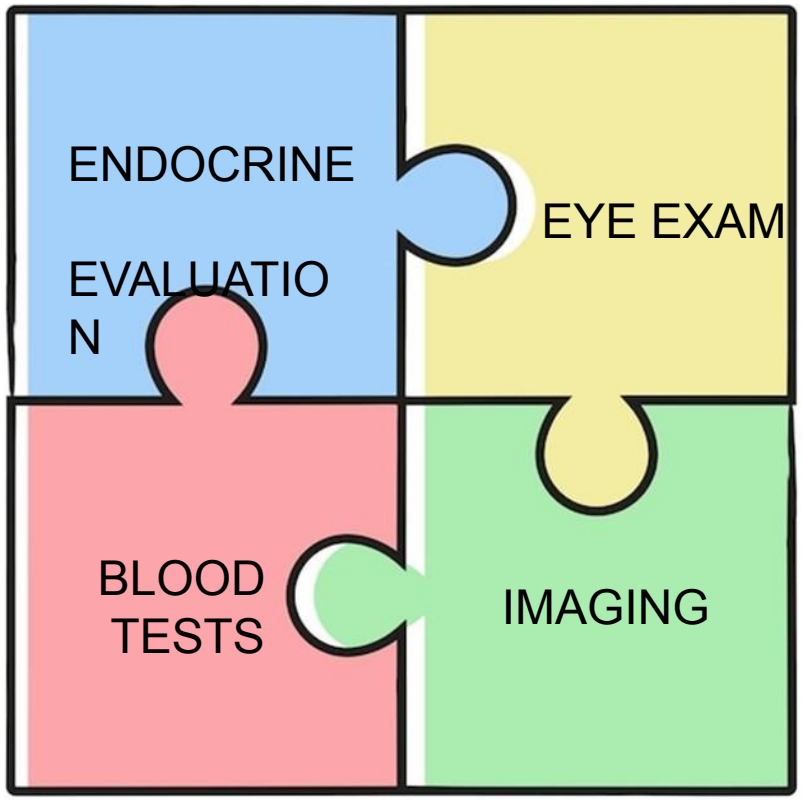
- ☐ Swelling of eyelids
- ☐ Swelling of conjunctiva
- ☐ Swelling of caruncle
- ☐ Redness of eyelids
- ☐ Redness of conjunctiva
- ☐ Spontaneous retrobulbar pain
- ☐ Pain with eye movements



Degree of severity	Features
Mild	One or more of: Lid retraction <2 mm Mild soft tissue involvement Exophthalmos <3 mm above normal No/intermittent diplopia
Moderate to severe	Two or more of: Lid retraction ≥2 mm Moderate-to-severe soft tissue involvement Exophthalmos ≥3 mm above normal Inconstant/constant diplopia
Sight threatening	Presence of DON and/or corneal breakdown

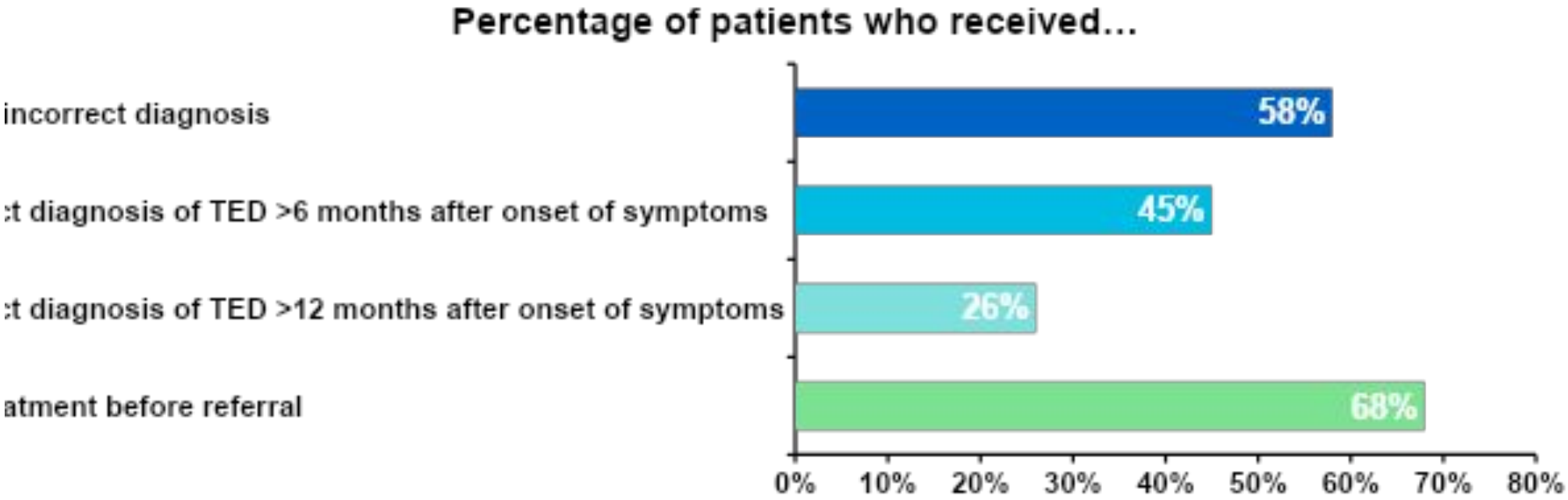
Bartalena et al (EUGOGO guidelines) Eur J Endocrinol 2021

Diagnosis of TED - pitfalls



- subjective and potentially inconsistently reported clinical signs and symptoms □treatment delays and risk of vision loss
- confounding diagnoses (i.e., lymphoma, sarcoid, cellulitis)
- initial nonspecific symptoms of TED (e.g., eye redness, watery eyes, eye pain) may be misdiagnosed as chronic conjunctivitis, dry eyes, and/or ocular allergies and lead to incorrect treatment
- anatomical variations between different racial and ethnic groups

Patients With TED Often Experience Delay in Diagnosis and Referral to the Proper Specialists



MEDIAN TIME SINCE ONSET OF SYMPTOMS BEFORE PATIENTS SEE A TED SPECIALIST IS 16 MONTHS

Estcourt S, et al. Eur J Endocrinol. 2009;161:483-487; Prummel MF, et al. Eur J Endocrinol. 2003;148(5):491-495.

Treatment of TED

Recommended immediately after diagnosis to target the acute inflammatory (active) phase; however, treatment is dependent on both the activity and severity of disease

ACTIVE, MILD TED	MODERATE-TO-SEVERE TED
• control modifiable **risk factors** (smoking cessation, dietary changes i.e., adopting a diet low in salt and sugar, • use of **topical** lubricating eye drops, • 6-month **selenium** supplementation for individuals residing in selenium-deficient areas (i.e., China, Russia, Europe) • it also is recommended that individuals be referred to **centers that provide both endocrinological and ophthalmological expertise** as well as expertise in the **restoration of euthyroid status**	• target **activity** • improve eye manifestations • **intravenous glucocorticoids** for individuals where severe proptosis/diplopia is absent and disease activity is the predominant feature

Bartalena et al (EUGOGO guidelines) Eur J Endocrinol 2021, Burch et al ATA-ETA guidelines Thyroid 2022

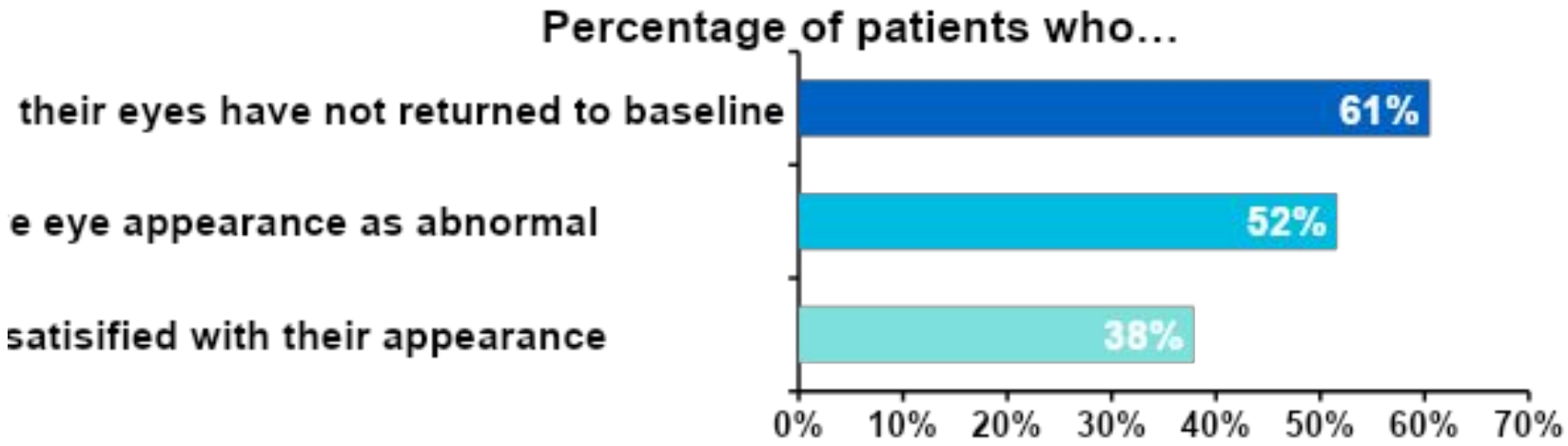
Intravenous glucocorticoids

12 weekly infusions of methylprednisolone

Due to numerous steroid-related adverse effects, patients require close monitoring

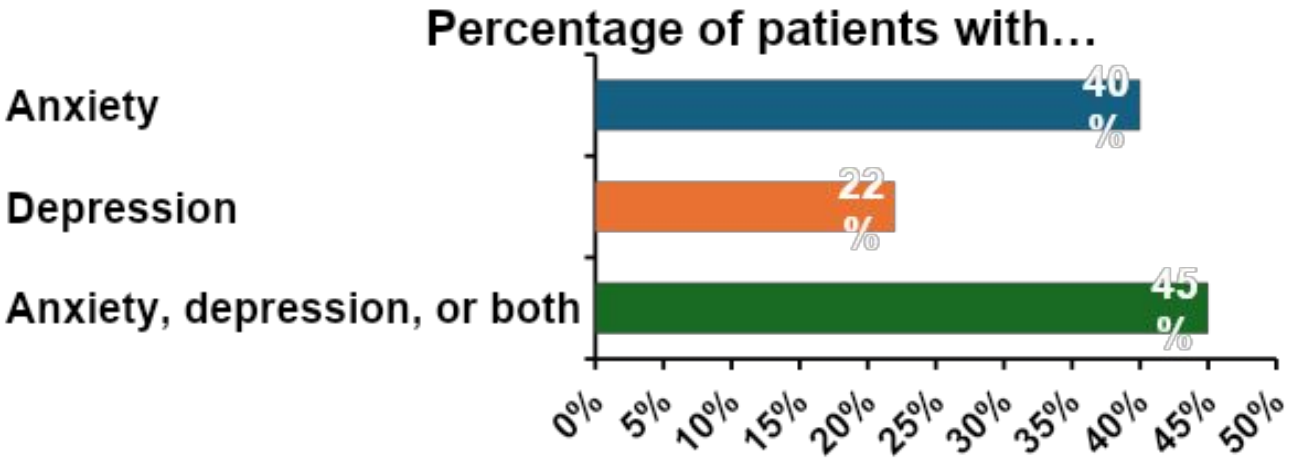
Intravenous glucocorticoids do not consistently reduce long-term diplopia and proptosis

Relapse rates of 20% to 40%



Bartley GB, et al. Ophthalmology. 1996;103(6):958-962; Sasim IV, et al. Graefes Arch Clin Exp Ophthalmol. 2008;246(9):1315; Ponto KA, et al. Dtsch Arztebl Int. 2009;106(17):283-289; Terwee C, et al. Br J Ophthalmol. 1998;82:773-779.

Patients with TED Experience Significant Psychological Burden From Their Disease

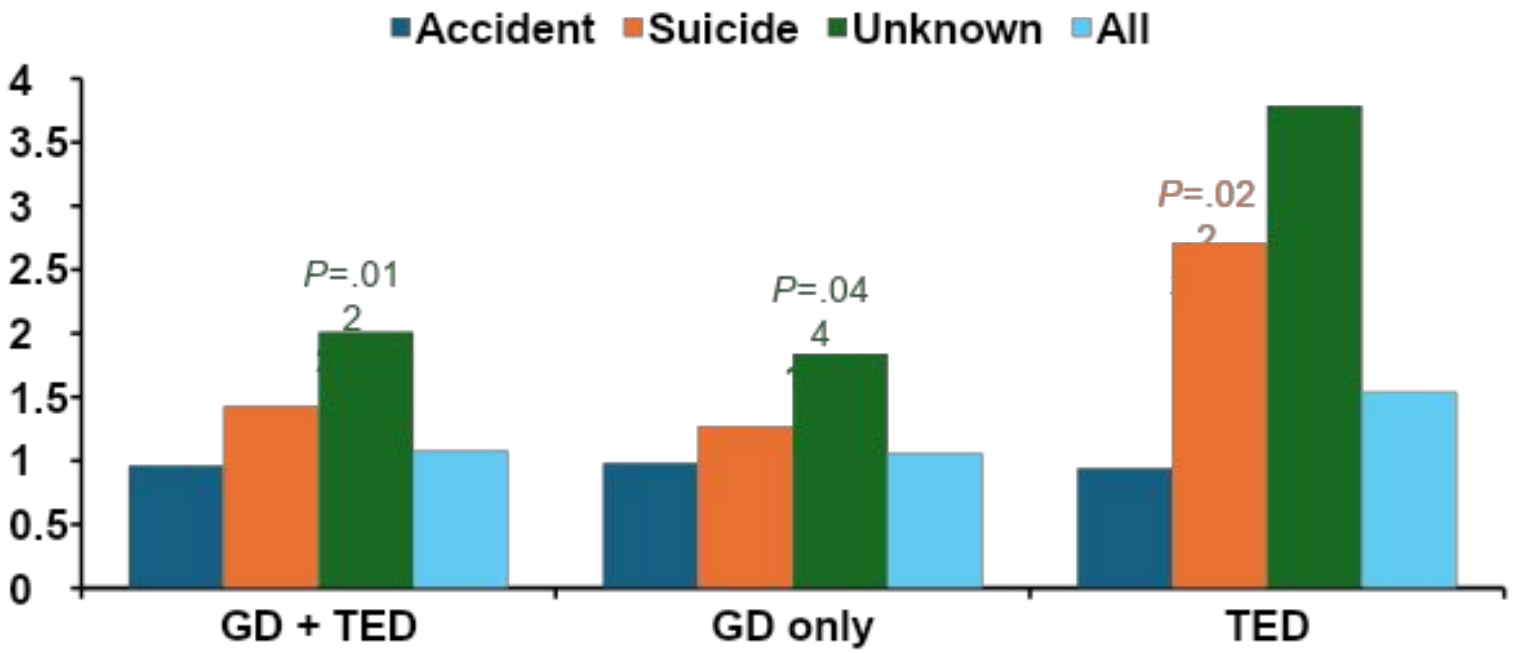


Impaired Quality of Life
Social isolation

Guidelines recommend physicians offer psychosocial support to patients who have difficulty coping with their diseas; however, only 21% of patients receive psychotherapy

Kahaly GJ, et al. *Clin Endocrinol (Oxf).* 2005;63(4):395-402;. Perros P, et al. *Clin Med (Lond).* 2015;15(2):173-178; Ponto KA, et al. *Dtsch Arztebl Int.* 2009;106(17):283-289.

Patients With TED Are at Increased Risk for Suicide



- Patients with GD and patients with TED both have increased risk for death due to unknown unnatural circumstances (accident, suicide, violence/homicide, and unknown) compared with age- and sex-matched controls (HR: 2.01; CI: 1.17–3.45; P=.012)
- However, only patients with TED and not patients with GD have increased risk for suicide compared with controls (HR: 2.71, CI: 1.16–6.32, P=.022)

HR, hazard ratio; GD, Graves' disease; TED, thyroid eye disease. *__Adjusted for both somatic morbidity (using the Charlson score) and for psychiatric morbidity__ prior to the thyroid diagnosis. Only P values for significant differences vs controls are listed.

Ferløv-Schwensen C, et al. *Thyroid*. 2017;27(12):1475-1480.

TED ECONOMIC BURDEN – direct costs

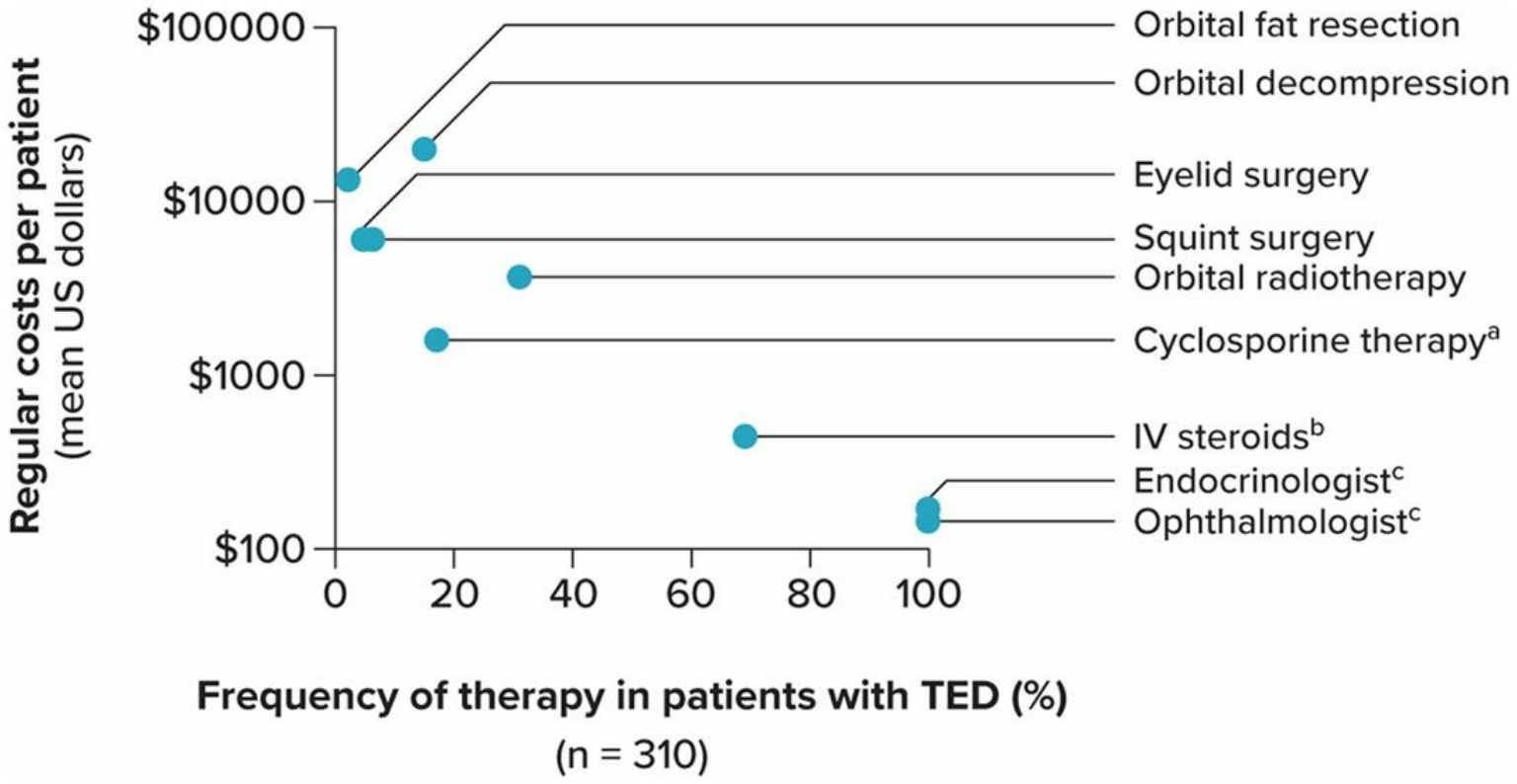


FIGURE 4
Direct costs in patients With TED. IV, intravenous; TED, thyroid eye disease. Standard deviation not shown. [a] Body weight adapted.
[b] Methylprednisolone, 6 weeks of 500 mg weekly, followed by 6 weeks of 250 mg weekly. [c] Outpatient treatment. Source: Ponto, Merkesdal (103).

Tamhankar et al Frontiers_2025
Ponto et al JCEM 2013

TED ECONOMIC BURDEN – indirect costs

Work Transitions for Patients with TED, HR (95% CI)[1]					
TED	Sickness Absence	Return to Work from Sickness	Unemployment	Return to Employment	Disability Pension
<1 year	**6.94 (4.19-11.50)**	0.63 (0.33-1.19)	0.49 (0.14-1.78)	0.40 (0.14-1.16)	†
>1 year	**2.08 (1.48-2.93)**	**0.51 (0.40-0.66)**	0.91 (0.49-1.69)	**0.52 (0.37-0.75)**	**4.40 (2.61-7.42)**

Statistically significant estimates shown in bold. †Too few instances to allow for estimation.

Almost **one-third** of patients with TED are temporarily or permanently **disabled** due to TED[2-3]

2%-5% lose their jobs or retire early due to their physical impairments[2-3]

Patients miss more than 3 weeks of work because of TED[3]

Increased disease severity leads to longer durations of sick leave[3]

*Studies on work disability have only been conducted in a European setting.
CI, confidence interval; SA, sickness absence; U, unemployment.

1. Nexo MA, et al. J Clin Endocrinol Metab. 2014;99(9):3184-3192. 2. Ponto KA, et al. Dtsch Arztebl Int. 2009;106(17):283-289. 3. Ponto KA, et al. J Clin Endocrinol Metab. 2013;98(1):145-152.

Take Home Messages

- TED requires timely and multidisciplinary management
- Available treatments have significant side effects, but limited effectiveness
- TED has non-negligible direct and indirect costs
- TED is a disease with a high impact on the quality of life of the patient (and the physician!)