Thyroid Eye Disease
An update on management
2020

The D H Verity Eye Practice Ltd.

The management of TED requires an understanding of the natural history of disease, knowledge of the relative roles immunosuppression and surgery, and when to intervene. Practice varies between units and countries, with few agreed treatment protocols.

Overview of TED

- TED presents in almost 50% of Graves' disease patients.
- It can also occur in hypothyroid patients, or those who are euthyroid.
- **The majority have mild, self-limiting, and nonprogressive ocular involvement.**
- It is an idiopathic lymphocytic orbital inflammation.
- The fibroblast plays a central role.
- Only 5% of all patients with TED will develop severe disease.
- Women are more frequently affected.
- Men can present with progressive exophthalmos and minimal inflammation.
- Uncontrolled thyroid function and smoking are the only known two modifiable risk factors.
- Grading systems for clinical severity and activity enable reliable documentation (EUGOGO and VISA grading systems).

Aetiology

- Orbital fibroblasts display TSH receptors and produce inflammatory cytokines.
- Their activation in TED is accompanied by an increase in orbital adipocytes and extracellular matrix.
- When severe, the consequent increase in orbital soft tissue volume can compromise blood flow at the orbital apex.
- Optic nerve ischaemia and reduced axonal flow (optic neuropathy) can result.

Physical signs – acute phase (Table 1)

- The active inflammatory phase lasts 12 to 24 months.
- Physical signs include ocular surface inflammation and/or exposure, eyelid oedema and inflammation (figure 1), upper eyelid retraction and /or lateral 'flare' (Figure 2), 'phase lag' of the upper lid from up- to down-gaze, conjunctival chemosis.
- In more severe forms of disease, reduced ocular ductions, proptosis (Figure 2) and congestive features, including raised intraocular pressure and compressive optic neuropathy, occur.

Figure 1 – Acute TED: Orbital and periocular inflammation, lid retraction and optic neuropathy

Physical signs – chronic phase

- Lid fullness, due to proptosis, tissue hypertrophy.
- Lid retraction, due to fibrosis of the upper lid levator complex.
- Incomplete blink cycle.
- Lagophthalmos (inability fully to close the eye).
- Limitations in ocular ductions with diplopia in any position of gaze.
- Stable exophthalmos.
- Established optic neuropathy (rare, given availability of medical and surgical treatments).

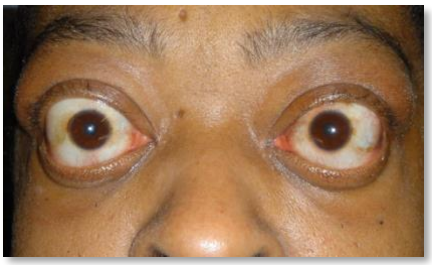


Figure 2 – Established TED: Marked proptosis, upper lid retraction, and lower lid displacement

Treatment – mild disease

- In all cases, thyroid control and smoking cessation are essential.
- In most patients with TED, ocular and adnexal changes are *mild* and management involves controlling thyroid dysfunction, cessation of smoking, and addressing ocular surface inflammation and exposure.
- In women, selenium (an antioxidant) can reduce the risk of progression to more severe forms of disease.
- Thus, in the absence of significant ocular exposure, orbital congestion, diplopia and optic neuropathy, the majority of patients are managed with topical lubricants alone.

Treatment – moderate disease

- In patients with acute *moderate* disease, this being sufficient to impair orbital functions, Immunosuppression reduces the long-term sequelae of acute inflammation.
- Intravenous methyl prednisolone (IVMP) is given on a weekly basis of 500 mg – 1 g, but should not be continued beyond a total dosage of 4.5 g (Table 2). Medical review must precede the first dose to reduce the risk of cardiac and hepatic side effects. Serious side effects are reported with daily high-dose regimes, but not, in general, with weekly regimes.
- Adjunctive fractionated low-dose orbital radiotherapy (20 Gy over 10 sessions) is used as a steroid-sparing measure, and generally advocated following clear improvement on steroid treatment.
- Surgical intervention during the active phase of moderate disease is rarely indicated.
- However, early decompression may limit progression to more severe disease in cases of significant orbital congestion (which can mimic inflammation).

Treatment – severe disease

- Acute *severe* TED poses a major risk of irreversible loss of vision due to marked exposure keratopathy, 'hydraulic' orbital congestion, or compressive optic neuropathy.
- If performed promptly, retractor recession with or without a suture tarsorrhaphy protects the ocular surface from severe exposure.
- High dose IVMP should be given.
- Rituximab is considered in patients intolerant of steroid treatment – although its use acutely is often limited by cost and availability.
- Patients with severe congestion or optic neuropathy who do not respond to such treatment should be considered for early decompression of the deep medial orbital wall and postero-medial floor.
- Prompt decompression can rapidly relieve compressive optic neuropathy, as well as alleviate the inflammatory and congestive features of raised orbital pressure.
- Prolonged steroid or other (non-molecular) immunosuppressive treatment is not advisable unless surgery poses an unacceptable anaesthetic risk.

Newer targeted molecular approaches

- As the immune pathways in TED become better understood, more targeted treatments are becoming available.
- Rituximab is a monoclonal antibody directed against the B cell CD20 surface marker. The drug deletes the B cell population for up to 4 – 6 months, with significant improvement in CAS scores over a 1-year follow-up.
- Teprotumumab, a human monoclonal antibody inhibitor of the insulin-like growth factor I receptor (IGF-IR) is effective in reducing the degree of proptosis and inflammation in patients in patients with active, moderate-to-severe ophthalmopathy. This drug appears to be both safe and effective, and shows much promise for the future.

Treatment – inactive phase

- Elective surgery is often required following moderate TED.
- Indications include lid retraction or fullness, documented stable diplopia and proptosis.
- Surgery should be delayed until the disease is quiescent, with the patient stable and weaned off all immunosuppression.
- In general, when indicated, decompression should be performed before strabismus surgery, with lid surgery (typically retractor recession +/- blepharoplasty) performed last .
- Patient expectations can rise significantly over the course of treatment; surgery cannot restore the premorbid appearance, which, in many instances, may have been years or even decades earlier.

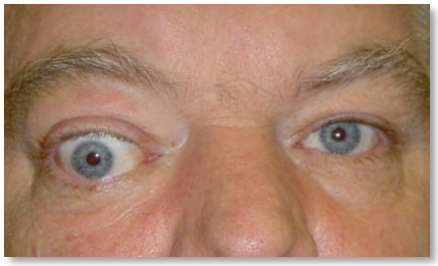
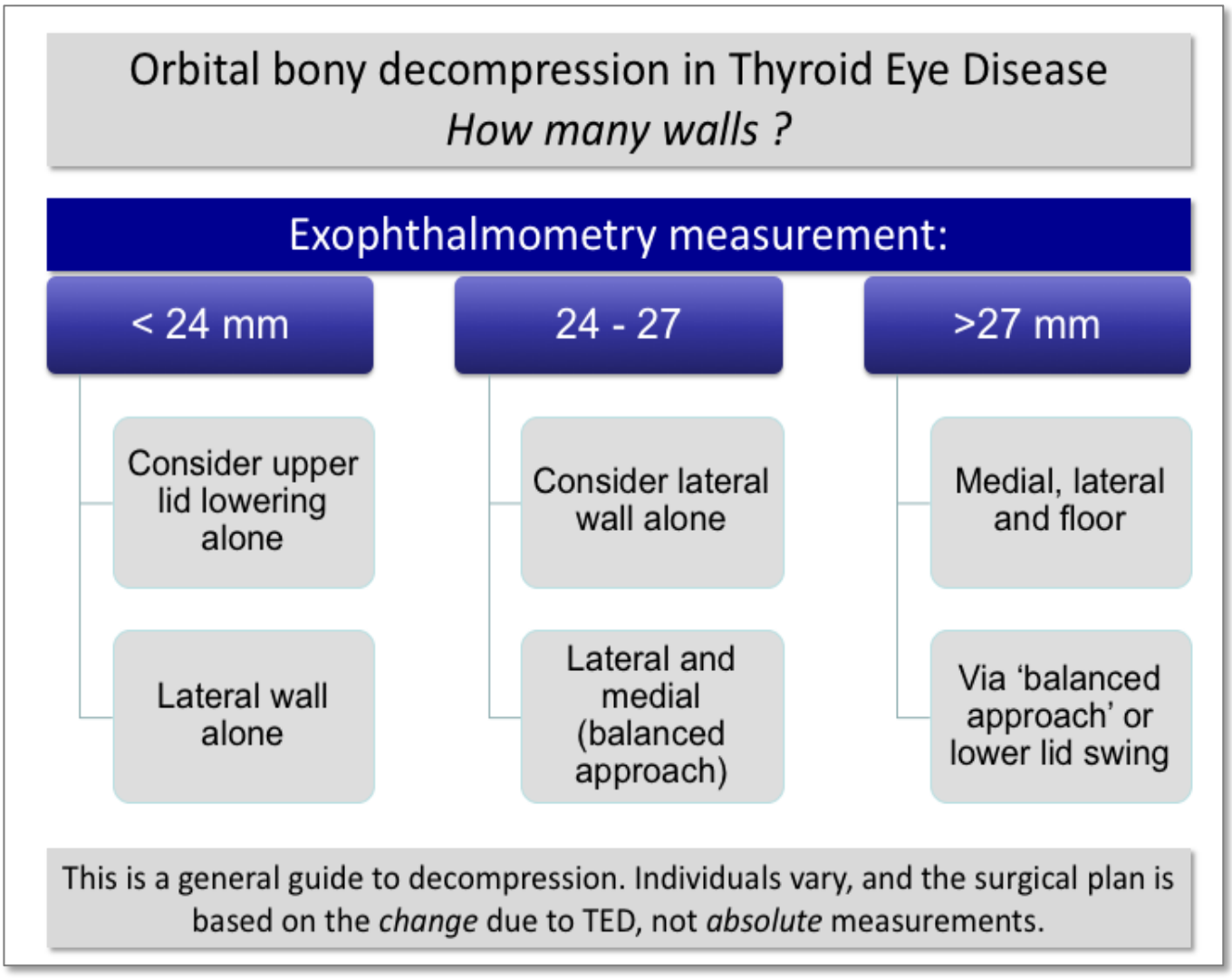


Figure 3 – Marked right exophthalmos, with hypotropia and lid retraction due to fibrotic reaction within muscles

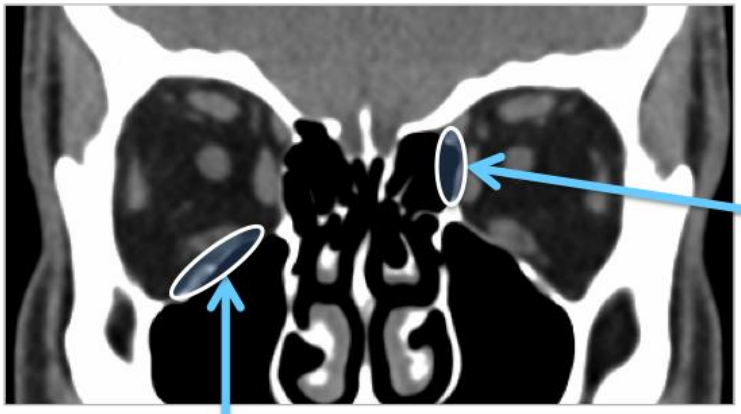
Orbital decompression surgery

- In optic neuropathy, prompt decompression of the medial orbital wall and postero-medial floor is indicated if early recovery of visual functions does not occur with medical treatment.
- In stable (chronic) cases of mild to moderate degrees of exophthalmos (< ~24mm), deep lateral wall decompression may be sufficient to restore globe position.
- For greater degrees of exophthalmos (~ 24mm – 26mm), a 'balanced' two-wall decompression is preferred, this involving the lateral and medial orbital walls.
- For greater than ~26 mm proptosis, a 2.5 to 3 wall decompression is generally advised.
- Fat decompression (in comparison to bony decompression) is favoured by many, although arguably is less effective for larger degrees of exophthalmos.



Orbital Decompression Surgery

With reference to the medial and lateral walls, and the floor, of the orbit.



A **medial wall decompression** takes this part of bone away.
It is usually done at the same time as decompression of the lateral wall in patients with moderate to severe stable exophthalmos.
It is also done in isolation in patients with compression of the optic nerve and who have visual loss. Decompressing this wall introduces a risk of double vision.

Decompression of the **orbital floor** takes this part of bone away. Generally, floor decompression is reserved for severe proptosis (bulging eye), and is done as part of a '3-wall' decompression. Temporary cheek numbness can occur after surgery.

A **lateral wall** decompression removes this part of bone. It can be done in isolation for less severe degrees of proptosis. It introduces almost no risk of double vision.

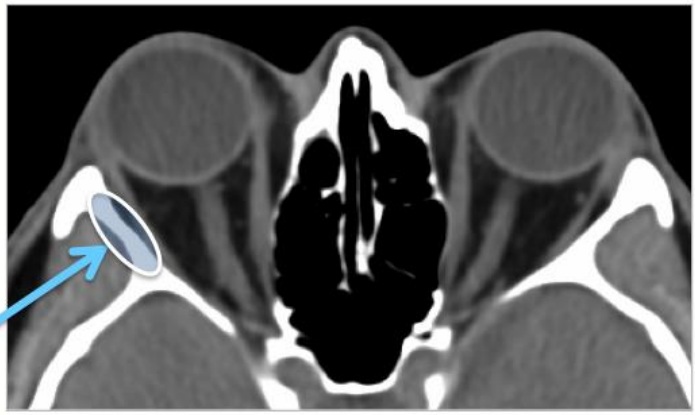


Table 1: Features of TED

(A) Ocular surface disease:

- Fiery foreign-body sensation due to:
  - altered blink frequency and cycle
  - impaired goblet cell function
  - eyelid retraction
  - widened palpebral aperture due to proptosis
- Epiphora due to ocular surface inflammation and exposure with reflex epiphora
- Superior limbic keratitis
- Microbial keratitis and corneal perforation in severe cases

(B) Orbital congestion:

- A deep orbital 'ache'
- Periocular and frontal 'headaches'
- 'Hydrostatic' orbital signs: dilated episcleral vessels and elevated intraocular pressure
- Oedematous eyelids
- Chemosis (which can be severe enough to prevent eyelid closure)
- Exophthalmos, reduced spectacle 'back vertex distance' (subjectively altered refractive error)
- Optic neuropathy: Reduced contrast sensitivity, blurred vision, reduction of visual field, relative afferent pupillary defect (can be absent with bilateral involvement)
- Acute visual loss due to compressive ischaemic posterior optic neuropathy or retinal vascular occlusion
- Endophthalmitis

(C) Inflammatory myopathy:

- A retro-ocular 'tethering' ache, particularly with eye movements
- Lid retraction and lateral flare
- Impaired ocular ductions and diplopia
- Tethering of the inferior rectus muscle:
  - Increased IOP on attempted upgaze
  - Reduced upgaze and Bell's phenomenon, compromising corneal protection

(D) Radiological changes (CT preferable to MRI)

- Enlarged and anteriorly displaced lacrimal glands
- Enlarged extraocular muscles and/or adipose tissue
- Increased crowding of the orbital apex

Table 2: Intravenous methylprednisolone (IVMP) treatment

Indication: Soft tissue inflammation or diplopia:

- Numerous reported treatment protocols
- 500 mg once weekly for 6 weeks, then 250 mg weekly for 6 weeks; total 4.5 g
- No protocols higher than 500 mg daily for three days, or a total of 3 g in the first week
- Consider adjunctive external beam low-dose orbital radiotherapy

Indication: Optic neuropathy:

- Similar to treatment for severe active TED as above.
- Commonly used protocols:
  - 500mg daily for 3 consecutive days, then continue either with 250mg weekly as required, or with slowly tapering course of oral prednisolone 0.7mg/kg/day.
  - 500mg weekly (as a single pulse) for 6 weeks, then 250mg weekly for 6 weeks.
- Prompt orbital decompression if inadequate response.

Notes:

1. In all cases at the start of treatment consider giving calcium / vitamin D supplements, and a biphosphonate (e.g. alendronate 70 mg once weekly)
2. Intravenous glucocorticoids should be administered in centres with adequate medical and resuscitation facilities.