Management of patients with thyroid eye disease

Graves' ophthalmopathy – also called Graves' orbitopathy, thyroid eye disease or thyroid-associated orbitopathy – is an autoimmune process characterized by of the orbital and periocular fibro-adipose tissues inflammation. The previous article (p. C2) discussed the pathogenesis of thyroid eye disease, its spectrum of ophthalmic manifestations, and the clinical assessment of patients presenting with thyroid eye disease. This article discusses the management of thyroid eye disease in clinical practice.

The general principles of thyroid eye disease management

Cases of moderate to severe thyroid eye disease are best managed with multidisciplinary care – including endocrinologists, ophthalmologists, radiologists and possibly radiotherapists – and patients treated according to disease severity and activity (*Figure 1*). Severe thyroid eye disease with dysthyroid optic neuropathy is sight-threatening and risk stratification with timely and appropriate management are key to successful outcome.

Treatment should focus on three main aims:

1. Restoration of euthyroid state
2. Symptomatic relief
3. Reduction of orbital inflammation by immunosuppression (usually glucocorticoid treatment), surgical orbital decompression and/or orbital irradiation, and cessation of smoking.

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Restoration of euthyroid state

As progression of thyroid eye disease is often associated with hyper- or hypothyroidism, establishing a euthyroid state – typically with antithyroid drugs (such as carbimazole or propylthiouracil) – is fundamental and tends to ameliorate orbitopathy.

Correction of abnormal levels of circulating thyroid hormones often improves eyelid retraction, but has minimal effect on the pathology of thyroid eye disease. Medical overcorrection of hyperthyroidism – with unintentional hypothyroidism – should be avoided, as this exacerbates thyroid eye disease (Marcocci and Marino, 2012). For patients treated surgically, near-total thyroidectomy is preferred to subtotal, as the former is associated with better long-term control of thyroid status and a lower risk of progressive ophthalmopathy.

Radioactive iodine ablation of the thyroid gland is associated with the appearance or exacerbation of ophthalmopathy in about 15% of patients (Tallstedt et al, 1992; Traisk et al, 2009; Vannucchi et al, 2009), this possibly resulting from transiently increased circulating thyroid-stimulating hormone-receptor antibodies and other thyroid antigens (McGregor et al, 1979), but more likely to be from precipitate and unaddressed post-radioactive iodine hypothyroidism (Perros et al, 2005; Acharya et al, 2008). As well as uncontrolled hypothyroidism, the risk of post-radioactive iodine thyroid eye disease is also higher among patients with prior or active eye disease, smokers, patients with high titres of thyroid-stimulating hormone-receptor antibodies, and with triiodothyronine (T3) levels ≥5 nM.

Figure 1. Recommendations for the management of thyroid eye disease depending on disease severity and activity.

- Treatment should focus in all cases on restoration of euthyroid state, symptomatic relief, and reduction of orbital inflammation by immunosuppression (usually glucocorticoid treatment), surgical orbital decompression and/or orbital irradiation depending on disease severity and activity. Severe thyroid eye disease with dysthyroid optic neuropathy can be sight threatening and risk stratification with timely and appropriate management are key to successful outcome.
- All patients with thyroid eye disease should receive smoking cessation advice. In all cases local measures for symptomatic relief should be considered and daily supplementation with selenium 200 μg orally initiated. Decision to refer to the ophthalmologist should be made based on disease activity and severity.
- For mild disease – where indicated, rehabilitative and cosmetic surgery should be considered when disease remains stable and inactive.
- For moderate disease – where indicated rehabilitative and cosmetic surgery should be considered when disease remains inactive and stable. In cases of active disease, glucocorticoids and orbital radiotherapy should be considered, and rehabilitative and aesthetic surgery should be deferred for when disease improves, and becomes stable and inactive.
- For severe, sight-threatening disease (i.e. dysthyroid optic neuropathy) – intravenous glucocorticoids should be administered and response to treatment assessed in 2 weeks. If response to treatment is poor, urgent surgical decompression should be considered. If disease remains active after decompression, further treatment with glucocorticoids and/or orbital radiotherapy should be considered. Rehabilitative and aesthetic surgery should be deferred for when disease improves, and clinical signs remain stable and disease inactive.

The simplest measure to prevent post-radioactive iodine thyroid eye disease is early and effective thyroxine replacement, preferably within about 2 weeks of treatment (Perros et al, 2005; Acharya et al, 2008). Alternatively, pre-treatment with glucocorticoids can reduce the risk (Vannucchi et al, 2009), but this is at the expense of treating about six patients unnecessarily for every one case prevented; in view of this, glucocorticoids should probably not be used routinely after radioactive iodine but rather reserved only for those at high-risk of flare-up. Steroid regimens vary after radioactive iodine, but oral prednisolone may be given at daily doses of 0.4–0.5 mg/kg, starting 2–3 days before radioactive iodine and continuing for a month after treatment, with the dose then tapered over a further 2 months. Although glucocorticoids enhance renal clearance of iodine, thereby reducing the effective half-life of the radionuclide, this does not seem to affect the efficacy of thyroid ablation.

Although most physicians would sensibly avoid radioactive iodine in the presence of active moderate or severe thyroid eye disease, this is not an absolute contraindication as the euthyroid patient has a better long-term prognosis for thyroid eye disease than a poorly-controlled patient; such patients should, however, receive adequate steroid cover during therapy and have regular ophthalmic assessments.

Achieving symptomatic relief in patients with thyroid eye disease

Cessation advice and assistance should be given to all smokers with thyroid eye disease, as observational studies show that stopping smoking reduces the risk of developing diplopia or exophthalmos.

Simple measures normally suffice for symptomatic relief with mild thyroid eye disease, such as the use of sunglasses, ocular lubricants (e.g. 1% methylcellulose) and deliberate eye closure during periods of prolonged visual tasks (for example, reading or visual display unit usage). Nocturnal lagophthalmos can be addressed by use of gel lubricants, with taping the eyelids closed, or with creation of a 'humidity chamber' – either an eyemask or else a square of cellophane food-wrap applied to the periocular skin and stabilized with some tape. Injections of botulinum toxin into the levator muscle can provide a reversible eyelid lowering, although it may cause diplopia and can occasionally exacerbate exposure keratopathy. Diplopia can be helped with application of stick-on Fresnel prisms to spectacles or, if the ocular deviation is too great, one spectacle lens can be occluded.

Randomized trials have shown selenium supplementation (200 μg) to be of value in ameliorating the symptoms of mild thyroid eye disease, and this therapy should be recommended to all patients with this disease (Marcocci et al, 2011).

Moderate to severe ophthalmopathy: the role of glucocorticoids

Where compressive optic neuropathy is present, high-dose glucocorticoids (i.e. 1 mg methylprednisolone daily for 3 consecutive or alternate days) are recommended; if no improvement is noted within 2 weeks, then surgical decompression – typically medial wall and medial floor – should be considered. Oral or intravenous glucocorticoids can also be used in moderate to severe active thyroid eye disease where there is worsening muscle disease (diplopia) or increasing proptosis.

The ophthalmic response should be assessed after a week of oral prednisolone (with initial dosage of about 1 mg/kg over the first 3–5 days) and, if a satisfactory response, the dosage should be gradually reduced towards prednisolone 20 mg daily over 4 weeks, with continued ophthalmic monitoring. About two-thirds of patients will respond well to systemic steroids, with intravenous glucocorticoids having a marginally greater reduction in disease activity (clinical activity score) and having fewer side effects than oral steroids (Bartalena et al, 2008a,b; Stiebel-Kalish et al, 2009); however, intravenous steroids are more costly, necessitate a specialized treatment setting, and can rarely induce severe morbidity such as hepatotoxicity and death.

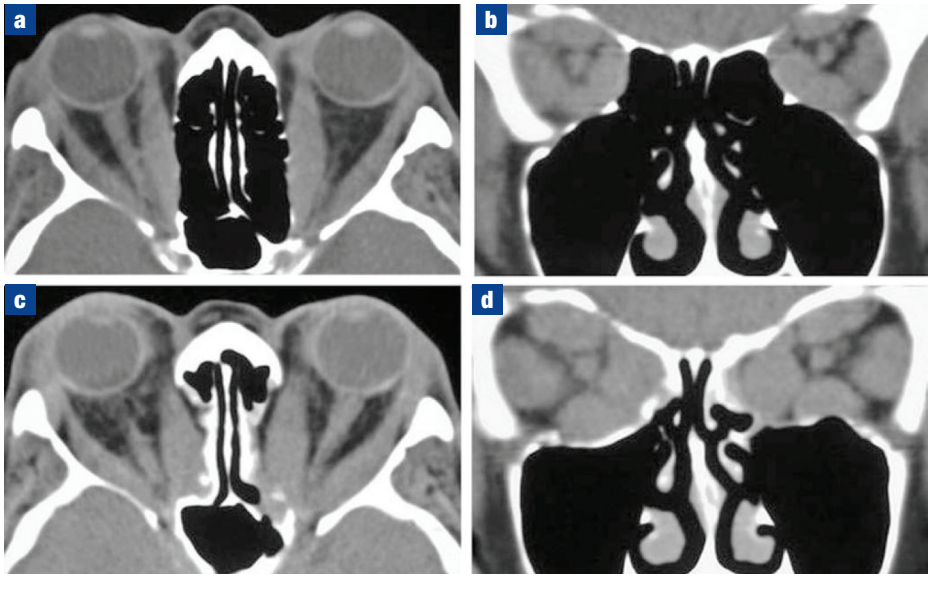
Orbital radiotherapy

The role of low-dose radiotherapy to the retrobulbar tissues remains controversial (Stiebel-Kalish et al, 2009) but, in practice, can help control active disease in ~60% of patients with impaired eye motility. Exophthalmos, eyelid retraction and soft tissue swelling show a poor response to irradiation (Bradley et al, 2008). Randomized studies have shown equal efficacy for orbital radiotherapy and systemic steroids, but superiority of combined therapy over either treatment alone (Stiebel-Kalish et al, 2009). Radiotherapy should probably be avoided in patients under 35 years of age, and also in patients with severe hypertension or diabetic retinopathy who have a much greater risk of radiation retinopathy.

Surgical decompression and other ophthalmic rehabilitation

Urgent surgical decompression is undertaken for compressive optic neuropathy unresponsive to high-dose systemic steroids (*Figure 2*) or for severe exposure keratitis

Figure 2. Computed tomography scan (a and b) before and (c and d) after orbital decompression for medically-resistant compressive optic neuropathy. A complete ethmoidectomy and removal of the medial half of the orbital floor has been performed to relieve compression at the orbital apex.



exacerbated by gross proptosis. Routine decompression is offered where a patient wishes for aesthetic improvement (Lyons and Rootman, 1994), or where there is a persistent hydraulic orbitopathy with extremely high intraorbital venous pressures (*Figure 3*).

Decompression for aesthetic purposes favours fenestration of the lateral orbital wall, possibly with removal of some orbital fat, as this procedure has practically no chance of inducing diplopia; complete ethmoidectomy is added where a greater reduction of exophthalmos is required, and – except in extreme cases – removal of the orbital floor should be avoided because of the high rate of troublesome diplopia. Removal of the orbital roof has no role in the contemporary treatment of thyroid eye disease. For medically-resistant optic neuropathy (where exophthalmos is less likely), it is important to remove all possible bone from around the optic nerve at the orbital apex – this dictating at least a posterior ethmoidectomy and removal of the posterior orbital floor (*Figure 4*); such surgery is readily accomplished through a transconjunctival route, without a skin incision.

With appropriate decompression, most patients can have their exophthalmometry returned to within the normal range (*Figure 4*). The effect of decompression on ocular motility is variable, with some patients having marked improvement and others experiencing an exacerbation, or new onset, of double vision. Squint surgery is often required where diplopia persists, this being more readily accomplished in the absence of exophthalmos (after effective decompression).

Most rehabilitative ophthalmic surgery is undertaken when the thyroid eye disease has been inactive for at least 6 months (Marcocci and Marino, 2012), and therapy (where needed) is generally undertaken in the order of decompression, squint surgery, and upper eyelid lowering (retractor recession) (*Figure 5*) – the latter with or without blepharoplasty of up to four eyelids. The use of lateral tarsorrhaphy alone has no role in eyelid retraction and corneal protection – the results neither having a good effect, nor persisting long term (*Figure 6*).

Figure 3. Gross engorgement of episcleral veins in a patient with inactive, but 'hydraulic' Graves' ophthalmopathy, the high pressure leading to postural obscuration of vision and relieved by orbital decompression. Although commonly misinterpreted as such, this is not active inflammation.

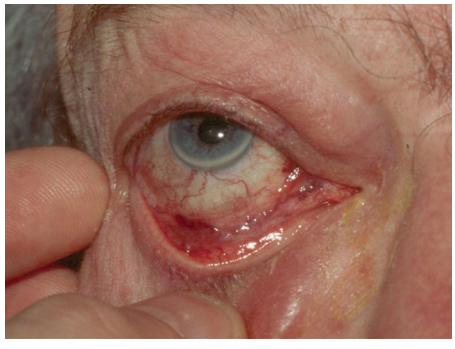


Figure 4. **a.** Patient undergoing bilateral three-wall orbital decompression for marked proptosis caused by Graves' ophthalmopathy; the right-sided surgery has just been completed through a small outer canthal incision. **b.** The same patient 5 months after decompression, having had 11 mm reduction in exophthalmos and no disruption of ocular motility.

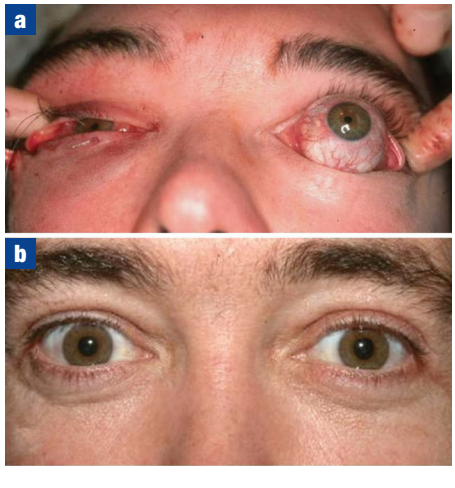
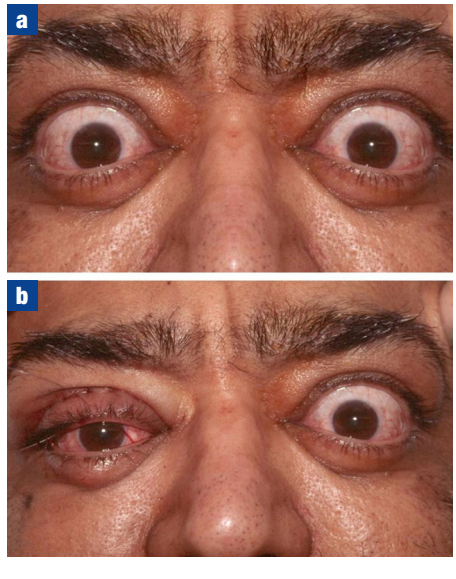


Figure 5. Patient with marked upper eyelid retraction **(a)** before and **(b)** after levator muscle weakening; surgery for the two sides, as an outpatient, is generally performed in quick succession.

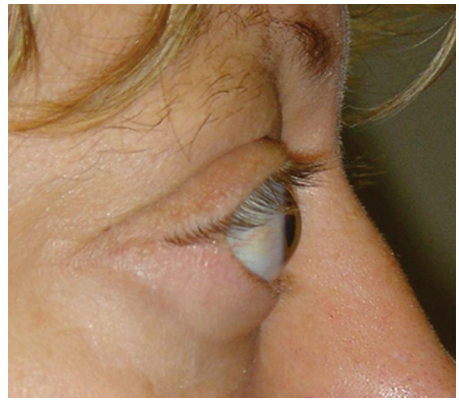


Immunotherapies and other treatment modalities

Although orbital fibroblasts express somatostatin receptors and long-acting somatostatin-analogues have shown some efficacy in trials (Marcocci and Marino, 2012), their very limited efficacy and high-cost limits usage in practice. Other treatments, with minimal benefit shown in trials, include intravenous immunoglobulins, ciclosporin either as a monotherapy or as a steroid-sparing agent, colchicine and pentoxifylline.

Rituximab (a monoclonal antibody that causes systemic depletion of mature B-lymphocytes) has been shown to be very effective in suppressing moderate or severe thyroid eye disease – including cases of steroid-resistant disease. Although the toxicity and high cost of this potent medication has previously limited its 'off-licence' application to patients with thyroid eye disease, it has now been shown to have efficacy at 10–20% of the doses used in early studies (Salvi et al, 2012), making it a much better tolerated and cost-effective treatment. Should this improved toxicity of low-dose rituximab be confirmed in larger studies, its much more sustained effect and lower morbidity (as compared with systemic glucocorticoids) might well render it a first-line treatment for moderate or severe thyroid eye disease.

Figure 6. Lateral tarsorrhaphy for corneal protection in patients with thyroid upper lid retraction has a poor outcome, both in terms of aesthetics and in longevity – the tarsorrhaphy often gaping widely within a few months.



KEY POINTS

- Treatment of thyroid eye disease should primarily focus on restoration of euthyroid state. Steroid and immunosuppression may be considered in order to suppress inflammation.
- Surgical decompression and/or irradiation may be required, depending on disease severity.
- Management of thyroid eye disease requires a multidisciplinary approach.
- Thyroid eye disease complicated by dysthyroid optic neuropathy is sight threatening and risk stratification is key to successful outcome.

Conclusions

The successful management of thyroid eye disease requires a multidisciplinary approach. The cornerstone of the management is restoration of euthyroidism, whereas steroid administration and immunosuppressants, surgical decompression and/or irradiation are used depending on disease severity. Dysthyroid optic neuropathy is sight threatening and appropriate risk stratification and treatment escalation is key to a successful outcome. **BJHM**

Conflict of interest: none.

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TOP TIPS

- Cases of moderate to severe thyroid eye disease are best managed with multidisciplinary care.
- Multidisciplinary care teams dealing with thyroid eye disease should include at least one professional from each of endocrinology, ophthalmology, radiology and radiotherapy.
- Clinical activity and disease severity and activity should be accounted for when deciding on how to best treat a patient with thyroid eye disease.
- Severe thyroid eye disease with dysthyroid optic neuropathy is sight-threatening and risk stratification with timely and appropriate management are key to successful outcome.
- Treatment of thyroid eye disease should focus on restoration of a euthyroid state and symptomatic relief.
- Smoking cessation advice should be given to all patients.
- All patients with thyroid eye disease should receive selenium supplementation at 200 μg daily.
- Patients with moderate or severe thyroid eye disease should receive glucocorticoids and possibly orbital radiotherapy.
- Unless decompression is required for persistent optic neuropathy, surgical rehabilitation for thyroid eye disease is generally performed after a period of inactivity.
- Surgical decompression for thyroid eye disease may involve a sequence of orbital decompression, squint surgery and finally eyelid surgery.
- Novel therapies such as rituximab are increasingly used with emerging new evidence in their favour.