Management of Thyroid Eye Disease

Dr. E. Ravindra Mohan, MD, FRCS¹, Dr. Malay Verma, MS¹, Dr. Charuta Bhadre, MS, DO, DNB², Dr. S. Meenakshi, MS, FRCS²

Thyroid eye disease is an autoimmune disease producing symptoms related to inflammation, accumulation of fluid in the orbit and also to adipogenesis raising intraorbital pressure. The management strategies revolve around reducing this inflammatory response, providing symptomatic support and preventing complications.

Assessment of clinical activity as well as staging of the disease is of prime importance because it determines the management strategies, timing of intervention and is important for follow up. Different staging methods and classifications like Rundel's staging, Mourits scale and Werner’s NOSPECS classification have been proposed but none of them are universally acceptable.

Medical Management

Basically thyroid eye disease consists of three different phases: - active, stable and burnt out. Medical management is tailored according to these phases. As far as prevention is concerned, the occurrence of the disease cannot be prevented however its progression can be arrested by avoiding smoking and controlling thyroid dysfunction with the help of the endocrinologist.¹ Smokers have more severe form of the disease as compared to non-smokers.² Smokers respond poorly to the treatment in a dose dependent manner.³ Tertiary prevention (preventing complications) can be achieved by early diagnosis and institution of anti-inflammatory treatment.

Before instituting any treatment, patients should be explained about the self-limiting nature of the disease, prolonged course over one or more years, non-availability of any immediate cure and the importance of follow-up.

Broadly management modalities are:
1. Supportive treatment
2. Steroids
3. Immunosuppressants
4. Radiotherapy
5. Antithyroid therapy
6. Others

Supportive treatment

Supportive treatment forms the mainstay of medical management in early stages of the disease. Aim is to reduce the dryness of eyes due to exposure, reduce morning lid edema and to prevent the progression of the disease.

Modalities

A. Artificial tear supplement : Gel preparations of tear supplements have the added advantage of reduced dosing while preventing any blurring of vision. Ointments can be used at bedtime.

B. Moisture chambers are used at night. These are commercially available. Alternatively they can be made simply from any clean transparent plastic or cellophane sheet available at stationary shops and can be pasted using strips of adhesive material. Direct taping of the eyes to avoid exposure keratopathy should be avoided as there is a risk of the tape getting

¹ Department of Orbit & Oculoplasty service, Medical and Vision Research Foundation, 18, College Road, Chennai – 600 006 India Tel: 91-044-28271616 E-Mail: drerm@snmail.org
² Department of Paediatric Ophthalmology, Medical and Vision Research Foundation, Sankara Nethralaya, 18, College Road, Chennai – 600 006 India, Tel: 91-044-28271616, Fax: 91-044-28254180, E-Mail: mrf@sankaranethralaya.org
stuck to the already compromised cornea due to the lids opening up during sleep.

C. Head end of the bed can be elevated to reduce the accumulation of fluids which results in periorbital puffiness and increased symptoms in the mornings.

D. Spectacles are prescribed. Bifocal spectacles are avoided as limitation of ocular motility may prevent the eye from looking through the near segment. Fresnel prisms are prescribed for diplopia resultant from small angle deviations. As a temporizing measure in cases with large angle strabismus waiting for surgery, occluders can be tried.

Steroids

Glucocorticoids are the mainstay of the therapy by virtue of their immunomodulatory and anti-inflammatory action. The beneficial role of corticosteroids in thyroid eye disease has been documented in early 1950s by Kinsell et al. Brown et al used high doses of prednisone and reported good improvement in all the patients. Corticosteroids reduce the inflammation by reducing the cytokine synthesis and reduce the fibroblast activation. This reduces the mucopolysaccaride synthesis and reduces fluid accumulation. They also reduce the irritation and the dull aching pain associated with eye movements thereby providing symptomatic relief to the patient. Steroids are reserved for cases with moderate to severe inflammation or in cases with compressive optic neuropathy. It is also used as a temporizing measure in cases that are waiting for surgery, occluders can be tried.

Corticosteroids by intravenous route is more than by oral route. Apart from that, some studies have found that the response to steroids depends upon the duration of the disease. Better response is seen in conditions of recent onset. Some studies have advocated titrating the steroid according to the thyroid status as there is reduced response to steroids in hyperthyroidism. Adverse effects noted with steroid therapy are peptic ulcer disease, weight gain, psychosis, aseptic necrosis, acne, hepatotoxicity and glucose intolerance. Oral antacids, H2 blockers and calcium supplements are warranted to prevent the risk of gastrointestinal bleeding. Monitoring of electrolytes and blood sugars is necessary as long term steroid therapy can cause potassium depletion and glucose intolerance.

Immunosuppressants

Immunosuppressives act by inhibiting the activation of cytotoxic T cells and by preventing cytokine synthesis. They also activate suppressor T cells. The immunoglobulin release by activated B lymphocytes is also reduced by them. They have been used to prevent relapse, co-therapy with steroids for nonresponsive cases and as a temporizing measure while awaiting definitive treatment. The various drugs used are Azathioprine 1-4 mg/kg/day in two divided doses, Cyclosporin A, 5-7 mg/kg for 4-12 months (maximum daily dose 5.0 mg/kg/day) or cyclophosphamide. The immunosuppressive agents are inferior to prednisolone in efficacy as a monotherapy. However the response is much better if given as a combination therapy with oral steroids. Combination therapy reduces the risk of relapse also. Kahaly et al found that cyclosporine reduced the clinical activity of the disease faster if given after a course of high dose steroids. It also reduced the muscle thickness faster as evident on CT scan. Immunosuppressive agents stabilize the condition faster thereby reducing the interval before corrective surgery.
The adverse effects noted with cyclosporine therapy are hypertension, liver enzyme elevation, renal insufficiency, gum hypertrophy, hypertrichosis and paresthesias. With azathioprine bone marrow depression is the main concern. Other side-effects are rashes, nausea/vomiting, reversible jaundice and hyperuricemia.

Taking the medications after meals reduces the nausea and vomiting associated with it. Use of azathioprine is not recommended during pregnancy. It may cause birth defects if either the male or the female is using it at the time of conception. Azathioprine passes into breast milk also so it is not recommended in nursing mothers. As the patient is immunosuppressed, use of or contact with people who had live vaccines should be avoided while on immunosuppressant therapy. Total leucocyte count and platelet counts should be done every 2 weeks in patients on azathioprine therapy. Azathioprine should be stopped if the total leucocyte count falls below 4,000/cmm and platelet count falls below 1,00,000/cmm. Patients on azathioprine should be instructed to report immediately if they notice petechiae or bruising which suggests bone marrow depression.

In patients on cyclosporine therapy, nephrotoxicity is the main concern. Serum creatinine should be routinely checked in such patients as baseline and subsequently. Feutren et al have suggested a maximal daily dose of 5 mg/day. The dose should be modified to prevent the serum creatinine from increasing above 30% of the baseline value.

**Antithyroid therapy**

It is well known that control of hyperthyroidism can reduce the sign and symptoms of thyroid eye disease. However the modality of choice to achieve this still remains elusive. The thyroid function can be improved by antithyroid drugs or by radio-iodine therapy or total thyroidectomy. Carbimazole/methimazole (30-60mg/day for 12-18 months) and Propylthiouracil (300-450 mg/day in 3 divided doses) in cases of hyperthyroidism and thyrin replacement therapy in a dose sufficient enough to suppress TSH, in hypothyroidism can be used. The therapy can be given either by the Block-Replace regimen (where a higher dose of antithyroid drug is used with a replacement dose of thyroid hormone) or by the Titration regimen (where the antithyroid drug dose is reduced by titrating treatment against thyroid hormone concentrations). The Titration regimen is as effective as the Block-Replace regimen and has significantly lower incidence of adverse effects. The optimal duration of anti-thyroid drug therapy for the Titration regimen is 12-18 months. Agranulocytosis is the main complication so total and differential leucocyte count should be done regularly. Patients having agranulocytosis often present with sore throat and the patient must be warned about this.

The role of radioiodine therapy or total thyroidectomy is controversial. The ophthalmopathy may worsen after radioiodine administration or thyroidectomy because of release of thyroid antigens and activation of the autoimmune response. However total thyroidectomy and radioiodine therapy result in less potential for Major Review relapse of hyperthyroidism as compared to oral antithyroid drugs and require less visit to the clinics. Surgical treatment and radioiodine therapy can be considered in cases where the eye disease has not yet manifested or is in early stages. Oral steroids need to be added after the therapy.

**Radiotherapy**

Radiotherapy as a treatment modality was tried when poorly focused rays directed to pituitary gland resulted in reduction of the thyroid eye disease. Donaldson et al first described the use of orbital radiotherapy for thyroid eye disease. They found that nearly 65% of their patients showed good response to the treatment. Later on several studies were conducted to assess its impact but a well-controlled study free from any confounding factor is lacking.

Radiotherapy is postulated to arrest the fibroblast activation and lymphocyte proliferation thereby reducing glycosaminoglycan deposition and inflammation. It has been used in severe congestive phase, in compressive optic neuropathy prior to decompression, as a temporizing measure while awaiting definitive therapy or in patients in whom steroids are either contraindicated or who develop serious side effects of steroid therapy. Radiation therapy has also been used after surgical decompression if optic nerve function shows only mild improvement.

Radiotherapy is given in 8-10 daily fractions of 2 Gy each over a period of 2 weeks. It is preferable to use a
megavoltage linear accelerator for the delivery of well collimated, high energy beams. This delivers the dose exactly to the retro-orbital structures minimizing damage to the lens and the retina.\textsuperscript{24}

The role of radiotherapy is still controversial. Maalouf et al found that following radiotherapy improvement of the amplitude of gaze and reduction of the thickness of extraocular muscles were not statistically significant even after a gap of 3 months.\textsuperscript{25} However Mourits et al found that ocular dysmotility was the only factor which showed some response to radiotherapy.\textsuperscript{26} Conditions where fibrosis has already set in are not responsive to radiotherapy.\textsuperscript{27} Orbital inflammatory signs and symptoms are eliminated within weeks of the therapy when radiation is combined with oral corticosteroids. Optic nerve compression is alleviated within 1 month.\textsuperscript{27} However there is minimal improvement in proptosis. The best response is seen if the treatment is started within 7-8 months of the onset of the disease when the patient is in congestive phase. Claridge et al noted that combined radiotherapy and immunosuppression using azathioprine and low dose steroids was able to control the disease most effectively.\textsuperscript{28} Mourits felt that use of radiotherapy atleast enables the rehabilitative surgery like decompression and strabismus correction to be done at an earlier stage by controlling the disease activity.\textsuperscript{29}

Radiotherapy usually results in an increase in irritation and inflammation due to the release of antigens after 2 weeks of the therapy hence concomitant oral steroids are needed that are tapered over 2-3 months. Radiotherapy is relatively contraindicated where vascular insufficiency in any form is present e.g. diabetes mellitus, vascular diseases and in children because of the risk of retinopathy.

Adverse effects noted with radiotherapy are usually limited to local irritation. The risk of cataract and retinopathy has reduced with better collimated beams avoiding unwanted radiation to the anterior orbit.

**Other modalities**

Various other modalities have been tried out but none of them have shown good response consistently hence, they are not universally accepted. They are:-

1. Somatostatin analogue like octreotide are postulated to reduce the lymphocyte proliferation and activation. However Wemeau et al didn't find any significant benefit after 16 weeks of therapy.\textsuperscript{30}

2. Studies on the use of plasmapheresis have found mixed results. However all the studies are confounded by the fact that immunosuppressants have been used after the therapy. It is not being advocated for the treatment of thyroid eye disease as yet.\textsuperscript{31, 32, 33}

3. Guanethidine eye drops in various concentrations to reduce lid retraction, lid lag and palpebral fissure width. However, due to a high frequency of local irritation and unpredictable effectiveness, this form of therapy is rarely encouraged today.\textsuperscript{4}

**Newer Modalities**

1. Botulinum toxin in the dose of 5-10 IU as a single subconjunctival injection is now being used for eyelid retraction in patients on active inflammatory stage as a temporizing measure. Self-resolving ptosis and vertical diplopia are the adverse effects. The effect stays for 1-3 months.

2. Pentoxyphilline and nicotinamide are thought to reduce the cytokine synthesis. However their role in the treatment of thyroid eye disease is not well defined as yet and studies are on to better define their role in the treatment of thyroid eye disease.\textsuperscript{4}

**Special conditions**

**Pregnancy:** Thyroid eye disease increases in severity in pregnancy. Most of the patients just require observation. However if compressive optic neuropathy develops then it is better to control with steroids. Steroids are safe in pregnancy. However they should be used when benefits outweigh risks. Surgical decompression and radiotherapy are best reserved till the delivery of the baby. Immunosuppressants are contraindicated in pregnancy. In severe, sight threatening conditions not responding to oral steroids, orbital decompression can be done as a last measure after explaining risks associated with general anesthesia.

**Diabetes:** Radiotherapy is contraindicated in diabetics. For severe congestive phase, steroids can be used as an extreme measure, with suitable modification in antidiabetic treatment and regular monitoring of blood sugar. Steroid sparing immunosuppressants can also be used with low dose steroids.
Follow-up

Most patients with thyroid eye disease can be observed over time; the follow-up interval and frequency will depend on the disease activity: every 2 months for severe disease and at 6 months interval for milder condition.

Disease activity is probably the prime determinant of response. Monitoring is particularly required for vision loss as a result of exposure keratopathy and optic neuropathy as well as for development of strabismus. At follow up, investigations should be tailored to screen these parameters. Visual field and color vision testing may help in early detection of visual loss. Ultrasonography is useful in cases with muscle enlargement; however CT scan is better able to pick up the ‘nerve-at-risk’ due to apical crowding. Thyroid function tests particularly free T4 and TSH are important for the assessment of thyroid status and activity. Anti-Thyroid stimulating hormone receptor antibodies are considered to be the most sensitive indicator of euthyroid Graves ophthalmopathy. Their levels in serum closely mimic the disease activity.

Recommendations

Active phase:

I. Ocular discomfort, transient oedema and mild proptosis
1. Tear supplements
2. Non-Steroidal Anti-Inflammatory Drugs
3. Supportive treatment

II. Eyelid retraction, conjunctival oedema, ocular ache and moderate proptosis
1. Oral steroids for 4-8 weeks (or oral NSAIDS for 4-6 weeks).
2. Supportive treatment

III. Ocular motility disturbance with diplopia, chemosis and marked proptosis.
1. Oral prednisolone (starting with 1-1.5 mg/kg for 4 weeks and then tapering down over a further 8 weeks).
2. Steroid-sparing agents such as Azathioprine 50-150 mg/day or Cyclosporin A, 5-7 mg/kg for 4-12 months in cases with persistent diplopia.
3. Orbital radiotherapy is a controversial option.

IV. Optic nerve dysfunction with reduction of color vision and visual acuity loss.
1. Intravenous methyl prednisolone (0.5-1 gram/day for 3-5 days) followed by 1mg/kg oral steroid and/or a steroid-sparing agent.
2. In cases of poor response 10 sessions of 2 Gy orbital radiotherapy should be considered.
3. In cases of persistent nerve compression, surgical orbital decompression with immunosuppression cover may be necessary.

Stable phase (stable condition for 5-6 months):
1. Review of patient’s thyroid status.
2. Prismatic correction for diplopia.
3. Avoid smoking.
4. Lubricants if required

Burnt out phase (decreased signs and symptoms or stable for more than 5-6 months):
1. Selective or cosmetic orbital decompression (24mm proptosis or more)
2. Extra-ocular muscle surgery
3. Finally, eyelid surgery (levator recession, blepharoplasty).

Surgical Management

The majority of patients with thyroid eye disease do not need any form of surgical treatment, either for functional, or cosmetic reasons.

Broadly, the indications for surgical management are
- compressive optic neuropathy, severe orbital congestion or cosmetically unacceptable proptosis (orbital decompression surgery)
- intractable diplopia in functional positions of gaze (strabismus surgery)
- severe ocular discomfort or cosmetically unacceptable appearance resulting from eyelid retraction (eyelid surgery)
- sight threatening corneal exposure (tarsorrhaphy)

Surgery on patients with thyroid eye disease is challenging for many reasons. The presence of a serious multi system disease has important implications in terms of anesthesia risk and potential life threatening conditions like thyroid crisis / storm. In general, surgical
operations are performed on an elective basis in a patient who has been euthyroid for several months, with stable eye findings. In patients with serious optic nerve compression or exposure related to severe proptosis, however, this may not be possible and the decision regarding surgery often needs to consider the serious risks and the potential to preserve or improve vision. In a small subset of patients, there may be need for more than one of the above mentioned types of operations. In such cases, the orbital surgery is performed first placing the eyeball in a more normal position within the bony orbit, followed by aligning the eyes better, and lastly correcting the eyelid position. Each of the operations for thyroid eye disease – orbital, eyelid and strabismus is plagued by relative unpredictability of outcome. Hence, the techniques have evolved over time, and constant modifications and innovations characterize these operations, the aim of greater predictability being a driving force. Also, while these operations are based on fairly simple, mechanical principles of creating greater space for orbital soft tissues (orbital decompression), weakening eyelid retractors (eyelid retraction surgery) or weakening – strengthening of relevant extraocular muscles (strabismus surgery), the outcomes vary to a great extent and patient's education regarding this aspect is of immense importance. A brief review of each of these categories of surgical operations is presented.

**Orbital Decompression Surgery**

**History**

Dollinger is credited with the earliest reported orbital decompression, in 1911, removing the lateral wall. In 1931, the famous neurosurgeon Naffziger advocated orbital roof decompression. Sewall’s approach, half a decade later was via an external ethmoidectomy. Hirsh, 1950 developed an inferior orbitotomy approach. In 1957, Walsh and Ogura used a transantral Caldwell – Luc approach, a procedure of choice for the next nearly four decades. In 1981, Mc Cord described the ‘swinging eyelid’ or canthoforniceal approach which has thence been promoted by Jack Rootman and other orbital surgeons. Since 1990, when Kennedy described the use of transnasal endoscopic approach, this technique has gained increasing popularity.

**Indications**

Severe orbitopathy with optic nerve compression and risk of progressive visual loss has been the most important indication for orbital decompression surgery. As the techniques of surgery and safety of anesthesia have improved over time, with fewer complications, the indications for surgery presently include exposure related problems, orbital pain or related symptoms, unacceptable side effects of medical therapy and disfiguring proptosis. An increasing cosmetic awareness, and the demands of present day life have resulted in the cosmetic consideration being the sole indication for an increasing number of orbital decompression operations.

**Approaches**

Numerous ones have been described and practised. In the recent years, the trend has been in the direction of minimal scar visibility and the transconjunctival, transcaruncular approach is a widely preferred one. In addition, the nasal endoscopic approach also has gained popularity. Centres with specific interest and expertise persist with less used approaches like the transcoronal approach. Incisions resulting in skin scarring are only occasionally used and the ‘swinging eyelid’ approach possibly is the single most used.

**Walls**

Techniques have been described for one-two-three and four wall bony orbital decompression. While orbital roof decompression and 4 wall decompression are very rarely used, if at all, at the other extreme, a single wall decompression is also rarely used. Effectively, most patients receive a two or three wall orbital decompression. While controversies exist and opinions vary, the greater the extent of bone removed the greater is the degree of reduction in proptosis achieved. The floor and medial wall are most commonly decompressed, while the role of lateral wall removal is being increasingly described for achieving maximal reduction in proptosis. The concept of a ‘balanced decompression’ involves the removal of lateral and medial walls, sparing the floor with the aim of limiting inferomedial globe displacement and consequent motility disturbance and diplopia. The preservation of the inferomedial strut at the junction of maxillary and ethmoid sinuses is another surgical innovation with this end in mind.
increasingly described modification involves deep sculpting of the lateral orbital wall in the area of the lacrimal gland fossa.

**Soft tissue decompression**

Fat removal orbital decompression (FROD) aims to reduce the increased intra orbital fat content, thereby achieving a degree of reduction of proptosis. Fat removal is achieved through appropriate approaches to extra and intraconal fat. The operation is associated with lower motility disturbances than bone removal orbital decompression (BROD). Broadly speaking, while FROD is often combined with BROD, its role, in isolation for achieving significant orbital decompression is rather limited, if at all.

**Timing of surgery**

In view of the serious risks associated with anesthesia and surgery in a patient with uncontrolled thyroid status, appropriate therapy, Endocrinologist opinion and clearance is essential prior to surgery. In progressive compressive optic neuropathy, the operation being a relatively early intervention in the interest of preservation of vision, stability of signs is not important. In surgery for other indications, e.g. Cosmetic, having stable findings and eye signs for a few months, six months or so, is vital to surgical decision making and success.

**Complications**

A large number of complications have been described including strabismus, infraorbital anesthesia, CSF rhinorrhea, nasolacrimal duct obstruction, oro-antral fistula, blindness and hypoglobus. Other complications, depending on the approach used include complications associated with craniotomy, nasal endoscopic surgery, and general surgical complications eg. skin scarring, infection, bleeding.

Of these, the most common and troublesome is possibly persistent diplopia, strabismus and motility disorder. The management of this condition is a challenging one both for the strabismologist and the treating orbital surgeon.

**Our technique**

At Sankara Nethralaya, we have used a combined approach two wall, bony orbital decompression involving a canthoforniceal swinging eyelid approach for the removal of the floor or lateral wall, and a nasal endoscopic approach by an Otorhinolaryngologist for the medial wall.

In our initial series of cases, 12 orbits in 7 patients underwent combined approach orbital decompression with a mean reduction in proptosis of 5.72 mm, no major surgical complications, and excellent cosmesis. In 10 orbits of 6 patients with compressive optic neuropathy, vision improved in 8 eyes and was maintained in 2 eyes and a mean proptosis reduction of 6.88 mm was achieved. Disc edema resolved and visual field defects improved in all cases.

**Eyelid surgery**

Eyelid retraction, the commonest cause of which is thyroid eye disease, involves the displacement of the eyelids towards the respective superior or inferior orbital rim, exposing sclera between the corneal limbus and the eyelid margin.

Apart from the obvious cosmetic blemish and startled, staring appearance it confers on the affected patient, lagophthalmos resulting in symptoms of corneal and ocular surface irritation and leading to sight threatening exposure keratitis can result from eyelid retraction. A lateral ‘flare’ is commonly seen in eyelid retraction resulting from thyroid eye disease.

Milder degrees of eyelid retraction are managed conservatively with lubricants and avoidance of exposure to dust, smoke, bright sunlight etc. Surgical correction is performed for significant degrees of eyelid retraction. Except for the rare patient who needs the operative correction on an urgent basis for corneal exposure related problems, the surgical correction is

![Fig. 1. A. Preoperative photograph of a patient showing proptosis, eyelid retraction and conjunctival congestion in both eyes. B. Preoperative coronal CT scan of the patient showing bilateral enlargement of the extraocular muscles producing apical crowding.](image-url)
an elective procedure performed in a patient with stable findings preferably for six months or more. 43

**Upper eyelid retraction**

Broadly the operations for correction of upper eyelid retraction are

i) Excision or recession of Mullers’ muscle

ii) Recession of levator aponeurosis

iii) Myotomy of levator muscle

iv) Insertion of a spacer material between the distal end of levator aponeurosis and the tarsal place. 43

**Lower eyelid retraction**

Treatment involves tightening of the eyelid lateral canthal unit combined with grafting of a spacer material between the lower eyelid retractors and inferior tarsal border. Autogenous materials used include hard palate mucosa, auricular cartilage and fascia lata. While preserved sclera and banked fascia lata have also been used, the inflammatory reaction is greater. Spacer material made of porous polyethylene (Medpor) has been used but the superficial location of its implantation in a mobile organ makes functional and cosmetic success a challenge.

**Non surgical management**

In addition to lubricants medications, a variety of moisture retaining techniques are used including swim goggles, moisture chambers, punctal plugs and temporary tarsorrhaphy. In addition, while guanethidine was reported as being useful as a topical drug effective in treatment of milder forms of eyelid retraction, its lack of availability and side effects have limited its use. Botulinum toxin is also useful in chemical reversal of upper lid retraction.

**Upper Eyelid Retraction – Surgical Correction**

- **Levator recession:** Usually performed through a conjunctival approach and combined with a Mullerectomy. A skin approach via lid crease incision is used as an alternative. Precautions taken during surgery include avoiding use of epinephrine in any form, avoidance of patient sedation and use of a traction suture to keep the lid on a stretch in the early postoperative period.

- **Marginal myotomy:** This involves the making of incisions in the levator aponeurosis much in the fashion of such operations used in strabismus surgery as a weakening procedure.

**Spacers**

These are used for greater degrees of eyelid retraction and for revision operations and are needed for retraction of more than 3 mm. Spacers can be introduced through an anterior or posterior approach after performing a levator recession.

Fig. 2. A. Postoperative photograph of the patient in figure 1 showing reduction in the proptosis and resolution of lid retraction and conjunctival congestion. B. Postoperative coronal CT scan of the patient showing the reduction in the apical crowding and increased volume of the orbit following two wall decompression surgery.

Fig. 3. Photograph of a 55 year old patient showing reduction in soft tissue changes and proptosis following three wall orbital decompression surgery. (A- preoperative, B- 1 week postoperative stage)
All the operations described above have complications of a similar nature – under correction, overcorrection, lid contour abnormalities, scaring persistent edema, corneal complications resulting from exposure or suture knot contact.

Since postoperative under correction is almost a rule, the target eyelid position at the end of surgery is an overcorrection by 2 mm or so.

**Strabismus in thyroid eye disease**

Grave’s Disease is an autoimmune disease in which there is inflammation of extraocular muscles.

**Pathogenesis**

Genetically abnormal suppressor T-cells fail to abort proliferation of abnormal plasma cells, leading to production of auto-antibodies. These cause target somatic cells like the extraocular muscles to be coated with auto-immune complexes that cause stimulation of fibroblasts. These in turn release muco-polysaccharides and collagen which causes hypertrophy of muscles with degeneration of muscles fibres. The site of involvement is the muscle belly. The tendon is spared.

**Phases of the disease**

1. Acute phase – in this initial phase there is lymphocytic infiltration of the muscles, leading to their enlargement, especially posteriorly. This leads to increased muscle tension and decreased elasticity, which in turn causes muscle dysfunction.

2. Chronic/ Cicatricial phase - there is quiescence of inflammation with replacement of muscle fibres by fibrous tissue, leading to secondary contracture, inability to relax and restrictive strabismus.

**Frequency of involvement of muscles**

In decreasing order of frequency – Inferior rectus, Medial rectus, Superior rectus, Lateral rectus.

It is postulated that the reason for the most frequent involvement of inferior rectus may be due to the proximity between the inferior rectus and oblique muscles with each other and with the ligament of Lockwood. Inflammation causes anomalous connections between them, causing restriction.

The oblique muscles are rarely involved. There are reports in literature of superior oblique involvement in thyroid ophthalmopathy.
**Clinical features:**

**Symptoms**

i) Diplopia: Insidious onset

ii) Asthenopia

iii) Staring look

iv) Pain on ocular movements: in initial phase

**Signs**

i) Periorbital oedema

ii) Lid retraction especially on upgaze: due to spill over of the increased innervation required by superior rectus to counteract tight inferior rectus.

**Restrictive strabismus**

It is usually bilateral, but may be unilateral or asymmetric. Most common form is vertical strabismus with hypotropia of involved eye, with small degree of excyclotorsion and esotropia due to involvement of inferior rectus. It is incomitant with greatest deviation in upgaze. It may occur in absence of other thyroid eye signs. Esotropia may be due to inferior rectus involvement itself, or if large may be due to involvement of the medial rectus. This can be assessed intraoperatively by a forced duction test for abduction after recession of the inferior rectus.

**Ocular motility findings**

In decreasing order of frequency, there is limited elevation, limited abduction, limited depression and limited adduction. Restriction is described as “leash-like” as the eye rotates fairly well up to a point where marked restriction is encountered. Saccades are less conjugate than normals. Paresis of lateral rectus may coexist due to pressure on nerve supply to muscle from enlargement of muscle cone. Limited motility may come even before the onset of proptosis.

**Special tests**

Increased intraocular pressure on upgaze is not reliable as it can occur in normals also. Forced duction test is positive for inferior rectus. Force generation test and tensilon tests are performed if the restrictive component does not fully explain the ocular motility deficit. CT Scan of the orbits is an essential investigation in the assessment of thyroid eye disease.

**Treatment**

In the acute phase, treatment includes the following:

1. Systemic steroids

2. Immunosuppressive therapy: Cyclophosphamide, Azathioprine, Cyclosporine

3. Radiotherapy: it is not much effective in improving restrictive strabismus.

4. Prisms: These can be used as a temporary measure. If the deviation is less than 12-14 prism diopters (PD) prisms can be ground into the glasses, vertical and horizontal into each lens. If the deviation is larger Fresnel prisms can be used. Problems in prescribing prisms are the incomitance of the deviation in different positions of gaze, variability of deviation with time, decreased visual acuity with prisms of larger power.

5. Occlusion (Segmental/ Complete): Frosted glasses can be prescribed if prisms are not tolerated.

6. Botulinum toxin: It has been found to be effective in acute stage and may allow patient to regain fusion. In chronic stage it is not effective.

**Surgical principles**

In the chronic phase, surgery is contemplated only when the acute phase has subsided and the deviation has been stable for at least 6 months. Earlier surgery
can lead to exacerbation of inflammation, post-operative complications and improper alignment. Orbital decompression if required should be performed before strabismus surgery. 2/3rd patients with motility restriction ultimately require surgery. Aim of surgery is to restore single binocular vision in those positions of gaze which are functionally important for the patient, most commonly primary position and downgaze; and some increase in the range of rotation. It is not to restore full range of versions. It is important for the patient and clinician to have realistic expectations to avoid late over-corrections. Recessions are the surgery of choice. Resections will cause further restriction of motility. If hypotropia in primary position is less than 15PD, ipsilateral inferior rectus recession can be performed. About 3PD of correction can be expected from 1mm of recession. If hypotropia in primary gaze is more than 18-20PD, inferior rectus recession of more than 5mm may be required. In severe cases recession of contralateral superior rectus is performed.

An under-correction is aimed at as there is 50% chance of late over-correction after 4-6 weeks.

Adjustable sutures are preferred due to the unpredictability of the results. There are several studies in literature showing it as an effective technique. However late over-corrections have been observed with adjustable sutures due to loss of strength of the suture allowing the tight muscle to retract posteriorly. Some authors did not find any advantage of adjustable over non-adjustable sutures. Randomized control trials will be required to reach a conclusion in this respect. Inferior rectus should be separated nicely from ligament of Lockwood to avoid lid retraction. This may however be difficult due to the tightness of the muscle. If there is excessive tightness recession can be performed on hang-back suture. Recession of conjunctiva and tenon’s capsule should be performed in long-standing cases. Small esotropia and excyclotorsion gets corrected by inferior rectus recession alone. For significantly limited abduction large recession of medial rectus is performed. If alignment is good immediate post-operatively, a satisfactory long term outcome is more likely. 40% cases require re-surgery. Further muscles may get involved. In bilateral cases asymmetrical bilateral inferior rectus recession can be performed. Subconjunctival injection of steroids decrease scarring.

**Post-operative complications**

Over-correction can cause asthenopia in downgaze. Prisms can help. If significant, recession of contralateral superior rectus or advancement of ipsilateral inferior rectus should be performed.

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**Fig. 7.** Baseline visual fields of the patient in figure 3 showing normal fields bilaterally prior to onset of compressive optic neuropathy. (Humphrey visual field analyzer, 30-2 strategy).
rectus is performed. Under-correction is treated with re-recession of ipsilateral inferior rectus if initial recession is small. Otherwise recession of contralateral superior rectus is performed.

Marked post-operative inflammation is treated with steroids. Late slippage of inferior rectus is prevented by using non-absorbable adjustable sutures. Lower lid retraction is due to recession of tarsal attachment of lower lid retractors. It can be avoided by proper separation and suturing of retractors to sclera. A-pattern exotropia may be seen after bilateral inferior rectus recession due to weakening of adduction in downgaze. It can be prevented by displacing each inferior rectus insertion nasally by ½ -1 tendon width.

**Challenges in Management**

The majority of patients with thyroid eye disease have mild, self limited disease needing supportive therapy and simple measures for treatment. It is the smaller population of patients with moderate and severe disease who need aggressive management. Thyroid eye disease is one of the few conditions in ophthalmology where most of the subspecialities of ophthalmology have to work in tandem for optimal management. The oculoplastic and orbital surgeon, neuro-ophthalmologist, glaucomatologist, strabismologist, and corneal surgeon need to be variably involved in the management of this complex, ill understood disorder. This need for a team care approach with close coordination poses one of the challenges in the management of moderate to severe thyroid eye disease.

Since the underlying cause of thyroid eye disease is only slowly being unraveled, with a still unclear understanding of the exact pathophysiology of the disease, the management remains essentially symptomatic. Being so, patients need close follow up, particularly during the active phase of the disease. The steps of management are hence, in a manner of speaking, reactive rather than proactive. The lag between disease damage onset, and appropriate steps in management determines tissue injury and complications of thyroid eye disease. The avoidance of this lag, and consequent complications, poses yet another challenge in the management of thyroid eye disease.

A third, and a serious challenge posed by the disease concerns the treatment modalities available. Moderate and severe thyroid eye disease is treated with oral or intravenous steroids, antimitotic chemotherapy, 

![Fig. 8. Preoperative visual fields of the patient in figure 3 showing inferior visual field defects bilaterally suggestive of compressive optic neuropathy. (Humphrey visual field analyzer, 30-2 strategy).](image-url)
radiation therapy or orbital decompression surgery or a combination of these forms of treatment. Each of these poses hazards to the patient in the form of serious systemic side effects or local (orbital) problems or a combination. Judicious selection of the modality of treatment importantly involves the weighing in of this factor of potential risks.

Yet another challenge is the unpredictability of treatment outcome. In addition to disease severity, the individual response to treatment also varies greatly and hence, the need to customize and individualize treatment.

The fifth challenge in the management of thyroid eye disease of moderate to severe nature is the inevitability of sequelae. These range from functional problems like diplopia to a cosmetic appearance of ‘stare’ and ‘bulgy eyes’. Hence patients with sequelae need prolonged follow up, long after the active phase of thyroid eye disease is over.

Lastly, and importantly, patients with the more severe forms of thyroid eye disease are seriously affected psychologically. The striking changes in their facial features, double vision and the real risk of loss of vision and blindness, is seriously disturbing to the patient and close family. Added to this are the difficulties in continuing with gainful employment, and in fruitful social interactions. The side effects of treatment, frequent need for hospital visits and financial loss compounds the psychological problems. Serious depression is a real risk. The treating ophthalmologist needs to provide a caring and supportive role for these disturbed patients. 51

References


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