# Thyroid Eye Disease-an Update

**Dr. Sima Das** MS, **Dr. Alankrita Muralidhar** MBBS

*Dr Shroff's Charity Eye Hospital, New Delhi, India*

Thyroid eye disease (TED), also called Graves' orbitopathy (GO) is a potentially sight-threatening ocular disease, mostly occurring in patients with hyperthyroidism or a history of hyperthyroidism due to Graves' disease (GD). However, it can occur in patients with euthyroid or hypothyroid chronic autoimmune thyroiditis as well and about 5-10% of patients with TED are euthyroid at presentation[1]. Thyroid eye disease is the most common cause of both bilateral and unilateral proptosis in an adult and is the most common orbital pathology in adults.

## DEMOGRAPHICS

Prevalence of thyroid eye disease ranges from 20 to 42 % among patients of Graves' disease. However, the reported prevalence in various series shows a wide variability because of the selection bias, lack of standardized ocular assessment criteria, non-uniform definition of Graves' orbitopathy etc. A prevalence of 34.7% has been reported in the in the Asian population and 28% prevalence has been reported in Indian studies among the Graves' disease patients[2,3]. Females are more commonly affected than males. However, for severe disease, this ratio reverses and severe thyroid eye disease is approximately 4 times more common in males than females[4].

## Etiology and pathogenesis

Thyroid eye disease is strongly associated with autoimmune thyroid diseases such as Graves' disease (90%) or Hashimoto's thyroiditis. Majority of patients with thyroid eye disease develops eye symptoms within 18 months of onset of the autoimmune thyroid disease. However, in 13% patients the ocular symptoms might present 2 years after the diagnosis and in 3% the diagnosis can precede the onset of GD by more than 12 months[5]. A fraction of these patients may also present with skin involvement in the form of pretibial myxedema and thyroid acropachy suggesting a single underlying systemic process.

Our understanding of the pathogenesis of TED is still incomplete. Pathological changes of the thyroid orbitopathy appear to involve both the extraocular muscles and the orbital fat, with most patients having a combination of extraocular muscle enlargement and orbital fat expansion[6]. Histopathological studies have found extensive deposition of hyaluronan in between the extraocular muscles, mixed inflammatory infiltrate and abundance of cytokines causing interstitial edema and soft tissue expansion and proptosis[7]. Recent studies also support the role of Insulin like growth factor 1(IGF-1) receptor in the pathogenesis of TED[8].

There exists substantial evidence to suggest that the principle cell involved in the pathogenesis of TED is the orbital fibroblast[9]. Activation of orbital fibroblasts leads to proliferation, hyaluronan secretion and soft tissue expansion. The proposed mechanism of fibroblast activation is centred around the fact that the orbit contains two subpopulations of fibroblasts, Thy1/CD90 surface marker positive and Thy1/CD90 negative fibroblasts, which have different structures and functions[10,11]. The process of activation of the orbital fibroblast and consequent mechanism of muscle or fat expansion is summarised in (Figure 1). The relative proportion of the activated Thy1 positive or negative fibroblasts determine whether fibrosis or adipogenesis predominates.

Orbital fibroblasts can be activated in TED in both an antigen dependent and antigen independent manner. The two significant autoantigens involved are the thyrotropin (TSHR) and IGF-1 and orbital fibroblasts have robust expression of receptor to these autoantigens. Autoantibodies against TSHR can be detected in up to 98% of patients with TED and has an

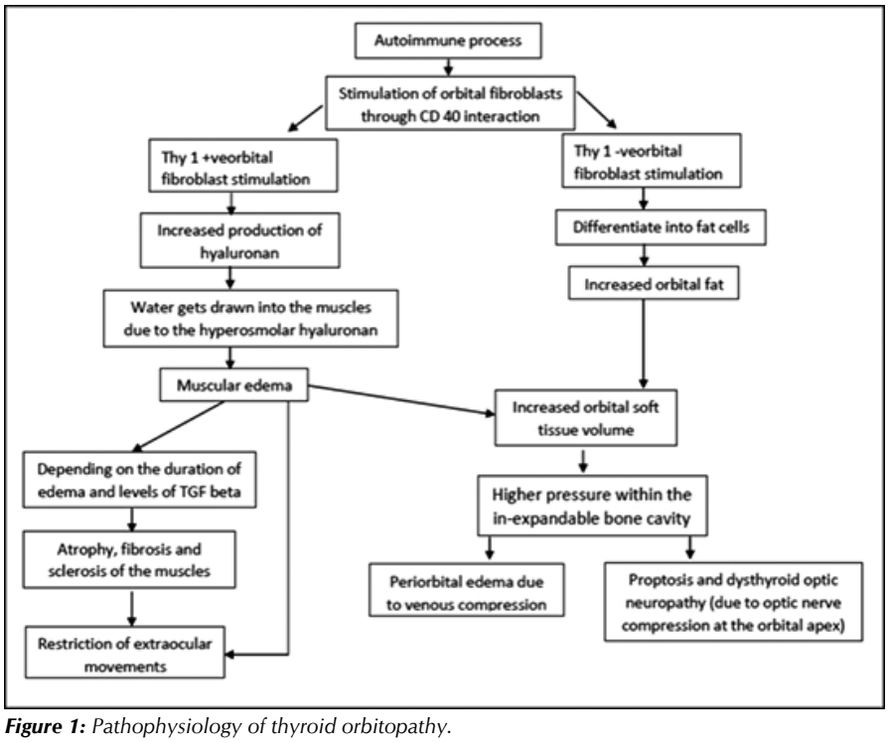


***Figure 1:*** *Pathophysiology of thyroid orbitopathy.*

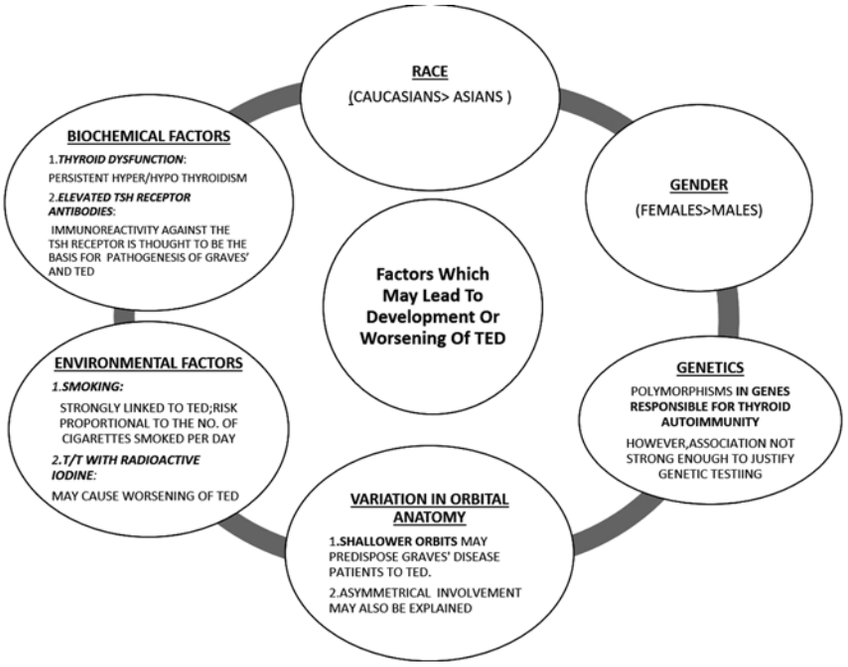


***Figure 2:*** *Risk factors for onset and progression of thyroid eye disease.*

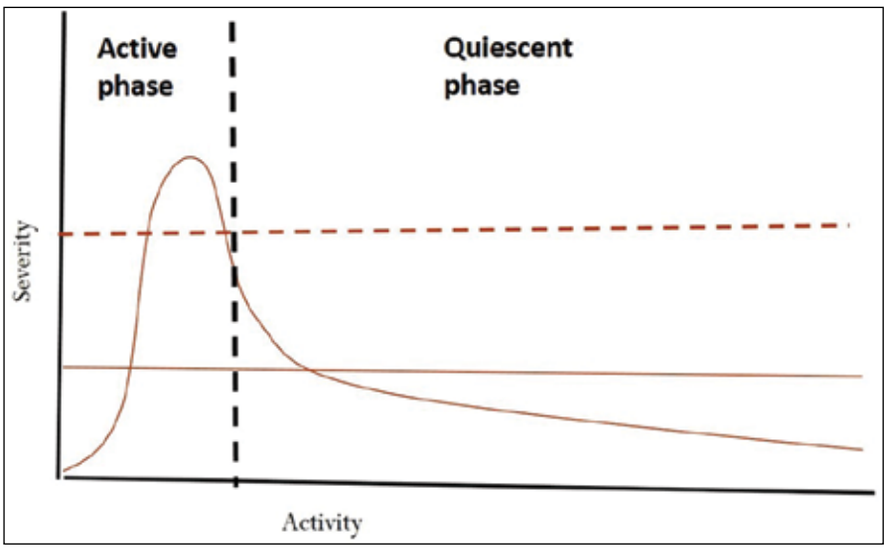


***Figure 3:*** *Rundle's curve showing the natural course of progression and severity of thyroid eye disease.*

established role in the pathogenesis of TED[12]. Also TSHR expression is higher in patients with active disease as compared to inactive disease and the level of this autoantibody can correlate with disease activity and severity[13].

IGF-1R is another potential autoantigen in the pathogenesis of TED and is overexpressed in TED orbital fibroblasts as compared to controls[14]. Activated fibroblasts also secrete potential T-cell chemoattractants, IL16 and CCL5, facilitating the recruitment of T lymphocytes into the orbit which activates orbital fibroblasts leading to secretion of prostaglandins and proinflammatory cytokines[15]. These T – cell mediated events eventually results in soft tissue remodelling and inflammatory events in TED. Long lasting edema leads to atrophy, fibrosis and sclerosis of the extraocular muscles subsequently leading to restrictive strabismus.

## Risk factors for development and progression of TED

These risk factors for development of TED have been summarised in (Figure 2)[16].

***Clinical course of thyroid eye disease:*** the Rundle's curve

A unique feature of TED as compared to other autoimmune disease is that it is a self-limiting disease. TED follows a biphasic course. There is a progressive or active phase lasting 6–18 months followed by a stable or inactive phase. This pattern was first described by Rundle, who plotted a graph of orbital disease severity against time (Rundle's curve) and can be plotted graphically for all patients[17]. The steepness of the graph in the active phase reflects the acuity of progression, with a steeper slope often leading to more severe disease (Figure 3).

## Clinical features of thyroid eye disease

***Appearance and exposure***

- Upper eyelid retraction:

Upper lid retraction is present when the lid margin lies at the superior limbus or higher, exposing the sclera. The retraction is more marked laterally causing the characteristic lateral flare and may fluctuate with emotion or fixation (Dalrymple's sign) giving the patient an angry look (Figure 4a). It is associated with lid lag on downgaze (Von Graefe's sign), apparent spasmodic lid overaction on upgaze (Kocher's sign) and incomplete lid closure while asleep (Figure 4b).

Proposed mechanisms of eyelid retraction include increased circulating catecholamines, overaction of the levator palpebrae superioris and superior rectus muscles to compensate for inferior rectus restriction, or inflammation and scarring of the levator complex.

**Lower eyelid retraction**

Lower lid retraction is present when sclera is visible inferiorly and occurs more frequently in patients of Asian origin[18].

**Proptosis**

This is the second most common finding in GO following eyelid retraction (Figure 4c). Expansion of the orbital fat and/or muscles limited anteriorly by the relatively tight eyelid tarsoligamentous diaphragm causes the proptosis.

**Corneal exposure**

Corneal exposure can occur secondary to lid retraction and proptosis and can manifest as irritation, photophobia, watering and blurred vision, corneal punctate epithelial erosions, and frank abrasions or in severe cases, ulcerations and corneal perforation.

Periorbital soft tissue inflammation and congestion:

Symptoms and signs of periorbital soft tissue inflammation include orbital ache at rest or with movement, conjunctival and caruncular injection and oedema, eyelid redness and oedema, and diurnal variation (worse with the head dependent after sleep). These are considered a clinical indicator of disease activity (Figure 4d).

***Ocular motility disruption and strabismus***

Although the levator muscle is commonly involved in GO resulting in upper lid retraction in over 80% of patients, the extraocular muscles become clinically involved in only 25%, often in older population. Inferior rectus is the most common muscle involved. During the active inflammatory phase, progressive restriction of motility develops, initially intermittently or with gaze. In the post-inflammatory phase, muscle atrophy, fibrosis or sclerosis may result in disabling diplopia in the primary gaze, which may be constant.

***Dysthyroid optic neuropathy (DON)***

Potentially reversible optic nerve dysfunction seen in 4-8% of all cases of GO caused by direct compression of the nerve by swollen muscles at the orbital apex, presumably impairing axoplasmic flow[19]. Symptoms include colour desaturation and blurring of central vision. An afferent pupillary defect is a specific sign of DON but is not detected in 35% of patients, often because of symmetric loss of vision[20]. Likewise, disc oedema is a specific sign when present, but is absent in over 50% of patients with DON. Visual evoked potential is the most significant clinical test for detection of DON and has been found abnormal in 18% of patients with DON who had good visual acuity. Patients who develop DON are more likely to be male, older, and diabetic compared with their non-DON counterparts. DON may occur in the absence of significant proptosis, usually in Asian population due to a shallower orbital cavity.

Assessment of the clinical features and grading of the disease:

Several classification systems have been used to assess the severity and activity of the clinical manifestations of TED.

1. NOSPECS Classification:

In 1969, Werner reported the NOSPECS Classification (No physical signs or symptoms, Only signs, Soft tissue involvement, Proptosis, Extraocular muscle signs, Corneal involvement, and Sight loss) which he modified and published again in 1977[21,22] (Table 1). It only graded the severity of disease and did not distinguish active and inactive disease. Hence, the indication for treatments used to be based exclusively on the severity of symptoms instead of the activity.

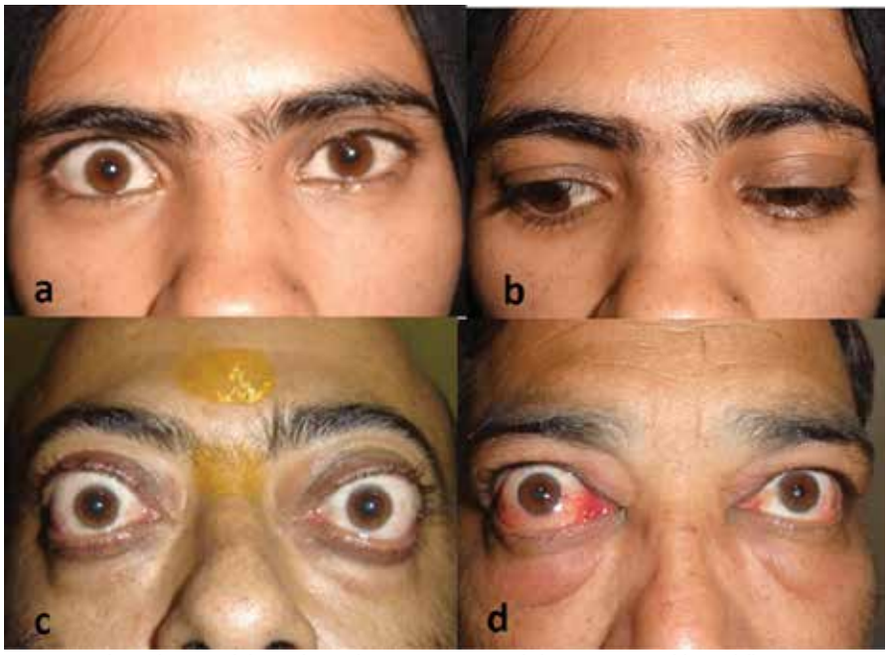


***Figure 4:*** *Clinical signs of thyroid eye disease. Upper eyelid retraction and lateral flare (Figure 4a) and lid lad on downgaze (Figure 4b) are the pathognomic findings in TED. Other findings include proptosis (Figure 4c) and signs of inflammation (Figure 4d) in patients with active disease.*

**Table 1: Modified NOSPECS classification of Thyroid Eye disease**

| **NO SPECS modified classification** | |
|---|---|
| **Class** | **Suggestions for grading** |
| 0 | No physical signs or symptoms |
| I | Only signs |
| II | Soft tissue involvement<br>0 Absent<br>(a) Minimal<br>(b) Moderate<br>(c) Marked |
| III | Proptosis (3 mm or more of normal upper limits with or without symptoms)<br>0 Absent<br>(a) 3 or 4 mm over upper normal<br>(b) 5 to 7 mm increase<br>(c) 8 mm increase |
| IV | Extraocular muscle involvement (usually with diplopia)<br>0 Absent<br>(a) Limitation of motion at extremes of gaze<br>(b) Evident restriction of motion<br>(c) Fixation of a globe or globes |
| V | Corneal involvement (primarily due to lagophthalmos)<br>0 Absent<br>(a) Stippling of cornea<br>(b) Ulceration<br>(c) Clouding, necrosis, and perforation |
| VI | Sight loss (due to optic nerve involvement)<br>0 Absent<br>(a) Disc pallor or choking, or visual field defect, vision 20/20–20/60<br>(b) The same, but vision 20/70–20/200<br>(c) Blindness, vision less than 20/200 |

2. Clinical Activity Score (CAS)

In 1989, Mourits et al. described the Clinical Activity Score (CAS), which was modified in 1997[23,24]. The scoring system is based on the classical signs of acute inflammation (pain, redness, swelling,

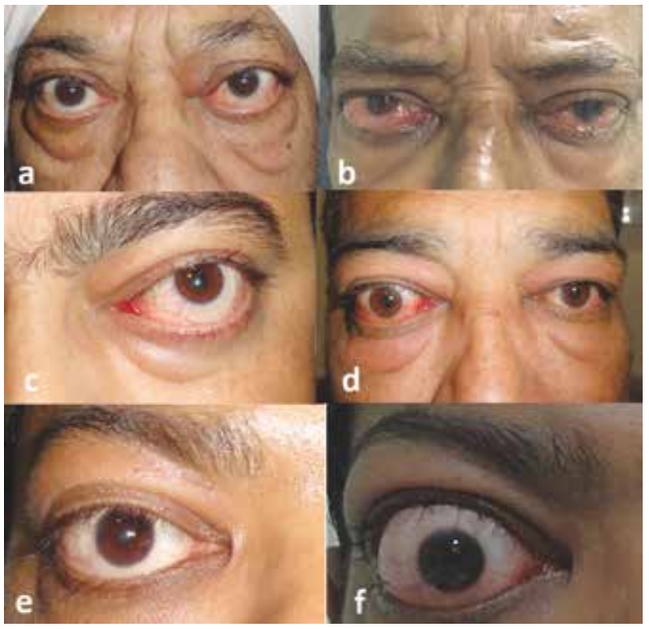


***Figure 5:*** *Signs of clinical activity. Conjunctival congestion (Figure 5a), conjunctival chemosis (Figure 5b), eyelid edema (Figure 5c), eyelid erythema and caruncular inflammation (Figure 5d), increase in proptosis by more than 2mm during the follow up evaluation (Figure 5e,5f).*

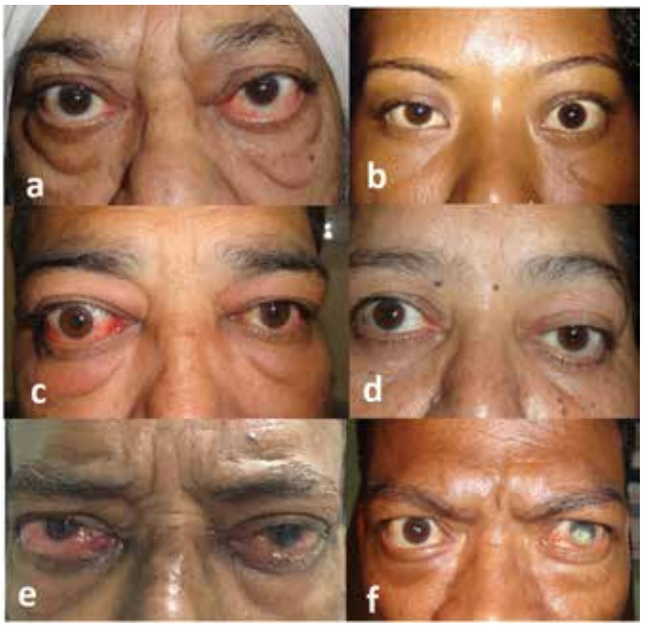


***Figure 6:*** *Grading of the severity of the disease in the active and inactive phase. Mild disease with minimal signs of activity (Figure 6a) and mild eyelid retraction (Figure 6b) and no activity. Moderate to severe disease with signs of activity (Figure 6c) and no signs of activity (Figure 6d). Sight threatening disease with compressive optic neuropathy in active phase (Figure 6e) and corneal exposure due to severe lagophthalmos in inactive phase (Figure 6f).*

and impaired function). This classification system attempts to differentiate active from quiet disease. One point is given for the presence of each of the parameters assessed (Figure 5). The sum of all points defines clinical activity: active ophthalmopathy if the score is above 3/7 at the first examination or above 4/10 in successive examinations (Table 2).

The currently used grading systems used for the assessment of TED are:

- VISA Classification (vision, inflammation, strabismus, and appearance)
- European Group of Graves' Orbitopathy (EUGOGO) Classification

Both the grading systems are based on the NOSPECS and CAS classification system and uses indicators to assess the signs of activity and the degree of severity. Importantly, they allow the clinician to plan and assess the treatment response of patients with GO. The classification systems are not interchangeable and only one classification system should be followed for an individual patient.

**Table 2: Clinical activity scoring system**

| CLINICAL ACTIVITY SCORE (CAS) (EUGOGO) |
|---|
| **For initial CAS, only score items 1–7**<br>1. Spontaneous orbital pain<br>2. Gaze evoked orbital pain<br>3. Eyelid swelling that is considered to be due to active GO<br>4. Eyelid erythema<br>5. Conjunctival redness that is considered to be due to active GO<br>6. Chemosis<br>7. Inflammation of caruncle OR plica<br><br>**Patients assessed after follow-up (1–3 months) can be scored out of 10 by including items 8–10**<br>8. Increase of >2mm in proptosis<br>9. Decrease in uniocular ocular excursion in any one direction of >8◦<br>10. Decrease of acuity equivalent to 1 Snellen line |

## VISA classification

The VISA classification system is based on four severity parameters, vision (V), inflammation (I), strabismus(S) and appearance (A) and is graded independently 25. A global severity score is the sum of score of each parametres graded independently. The score for each parameter is as follows, vision: 1 point, inflammatory score: 10 points, strabismus and diplopia: 6 points and appearance: 3 points (Table 3). The maximum score can be 20. The first visit and follow up assessment forms for patients with GO has been designed based on the VISA classification and has been adopted by International thyroid eye disease society (ITEDS, www.thyroideyedisease.org).

## EUGOGO classification

The EUGOGO classification is also based on the disease activity and severity parameters[26]. For grading activity, the modified clinical activity scoring system is used. The severity parameters are graded based on comparison with an image atlas that has been developed by the group. A classification system to guide the management of patients with GO have also has been developed based on the impact of the disease on the quality of life and the risk of vision loss and helps in deciding on the management strategy[27] (Table 4) (Figure 6).

## Approach to diagnosis

The diagnosis of thyroid eye disease is mainly clinical based on assessment of symptoms and signs. Investigations are directed to assess the systemic thyroid

| Table 3: VISA INFLAMMATORY INDEX (ITEDS) scoring system | | | |
|---|---|---|---|
| | **Symptoms** | **Clinical evaluation** | **Scoring** |
| Vision | Blurred vision<br>Colour desaturation | Visual acuity<br>Colour Vision<br>Afferent pupillary defect<br>Optic nerve evaluation<br>Visual field testing<br>Visually evoked potential | DON absent: 0<br>DON present:1 |
| Inflammation | Caruncular edema<br>Chemosis<br><br><br>Conjunctival redness<br><br>Lid redness<br><br>Lid edema<br><br><br><br><br>Retrobulbar ache at rest<br><br>With Gaze<br><br>Diurnal variation | External evaluation and slit lamp examination | 0: absent 1: present<br>0: absent<br>1: conjunctiva lies behind the grey line of the lid<br>2: conjunctiva extends anterior to the grey line of the lid<br>0: absent 1: present<br><br>0: absent 1: present<br><br>0: absent<br>1: present but without redundant tissues<br>2: present and causing bulging in the palpebral skin, including<br>lower lid festoon.<br><br>0: absent; 1: present<br><br>0: absent; 1: present<br><br>0: absent; 1: present |
| Strabismus and diplopia | Diplopia | Ocular motility<br>Cover test<br>Head posture<br>Diplopia charting<br>Field of binocular single vision | 0:Absent diplopia<br>1:Diplopia on horizontal or vertical gazes<br>2: Intermittent diplopia in straight gaze<br>3: Constant diplopia in straight gaze. |
| Appearance | Appearance concern like bulging eyes, lid retraction, fat bags.<br>Exposure symptoms like photophobia, grittiness | External examination<br>Slit lamp evaluation | |

**Table 4: EUGOGO Classification of the Severity of the Ophthalmopathy**

(1) ***Mild:*** Minimum impact on the patient's life.One or more of the following signs:
- Minor lid retraction (<2 mm).
- Mild soft tissue involvement.
- Exophthalmos <3mm(above the normal range for the race and gender).
- Transient or no diplopia.
- Corneal exposure responsive to lubricants.

(2) ***Moderate to severe:*** patients without sight-threatening GO whose eye disease has sufficient impact on daily life to justify the risks of immunosuppression (if active) or surgical intervention (if inactive). Patients usually present one or more of the following signs:
- Lid retraction (>2 mm).
- Moderate or severe soft tissue involvement.
- Exophthalmos ≥3mm(above the normal range for the race and gender).
- Inconstant, or constant diplopia.

(3) ***Sight-threatening GO:*** patients with dysthyroid optic neuropathy or corneal breakdown due to severe exposure. Other infrequent cases are ocular globe subluxation, severe forms of frozen eye, choroidal folds, and postural visual obscuration. This category warrants immediate intervention.

status and CT scan or MRI is indicated in cases of DON and for orbital bone assessment prior to orbital surgery.

## INVESTIGATIONS

1. Thyroid function tests (free T3, free T4, and TSH) to know whether the patient is euthyroid, hypothyroid or hyperthyroid
2. Thyroid specific antibodies (anti-thyroglobulin, anti-thyroid peroxidase and anti-TSH receptor) which may support the diagnosis, but may be negative, especially in late disease. The level of thyroid stimulating immunoglobulin (TSI) correlates with the development of ophthalmopathy in patients with Graves' disease.
- Orbital imaging helps in supporting

the diagnosis and may not be indicated if the clinical features are sufficient to arrive at the diagnosis. Non contrast CT Scan is indicated in the following situations (Figure 7):

- To identify orbital apical crowding in cases of optic neuropathy
- To know the status of the surrounding bone and sinuses prior to decompression surgery.
- For measurement of orbital fat, lacrimal gland and individual extraocular muscles when clinical diagnosis is not conclusive.
- Sequential scanning permits an assessment of natural progression or response to therapy.

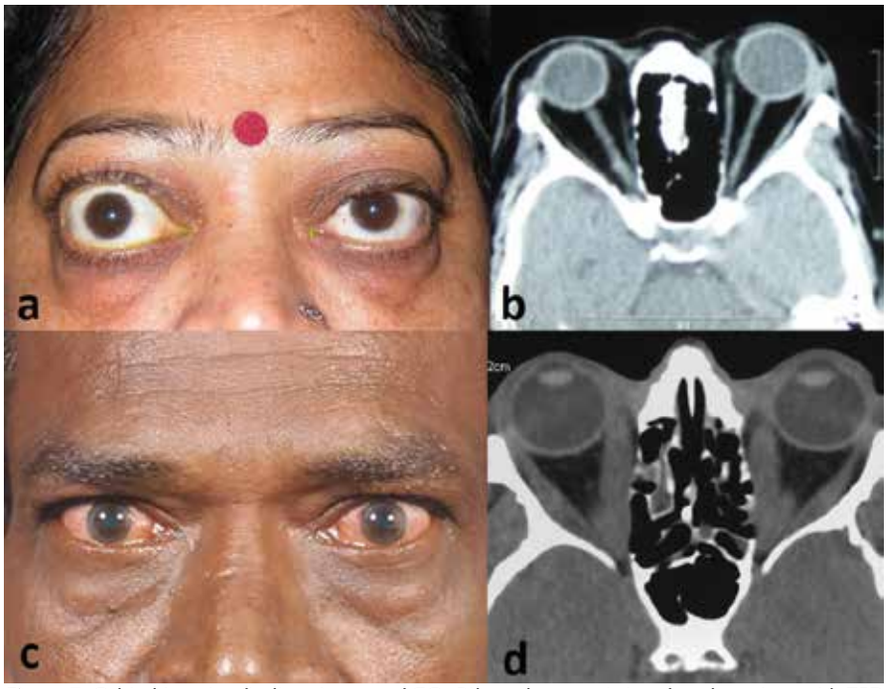


***Figure 7:*** *Orbital imaging findings in case of GO. Bilateral proptosis in a female patient with TED (Figure 7a) and CT scan showing increased orbital fat spaces and stretching of the optic nerve with minimal extraocular muscle thickening suggesting a predominantly fat disease (Figure 7b). Eyelid retraction and severe extraocular movement restriction and optic neuropathy with minimal proptosis in a male patient with TED (Figure 7c) and the corresponding CT scan showing massive enlargement of extraocular muscles causing crowding of the orbital apex in a predominantly muscle disease (Figure 7d).*

## MANAGEMENT

The management of thyroid eye disease needs a multidisciplinaray approach. A patient centred approach to treatment is recommended which takes into account the effect of the disease and the treatment on the quality of life and psychosocial well being of the patient.

### Treatment of thyroid dysfunction

Since persistence of thyroid dysfunction is a major risk factor for worsening of TED, it is important to make the patient euthyroid. Underlying thyroid dysfunction can be treated by:

- Medical intervention (propylthiouracil, carbimazole, thyroxine, radioactive iodine)
- Surgical intervention (thyroidectomy)
- Radioactive iodine therapy (RAI). Caution must be exercised while advising RAI since it can worsen TED. Hence patients must be screened before starting RAI therapy for the risk factors for worsening of orbitopathy like recent onset hyperthyroidism, severe hyperthyroidism, active Graves's orbitopathy, high serum TSH or TRAb levels or cigarette smoking. Concomitant oral steroids are started few days prior to the RAI therapy if risk factors are present[28].

### Risk factor modification

Tobacco smoking is the strongest modifiable risk factor for the progression of orbitopathy. Association between smoking and thyroid eye disease is well established including the following observations:[29,30,31]

i) Smokers tend to have a more severe ophthalmopathy.
ii) Smokers are more likely to show progression or development of ophthalmopathy after RAI therapy for hyperthyroidism
iii) Cessation of smoking is associated with a better outcome of GO.
iv) Smoking delays or worsens the outcome of immunosuppressive therapy for ophthalmopathy

Treatment of Ophthalmopathy:

All patients with TED should be assessed for activity and severity as par the standardised criteria and categorised into active or inactive or mild, moderate to severe or sight threatening ophthalmopathy.

### General measures

General Measures advised to all patients with TED should include preservative free topical lubricants, moisture goggles, smoking cessation and nocturnal head elevation. Increased tear osmolality is the main component of dry eye in these patients. Lacrimal gland expresses TSH receptors and circulating TSHR antibodies can bind and contribute to the lacrimal gland impairment, leading to secondary Sjogren's syndrome in long standing cases[32]. Hence, preservative free artificial tears with long retention time like sodium hyaluronate and those with osmoprotective action should be prescribed frequently to protect the ocular surface.

### Selenium supplementation

Selenium supplementation have shown to improve the clinical activity score in patients with mild active TED, improve quality of life and slow the disease progression in TED patients with mild GO[33]. However, there is an increased risk of type II diabetes with higher doses.

### Specific management

Treatment of TED depends on the activity and severity of the disease. Patients with a VISA score of >4/10 or a CAS score of >3/7 is considered to be active disease. An algorithm for the management of TED is provided in (Figure 8).

### Active Phase Disease Management

The aim of the active phase management is to reduce the risk of sight threatening complications and reduce the severe manifestation of the disease until the disease activity dies down. Mild disease can be managed by

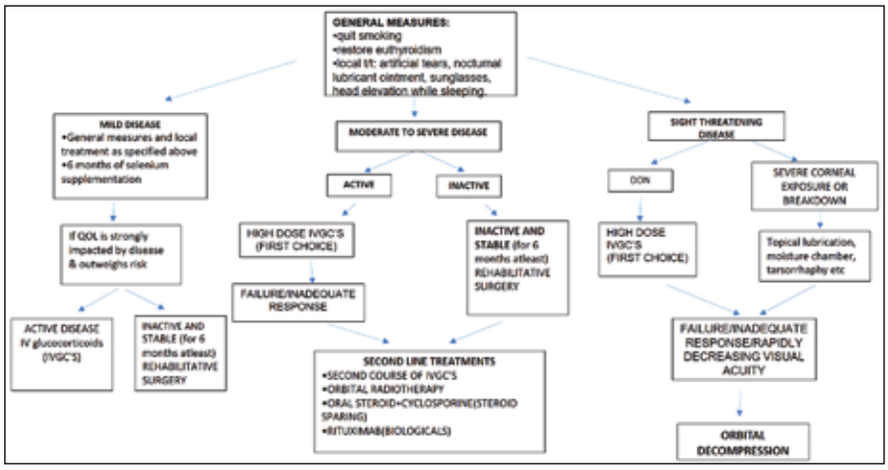


***Figure 8:*** *Algorithm for management of TED.*

supportive care including ocular surface lubrication, moisture goggles, and nocturnal head elevation. Moderate to severe disease requires treatment with anti-inflammatory medications.

1. Anti-inflammatory treatment

**a) Corticosteroids:**

Corticosteroids remain the first line anti-inflammatory therapy. It can be administered orally, intravenously (IV) or as local steroid injection into orbital soft tissues. Though IV steroids appears to be more efficacious and better tolerated than oral steroids, a recent survey of members of the American society of ophthalmic plastic and reconstructive surgery have found a preference for use of oral corticosteroids[34]. For moderate to severe active disease, IV methylprednisolone is prescribed at a dose of 0.5gm weekly for 6 weeks followed by 0.25g weekly for 6 more weeks for a cumulative total dose of 4.5gm[35]. High dose regimen is reserved for sight threatening GO and the total cumulative dose should not exceed 8gm to avoid the side effects like liver damage[36]. Safety data also suggest that single dose of IVMP should not exceed 0.75gm and consecutive day dosing should be avoided. Concomitant administration of proton pump inhibitors to prevent peptic ulcers and calcium and Vitamin D supplementation is recommended especially in patients who are at high risk for osteoporosis.

b) Orbital glucocorticoid injection:

Periocular or subconjunctival steroid injection is less effective than oral or IV steroids but can be considered when oral or IV steroids are contraindicated. Triamcinolone 20mg injected in the inferotemporal quadrant of the orbit at 4 weekly intervals has shown improvement in diplopia and significant reduction in the thickness of the extraocular muscles[37].

## Steroid sparing agents

Steroid-sparing agents such as azathioprine, methotrexate or cyclosporine may be considered if moderate, no improvement has occurred with systemic steroids, or patient is intolerant to steroids. Combined treatment with oral prednisolone and cyclosporine has been found to provide better outcome and lower recurrence rate of moderate-severe and active GO.

c) Biological agents:

Biological agents like Rituximab, Adalimimab and Teprotumumab has been the subject of research for treatment of thyroid eye disease. Biological agents have been focussed on improving the steroid sparing regimen and can target T cells, B cells, IGF-1 receptor, TSH receptor and various inflammatory cytokines[38].

- Rituximab is a monoclonal antibody against CD20, a transmembrane protein present on the B lymphocytes. Preliminary studies have shown promising result in treatment of moderate to severe active TED with a sustained reduction of the clinical activity score. The optimal dosing ranges from 100 to 1000 mg per infusion for 3 to 4 infusions[39]. Conflicting reports on progression of DON has been reported on patients on treatment with rituximab, especially those with longer duration of the disease. Hence, rituximab should be avoided in patients with impending DON or long standing cases.
- Adalimumab is a monoclonal antibody and TNF-alpha antagonist and is approved for the treatment of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis etc. Initial studies have shown promising results in treatment of TED with decrease in ophthalmopathy and steroid tapering possible in some patients[40].
- Teprotumumab is a monoclonal antibody and IGF-1 receptor blocker and is undergoing clinical trial as a treatment modality for TED. IGF-1 receptors are highly expressed in the fibrocytes of TED patients and thus teprotumumab might have a role in the reduction or prevention of TED[41].

**2. Orbital Radiotherapy:**

Orbital fibroblasts and lymphocytes are sensitive to ionizing radiation. Controversy remains over its benefits and its role in management of TED. However studies have shown an average improvement in VISA score in TED patients treated with orbital radiotherapy[42]. Orbital irradiation (OR) can be considered in patients with active disease who have diplopia or restricted motility and who are intolerant to or not responsive to systemic corticosteroids or biological agents. A cumulative dose of 20Gy fractionated over 10 sessions and administered over 2 weeks period is a commonly used regimen.

**3. Surgical intervention:**

Surgical intervention is usually avoided in the active phase of the disease as manipulation of the orbital tissues can worsen the orbital inflammation. Exposure keratopathy not amenable lubricants might benefit from tarsorrhaphy. Corneal breakdown might require tissue adhesive or corneal transplantation. Prism prescription might help in restoring fusion in patients with primary position diplopia and small angle squint (usually <15 PD) in the active phase of the disease. Orbital decompression in the active phase is reserved for patients intolerant or non responsive to steroids.

## CHRONIC INACTIVE PHASE TREATMENT

Rehabilitative surgery for TED is usually performed in the chronic inactive phase of the disease. Surgical management should proceed in the following sequence: orbital decompression, squint surgery, lid lengthening with or followed by blepharoplasty/browplasty.

## Orbital decompression

The usual indications for orbital decompression are compressive optic neuropathy, disfiguring exophthalmos, troublesome retroocular pain/discomfort related to orbital congestion, and/or

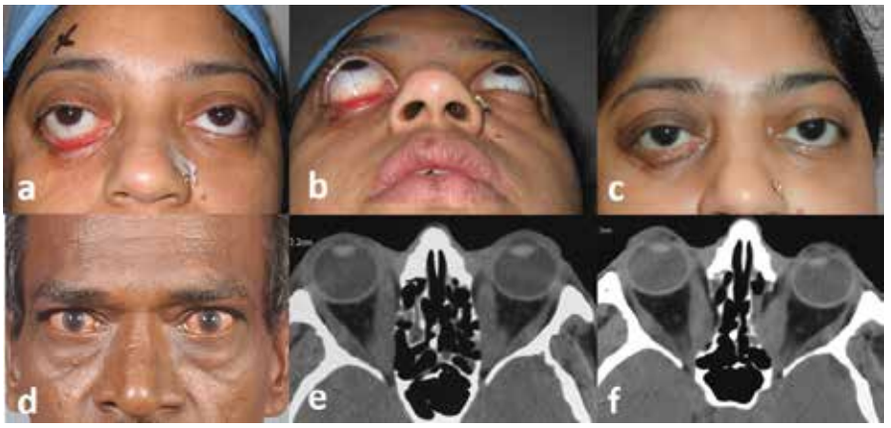

***Figure 9:*** *Orbital decompression for thyroid orbitopathy. Right disfiguring proptosis and lower lid ectropion in the quiescent phase of GO in a female patient (Figure 9a,9b). Appearance following deep lateral orbital and fat decompression (Figure 9c). Compressive optic neuropathy due to apical crowding by bulky extraocular muscles as seen on CT scan in a male smoker with TED (Figure 9d, 9e). Reduction in the apical crowding seen on CT scan following endoscopic medial wall decompression (Figure 9f).*

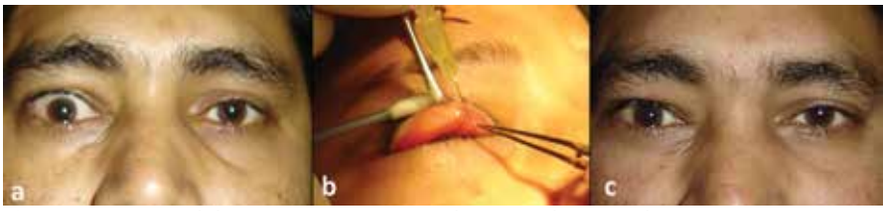

***Figure 10:*** *Upper eyelid retraction in a patient with Graves' disease with recent onset TED (Figure 10a). Transconjunctival injection of 5U of Botox (botulinum toxin) to the levator caused temporary reduction in the retraction with optimal cosmetic appearance (Figure 10b,10c).*

***Figure 11:*** *Mild inactive TED with right upper eyelid retraction (Figure 11a). Transconjunctival graded levator recession was done to correct the retraction (Figure 11b,11c).*

grittiness associated with minor exposure keratopathy not amenable to topical therapies. Orbital decompression for disfiguring exophthalmos is best deferred until the orbitopathy has been inactive for at least 6 months. Decompression can be done either by orbital approach, endoscopic endonasal approach or via transcranial route (Figure 9). Depending upon the amount of proptosis reduction desired, either fat, bone or a combination of fat and bone decompression can be done. Complications associated with orbital decompression include diplopia, ocular motility limitation and can be minimised by doing a 'balanced orbital decompression" which involves simultaneous medial and lateral wall decompression.

### Strabismus surgery

Strabismus surgery for correction of diplopia is done after the active phase of the disease is over and orbital decompression if indicated is done with. Strabismus measurement should be stable for at least 6 months before planning any surgical intervention. The aim of strabismus correction is to restore fusion in the primary gaze and downgaze and if that is achieved to correct any other residual incomitance. The extraocular muscles are usually tight and fibrotic in TED; hence recession of the extraocular muscles with adjustable suture technique and retroequitorial myopexy gives best results.

### Eyelid retraction

In the active phase of the disease, eyelid retraction can be minimised by botulinum toxin injection to the levator aponeurosis. Injection of 2.5 to 5U of Botox is given either via transcutaneous or transconjunctival route (Figure 10). Severe retraction and exposure keratopathy requires tarsorrhaphy to reduce the lagophthalmos. Conventional surgical management of eyelid retraction is levator recession (Figure 11). Treatment of lower eyelid retraction requires spacer placement in addition to recession of the retractors to provide height and necessary stiffness to support the eyelid against gravity. Injection of fillers in the levator plane can also cause temporary reduction in the eyelid retraction.

## CONCLUSION

GO is the most common extrathyroidal manifestation of Graves's disease. The pathophysiology of GO is still not completely understood, however newer studies have elucidated noble mechanisms of the involvement of the orbital tissues in this disease. Introduction of the newer and noble therapeutic modalities like biological agents, IGF-1 receptor antagonists monoclonal antibodies will make it possible to manage this disease better, if not eliminate it. Refinements in the surgical management techniques like minimally invasive and image guided stereotactic decompression have made the surgical management safer and efficacious.

## REFERENCES


1. Rebecca S. Bahn. Graves' Ophthalmopathy. N Engl J Med 2010. 2010 Feb 25;362:726–738.
2. Shueh Lin Lim, Andrew Keat Eu Lim, Malik Mumtaz et al. Prevalence, Risk Factors, and Clinical Features of Thyroid-Associated Ophthalmopathy in Multiethnic Malaysian Patients with Graves' Disease. THYROID 2008. 18:1297–301.
3. Reddy SV, Jain A, Yadav SB, Sharma K, Bhatia E. Prevalence of Graves' ophthalmopathy in patients with Graves' disease presenting to a referral centre in north India.Indian J Med Res. 2014 Jan;139:99-104
4. Perros P, Crombie AL, Matthews JN, Kendall-Taylor P: Age and gender influence the severity of thyroid-associated ophthalmopathy: a study of 101 patients attending a combined thyroid-eye clinic. Clin Endocrinol (Oxf) 1993, 38:367–372.
5. Dolman P. Evaluating Graves' Orbitopathy. Best Practice & Research Clinical Endocrinology & Metabolism. 2012;26:229–48.
6. Garrity JA, Bahn RS. Pathogenesis of graves ophthalmopathy: implications for prediction, prevention, and treatment. Am J Ophthalmol 2006;142:147–53.
7. Pappa A, Jackson P, Stone J, et al. An ultrastructural and systemic analysis of glycosaminoglycans in thyroid-

associated ophthalmopathy. Eye (Lond) 1998;12:237–44.
8. Smith T, Janssen J. Building the Case for Insulin-Like Growth Factor Receptor-I Involvement in Thyroid-Associated Ophthalmopathy. Frontiers in Endocrinology. 2017;7.
9. Wang Y, Smith TJ. Current concepts in the molecular pathogenesis of thyroid-associated ophthalmopathy. Invest Ophthalmol Vis Sci 2014;55:1735–48.
10. Koumas L, Smith TJ, Feldon S, Blumberg N, Phipps RP. Thy-1 expression in human fibroblast subsets defines myofibroblastic or lipofibroblastic phenotypes. Am J Pathol. 2003;163:1291–1300.
11. Koumas L, Smith TJ, Phipps RP. Fibroblast subsets in the human orbit: Thy-1+ and Thy-1- subpopulations exhibit distinct phenotypes. Eur J Immunol. 2002;32:477–485.
12. Ponto KA, Kanitz M, Olivo PD, Pitz S, Pfeiffer N, Kahaly GJ. Clinical relevance of thyroid-stimulating immunoglobulins in Graves' ophthalmopathy. Ophthalmology. 2011;118:2279–2285.
13. Wakelkamp IM, Bakker O, Baldeschi L, Wiersinga WM, Prummel MF. TSH-R expression and cytokine profile in orbital tissue of active vs. inactive Graves' ophthalmopathy patients. Clin Endocrinol (Oxf). 2003;58:280–287.
14. Tsui S, Naik V, Hoa N, Hwang CJ, Afifiyan NF, Sinha Hikim A, Gianoukakis AG, Douglas RS, Smith TJ. Evidence for an association between thyroid-stimulating hormone and insulin-like growth factor 1 receptors: a tale of two antigens implicated in Graves' disease. J Immunol. 2008;181:4397–4405.
15. Cao HJ, Wang HS, Zhang Y, Lin HY, Phipps RP, Smith TJ. Activation of human orbital fibroblasts through CD40 engagement results in a dramatic induction of hyaluronan synthesis and prostaglandin endoperoxide H synthase-2 expression. Insights into potential pathogenic mechanisms of thyroid-associated ophthalmopathy. J Biol Chem. 1998;273:29615–29625.
16. Rebecca S. Bahn MNS. Risk Factors for Development or Deterioration of Graves' Ophthalmopathy. THYROID 2010. 20:777–83.
17. Dolman PJ1. Evaluating Graves' orbitopathy. Best Pract Res Clin Endocrinol Metab. 2012;26:229-48.
18. Lim NC, Sundar G, Amrith S, Lee KO. Thyroid eye disease: a Southeast Asian experience. Br J Ophthalmol. 2015;99:512-8.
19. Ebner R. Semin Ophthalmol. 2002;17:18-21.Dysthyroid optic neuropathy (DON).
20. Trobe JD, Glaser JS, Laflamme P. Dysthyroid optic neuropathy. Clinical profile and rationale for management. Arch Ophthalmol. 1978;96:1199–1209.
21. Werner S. Classification of the Eye Changes of Graves' Disease. American Journal of Ophthalmology. 1969;68:646-648.
22. Werner S. Modification of the Classification of the Eye Changes of Graves' Disease. American Journal of Ophthalmology. 1977;83:725-727.
23. Mourits M, Koornneef L, Wiersinga W, Prummel M, Berghout A, van der Gaag R. Clinical criteria for the assessment of disease activity in Graves' ophthalmopathy: a novel approach. British Journal of Ophthalmology. 1989;73:639-644.
24. Mourits M, Prummel M, Wiersinga W, Koornneef L. Clinical activity score as a guide in the management of patients with Graves' ophthalmopathy. Clinical Endocrinology. 1997;47:9-14.
25. Dolman P, Rootman J. VISA Classification for Graves Orbitopathy. Ophthalmic Plastic & Reconstructive Surgery. 2006;22:319-324.
26. Bartalena L, Baldeschi L, Dickinson A, Eckstein A, Kendall-Taylor P, Marcocci C, Mourits M, Perros P, Boboridis K, Boschi A, Currò N, Daumerie C, Kahaly GJ, Krassas GE, Lane CM, Lazarus JH, Marinò M, Nardi M, Neoh C, Orgiazzi J, Pearce S, Pinchera A, Pitz S, Salvi M, Sivelli P, Stahl M, von Arx G, Wiersinga WM; European Group on Graves' Orbitopathy (EUGOGO).Consensus statement of the European Group on Graves' orbitopathy (EUGOGO) on management of GO.Eur J Endocrinol. 2008;158:273-85.
27. Bartalena L, Baldeschi L, Boboridis K, Eckstein A, Kahaly GJ, Marcocci C, Perros P, Salvi M, Wiersinga WM; European Group on Graves' Orbitopathy (EUGOGO).The 2016 European Thyroid Association/European Group on Graves' Orbitopathy Guidelines for the Management of Graves' Orbitopathy. Eur Thyroid J. 2016;5:9-26.
28. Bartalena L, Marcocci C, Bogazzi F, et al. Use of corticosteroids to prevent progression of Graves' ophthalmopathy after radioiodine therapy for hyperthyroidism. N Engl J Med 1989;321:1349–52.
29. Prummel MF, Wiersinga WM: Smoking and risk of Graves' disease. JAMA 1993; 269:479–82.
30. Bartalena L, Marcocci C, Tanda ML, Manetti L, Dell'Unto E, Bartolomei MP, Nardi M, Martino E, Pinchera A: Cigarette smoking and treatment outcomes in Graves ophthalmopathy. Ann Intern Med 1998;129:632–35.
31. Eckstein A, Quadbeck B, Mueller G, Rettenmeier AW, Hoermann R, Mann K, Steuhl P, Esser J: Impact of smoking on the response to treatment of thyroid associated ophthalmopathy. Br J Ophthalmol 2003;87:773–76.
32. Renzing-Kohler K, Esser J, Krüger C, Quadbeck B, Steuhl KP, Gieseler RK: Dry eye syndrome in thyroid-associated ophthalmopathy: lacrimal expression of TSH receptor suggests involvement of TSHR-specific autoantibodies. Acta Ophthalmol Scand 2004;82:291–97.
33. Marcocci C, Kahaly GJ, Krassas GE, Bartalena L, Prummel M, Stahl M, Altea MA, Nardi M, Pitz S, Boboridis K, Sivelli P, von Arx G, Mourits MP, Baldeschi L, Bencivelli W, Wiersinga W; European Group on Graves Orbithopathy: Selenium and the course of mild Graves' orbitopathy. N Engl J Med 2011;364:1920–31.
34. Perumal B,Meyer DR. Treatment of severe thyroid eye disease: a survey of the American Society of Ophthalmic Plastic and Reconstructive Surgery (ASOPRS). Ophthal Plast Reconstr Surg 2015;31:127–31.
35. Kahaly GJ, Pitz S, Hommel G, Dittmar M: Randomized, single blind trial of intravenous versus oral steroid monotherapy in Graves' orbitopathy. J Clin Endocrinol Metab 2005;90:5234–40
36. Zang S, Ponto KA, Kahaly GJ: Clinical review: intravenous glucocorticoids for Graves' orbitopathy: efficacy and morbidity. J Clin Endocrinol Metab 2011;96:320–32.
37. Riedl M, Kolbe E, Kampmann E, Kramer I, Kahaly GJ: Prospectively recorded and MedDRA-coded safety data of intravenous methylprednisolone therapy in Graves' orbitopathy. J Endocrinol Invest 2015;38:177–82.
38. Kahaly G, Schrezenmeir J, Krause U, Schweikert B, Meuer S, Muller W, Dennebaum R, Beyer J: Ciclosporin and prednisone v. prednisone in treatment of Graves' ophthalmopathy: a controlled, randomized and prospective study. Eur J Clin Invest 1986;16:415–22.
39. Salvi M, Vannucchi G, Curro N, Campi I, Covelli D, Dazzi D, Simonetta S, Guastella C, Pignataro L, Avignone S, Beck-Peccoz P: Efficacy of B-cell targeted therapy with rituximab in patients with active moderate to severe Graves' orbitopathy: a randomized controlled study. J Clin Endocrinol Metab 2015;100: 422–31.
40. Ayabe R, Rootman DB, Hwang CJ, et al. Adalimumab as steroid-sparing treatment of inflammatory-stage thyroid eye disease. Ophthal Plast Reconstr Surg 2014; 30:415–19.
41. Chen H, Mester T, Raychaudhuri N, et al. Teprotumumab, an IGF-1R blocking monoclonal antibody inhibits TSH and IGF-1 action in fibrocytes. J Clin Endocrinol Metab 2014; 99:E1635–E1640.
42. Bradley EA, Gower EW, Bradley DJ, et al. Orbital radiation for Graves' ophthalmopathy. Ophthalmology 2008;115:398–409.

**Correspondence to:**
***Dr. Sima Das***
*Oculoplasty and Ocular Oncology Services,*
Anterior segment, Oculoplasty and Aesthetics
Dr Shroff's Charity Eye Hospital,
New Delhi, India.