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Review Article

Recent advances in thyroid eye disease: An overview

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ABSTRACT

Thyroid eye disease (TED) is a chronic debilitating condition which causes physical discomfort, oculo-facial disfigurement and compromised visual function. Around 25% of people with Graves' hyperthyroidism are affected by TED, where 1 in 20 patients might report with moderate-to-severe, active disease that will require medical management for reducing both TED activity and severity. The mainstay of medical management involves intravenous corticosteroids for active moderate-to-severe TED. After accurate understanding of the mechanism and pathophysiology of this disease, investigations and randomized clinical trials have been conducted. The role of immunotherapy targeting and influencing different biomolecular pathways including that of T cells, B cells, cytokines and cell surface receptors have been investigated in various randomized clinical trials. This review article addresses the epidemiology, associated risk factors, recent advances in pathophysiology, newer diagnostic tools and current management options available for TED which include the use of immunosuppressive drugs like rituximab (RTX), tocilizumab, infliximab (IFX), etanercept (ETN) and teprotumumab etc.

1. Introduction

Thyroid eye disease (TED) is a cosmetically disfiguring,[1] visually crippling[2] and psychologically distressing[3] disease, alternatively known as thyroid associated orbitopathy (TAO) or Graves' Orbitopathy (GO), named after an Irish physician who first described thyrotoxicosis, Robert J. Graves.[4] Though hyperthyroidism is most commonly known to coexist with TED. Thyroid dysfunction can precede TED development; thyroid dysfunction and TED can present simultaneously, or TED can precede thyroid dysfunction.[5] TED is a highly complex autoimmune disease with inflammatory component involving extraocular muscles, orbital fat as well as lacrimal gland. The characteristic features of TED is the infiltration of the thyroid gland and orbital fat (which has TSH expression) by autoimmune cells and the production of autoantibodies against TSHR. Stimulatory autoantibodies against the TSHR and the insulin-like growth factor-1 receptor are responsible for excessive activation of orbital fibroblast which leads to tissue expansion and its remodeling along with fibrosis due to excessive secretion of glycosaminoglycans and its differentiation in to myofibroblast. The orbital inflammation in TED patients may give rise to proptosis, diplopia and symptoms of severe dry eye which affects the activities of daily living as well as the socioeconomic status of patients.[6,7]

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2. Epidemiology

Although majority of patients who are newly diagnosed with Graves' disease have no ocular component and moderate-to severe GO or sight-threatening GO are rare at presentation and develops rarely during ATD treatment,[8] 25 to 50% of patients diagnosed with Graves' disease have been found to have features of Orbitopathy and up to $1/3^{rd}$ may develop severe consequences.[9,10] Clinically apparent Graves orbitopathy is much higher in females than in males, i.e., 16 per 100000 in females and 2.9 per 100000 in males,[11] probably due to higher incidence of Graves' disease in the female population. But as the severity of the disease increases, the proportion of men who are affected also increases. In patients suffering from mild ophthalmopathy female to male ratio was 9.3:1, in cases of moderate ophthalmopathy it is 3.2:1 and in severe cases it is 1.4:1.[12,13] MRI evidence of Graves orbitopathy is found in an even larger percentage of the population, in the absence of clinical disease.[14] It has been reported that 2% of TED cases are vision threatening.[8,15] The peak incidence has been reported to be bimodal, occurring in the age groups 45 - 49 years and 65 - 69 years in men and 40 - 44 years and 60 - 64 years in women .Wiersinga reported that 23% of pediatric patients with Grave's disease were TED.[12] According to one, among patients with GO, approximately 90% had Graves' hyperthyroidism 1% had primary hypothyroidism, 3% had Hashimoto's thyroiditis, and 5% were euthyroid.[16]

3. Pathogenesis

The etiopathogenesis of TAO is a complex, it is an autoimmune process of recruitment of immune cells into the orbit, proliferation and differentiation of orbital fibroblasts on stimulation by immune cells, secretion of Hyaluronan, adipogenesis and perpetuation of orbital inflammation.[17]

3.1. Immune pathogenesis of orbital changes

TSHR is the primary autoantigen in TED which plays a vital part in pathogenesis of TED. Self-tolerance to the TSH receptor on thyroid epithelial cells is broken, as a result of which TSHR stimulating antibodies are formed. The adenylyl cyclase/cAMP pathway and the PI3K/AKT/mTOR pathway are two main pathways responsible for TSHR signal to induce thyrotoxicosis.[18]

There is scientific evidence that suggests the involvement of IGF1/IGF-1R in the pathogenesis of TO, but the true autoantigenic nature has no evidence yet. IGF-1R is said to be responsible for regulation of lymphocyte trafficking in the orbit, as well as HA synthesis, adipogenesis and to define phenotypic expression of T-lymphocyte and B-lymphocyte.[19,20] T cell infiltrates present in the orbital tissues of TED are mainly CD4+ in nature, but both CD8+ and CD4+ T cells may be present.[20,21] The autoantigens that are present on the orbital fibroblasts, when interact with T cells (a process that involves contact of T cell receptor with major histocompatibility complex class II molecule and CD40:CD154 signaling[22] lead to active proliferation of orbital fibroblast and their enhanced activity. CD40 ligation with CD154 causes increased production of intercellular adhesion molecule-1 (ICAM-1), translocation of nuclear factor-$\kappa\beta$ (NF-$\kappa\beta$), IL-6, IL-8 and MCP-1 in TO orbital fibroblasts.[23] Ultimately the molecular signaling.

That is triggered by CD40:CD154 ligation process has involvement of all three mitogen-activated protein kinase (MAPK) pathways, p38, ERK1/2 and JNK, which mediates the cellular activity processes such as expression of genes involved, proliferation of cells, their differentiation and apoptosis.[24]

3.2. Role of fibroblasts and Adipogenesis

Orbital fibroblasts (OFs) are key effector cell in TED which are involved in the early inflammation process and the subsequent remodeling process.[25] The two subpopulations of OFs are (i) Thy1-expressing OFs present in the perimysium of extraocular muscle which differentiate into myofibroblasts and (ii) Thy 1- deficient OFs present throughout orbit differentiate into mature adipocyte. The proportion of two activated OFs determine whether fibrosis or adipogenesis predominate in TED.

Figure 1 demonstrated immunopathogenesis of thyroid eye diseases. The overexpression of IL-1β, TNF-α, IFN-γ, IL-6, IL-10, and IL-8 are present in orbital adipose tissue in TO.[26] Orbital fibroblasts, when excited by IL-1β, upregulate the production of pro-inflammatory cytokines like IL-6 and IL-8, PGE2, IL-6R and T cell chemo attractants, IL-16 and Regulated on Activation, Normal T Cell Expression and Secreted (RANTES), which directs recruitment of T cells in the orbit, amplifying the entire process mentioned above.[20] B cell differentiation and immunoglobulin production is promoted by IL-6 and increases TSH-R expression in orbital fibroblast pre-adipocytes.[27] Hyaluronan synthesis is also stimulated by orbital fibroblast surface receptors for TSH-R and IGF-1R,[28] leading to an increase in soft tissue content of the orbit.

Both TSHR and IGF-1R play an important role in promoting adipogenesis and share the same intracellular AKT/PI3K signaling to affect the process.[29] The phosphorylated AKT protein, cAMP levels are increased by stimulatory TSHR antibody and enhanced adipogenesis via the PI3K signaling cascade, and IGF-1 has its effect channeled by first binding to IGF-1R and induction of phosphorylation of Src homology two domain-containing protein (Shc) and insulin receptor substrate (IRS) and also downstream AKT/PI3K pathway.

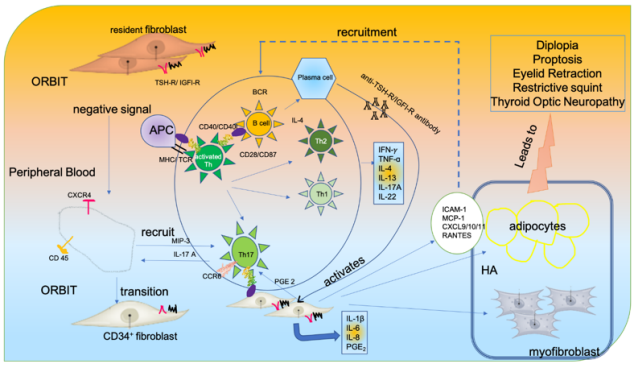


Fig. 1: Showing the complex interaction of the immune system, proinflammatory cytokines and autoantibody on orbital fibroblasts resulting into clinical manifestations of thyroid eye disease.

3.3. Role of Oxidative stress in the pathogenesis

Several studies have shown a potential role of reactive oxygen species, anions like (superoxide anions and hydrogen peroxide (H202)) in the pathogenesis of TED. The pro-inflammatory cytokines production (IL-1β, TGF-β1) is induced by ROS and also orbital fibroblast proliferation is stimulated in a dose-dependent manner by ROS.[30,31] One study proved that intracellular ROS levels were higher in GO orbital fibroblasts and exogenous H2O2 resulted in a more pronounced response of ROS metabolism in these cells and that increased stress-induced generation of ROS may cause more oxidative damage, including oxidative DNA damage and lipid peroxidation.[32] In addition, it has been observed that ROS on cell proliferation shows a biphasic effect, in which low concentrations of ROS induced growth but higher concentrations causes oxidative damage to DNA, proteins and lipids, which could be potentially leading to apoptosis or necrosis.[33,34] Bednarek et al reported increased serum concentration of superoxide dismutase (SOD) and catalase in Graves' diseases patients as compared to healthy controls.[35] Similarly, Tsai et al reported increased urinary concentration of 8-hydroxy-2'-deoxyguanosine (8-OHdG), a marker of oxidative DNA damage in patients with active TED than in healthy controls.[36] Akarsu et al estimated serum concentration of malondialdehyde (MDA), another biomarker of the oxidative stress in TED patients. He observed higher level of serum MDA in TED patients in comparison to Graves' disease patient without TED and healthy controls.[37]

3.4. Smoking and thyroid eye disease

An association of tobacco smoking with TED was first described in 1987,[38] and a positive association with an up to the 20-fold increased risk of TED for current smokers compared with non- or never-smokers has been noted over the years.[39] It has been proposed that smoking can have a direct irritant action on the eye, causing inflammatory changes,[13] or there could be a generalized activation of the autoimmune process in smokers.[40] Smoking by causing hypoxia in the retrobulbar space can effect cytokine secretion and activity[13,40] or altering TSH and making it more immunogenic.[13] The chemical components in cigarette smoke like endotoxin, nicotine, polycyclic aromatic hydrocarbons affect human immune system. Cigarette smoke enhances the production of several pro-inflammatory cytokines like TNFα, IL-1, IL-6, IL-8 & chemokines and decreases anti-inflammatory cytokines like IL-10. Cigarette smoking highly increases oxidative stress which play important role in TED. It increases HLA-DR and HSP-72 expression on orbital fibroblast which are involved in T cell recruitment and causing fibroblast proliferation and adipogenesis.[41] In conclusion, there is ample evidence of a causal relationship between smoking and TO, and all efforts must be undertaken to promote smoking cessation in such patients.

4. Diagnosis of TED

4.1. Clinical Investigations

4.1.1. Ophthalmological findings and complications

Though most often found bilaterally, the ophthalmic findings may present unilaterally or asymmetrically.[42] Early symptoms include, excessive tearing from dry eye, foreign body sensation, conjunctival or eyelid redness and swelling, blurred vision, and retro-orbital pain. Dilated conjunctival vasculature, keratoconjunctivitis, and corneal staining may be seen on slit-lamp examination. The most common clinical features encountered, in order of frequency, are eyelid retraction (in 91% cases), exophthalmos (62%), extraocular muscle restriction (43%), ocular pain 30%, lacrimation 23%, and optic nerve disease 6%.[15] Upper eyelid retraction is the most common finding in TED. The characteristic lateral flare gives rise to thyroid stare (angry look). Retraction of eyelids, reduced frequency of blinking, increased amount of tear evaporation, and lagophthalmos leads to dry eye (exposure keratopathy). Second most common finding due to orbital content enlargement is proptosis. It has been reported that the patients developing minimal proptosis have a much higher risk of developing compressive optic neuropathy because of a 'compartment syndrome ' caused due to expansion of the extraocular muscles in the volume of the orbit that is fixed.[43] There can be development of restrictive strabismus in TED is due to inflammation as well as fibrosis of the extraocular muscles, and the muscles involvement pattern most commonly encountered is inferior rectus, followed by the medial rectus, superior rectus, lateral rectus, and lastly the oblique muscles.[43] Symptoms of strabismus can be graded according to Bahn-Gorman scale: 0 =No diplopia, I=intermittent diplopia (present with fatigue), II= inconstant diplopia (with vertical or horizontal gaze), III = constant

diplopia in straight gaze, corrected with prism, IV =constant diplopia, not corrected with prisms.

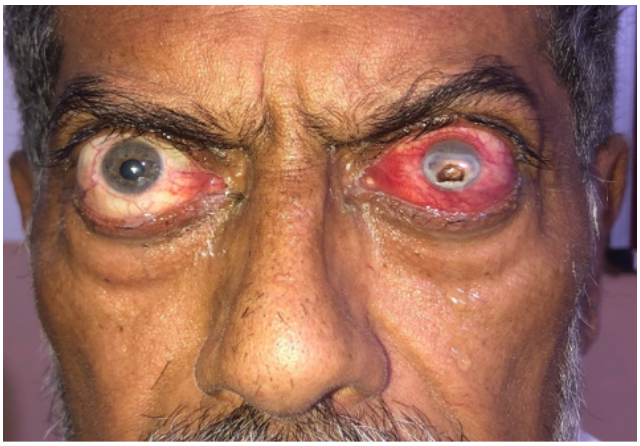


Fig. 2: Old male showing proptosis and bilateral both eyelid retraction with left eye exposure keratopathy.

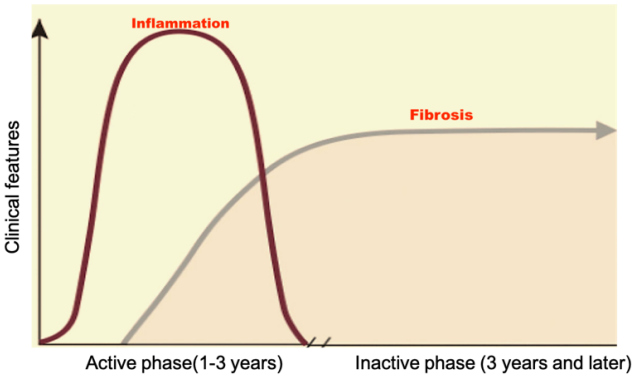


Fig. 3: Rundle's curve showing biphasic course of thyroid eye disease.

Corneal ulceration and compressive optic neuropathy seen in 3–5% of the patients are the cause of sight-threatening complications (Figure 2).[44] When compressive optic neuropathy (CON) develops there is a risk of permanent loss of vision and it contributes as a significant complication of TED. A Higher risk factor of TED-CON is seen to be associated with male sex, old age, and diabetes mellitus.[45,46] TED-CON is a clinical condition which can be described as collection of different signs and symptoms including impairment of color vision , reduction in visual acuity, a relative afferent pupillary defect, abnormalities of the optic disc along with significant visual field (VF) defects, proof of apical crowding phenomena on radiographic imaging, and reduction in amplitude of visual evoked potential. (VEP).[47,48]

The 'Rundle curve' (Figure 3) helps in describing and studying the natural course of the disease, which starts with an active phase of progression of about 6 to 24 months' duration and is characterized by proptosis, conjunctival congestion and chemosis, double vision, and rarely corneal ulceration or compressive type of optic neuropathy. When the active inflammation subsides, there comes a phase of spontaneous slow improvement which usually lasts for around an year. This phase has certain histopathological changes which include progressive fibrosis, leading to a static phase, characterized by proptosis, retraction of the eyelids, and a persistent type of restrictive strabismus.[49]

4.1.2. Classification of TED

It is no mean feat to classify a disease with a vast clinical profile and unpredictable course as thyroid eye disease. An abridged version of the detailed classification given by Dr S. C. Werner, the NOSPECS classification[50] (Chart 1), is often used in clinical practice.

ABRIDGED CLASSIFICATION OF EYE CHANGES OF GRAVES' DISEASE

Class*	Definition†
0	No signs or symptoms
1	Only signs, no symptoms (signs limited to upper lid retraction and stare, with or without lid lag and proptosis)
2	Soft tissue involvement (symptoms and signs)
3	Proptosis
4	Extraocular muscle involvement
5	Corneal involvement
6	Sight loss (optic nerve involvement)

* Each class usually includes the involvements indicated in the preceding class. Each class is graded: (a) mild, (b) moderate, (c) marked, or (o) absent. The "o" grade is unnecessary for Class 6.

† Note first letters of each definition constitute the mnemonic *no specs*. Apart from helpfulness for those who use mnemonics for recall, the *no* indicates the usually nonthreatening prognosis of Classes 0 and 1 (Class 1 was formerly mild or noninfiltrative) and the serious nature of the involvements of Classes 2 to 6 (formerly severe or infiltrative).

Chart 1: *Showing an abridged version of the detailed classification of TED given by Dr S. C. Werner*

Since this classification could not differentiate between active and inactive TED, in 1989, Mourits et al. had introduced a Clinical Activity Score (CAS) in order to stage and grade the phase of inflammation in this disease.[51] ("Active" disease means the presence of inflammatory features and suggests the potential for response to anti-inflammatory treatments, "Inactive" disease defines the phase when any inflammation is not present, yet residual fibrosis and its secondary effects persist, and only surgical treatment can alter the outcome). CAS is an inexpensive, convenient clinical classification, but it could not overcome the disadvantages of the NOSPECS classification, of being subjective, with a large inter-observer variation.

CAS was modified by the European Group of Graves' Orbitopathy (EUGOGO) as follows:

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

One point is given for the presence of each of the parameters assessed. 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.

The VISA system was developed by Dolman and Rootman in 2006[52] and assesses 4 severity parameters: V (vision); I (inflammation/congestion); S (strabismus/motility restriction); and A (appearance/exposure). Each feature is considered and graded independently. A global severity grade (maximum score is 20 points) is the sum of each of the involved systems graded independently: vision: 1 point; inflammation/congestion: 10 points; strabismus: 6 points (diplopia: 3 points plus restriction: 3 points); appearance/exposure: 3 points. (Chart 2)

EUGOGO Classification**:** The Europeans, in 1999, based upon activity and severity parameters, developed an assessment protocol for the evaluation of patients with GO. The disease is classified as mild, moderate, severe, or sight-threatening as follows based on modified Clinical Activity Score (CAS).[53]

1. Mild: This is characteristics of GO and has a minimum impact on the patient's life, presenting with one or more of the following signs:
   a. Minor lid retraction (<2 mm).
   b. Mild soft tissue involvement.
   c. Exophthalmos < 3 mm (more than the normal range for the race and gender).
   d. Transient or no diplopia.
   e. Corneal exposure responsive to lubricants.
2. Moderate to severe: This includes patients without sight-threatening GO but with eye disease sufficient to impact one's daily life, justifiable enough to the risks of immunosuppression (if active) or surgical intervention (if inactive). Patients complaints of one or more of the following signs:
   a. Lid retraction (>2 mm).
   b. Moderate or severe soft tissue involvement.
   c. Exophthalmos ≥ 3 mm (above the normal range for the race and gender).
   d. Inconstant, or constant diplopia.
3. Sight-threatening GO: This category warrants immediate intervention. This has patients with dysthyroid optic neuropathy or severe exposure keratopathy. Other infrequent causes are ocular globe subluxation, choroidal folds, postural visual darkening and severe forms of a frozen eye.

4.2. Laboratory Investigations

The most cost-effective and specific method is sensitive TSH assay. TSH should be less than 0.5 mU/L in significant thyrotoxicosis. Measurement of the level of FT4 or FTI (Free thyroxine index) with the degree of elevation of the FT4 above normal is also usually diagnostic.

Determination of antibody titers, thyroperoxidase or microsomal antigen (95% patients have positive TPO assays) and approximately around 50% of the patients have positive anti-thyroglobulin antibody assay. This provides an additional evidence for Graves' disease. In thyroiditis, the prevalence of positive TG antibody assays is found to be much higher. The diagnosis of Graves' disease is strongly supported by antibodies to TSH-Receptor-Thyrotropin receptor antibody (TRAb). Thyroid Stimulating Antibodies (TSAb, TSI) are more specific for the diagnosis.

BMR measurement, TRH testing, T3 suppression of RAIU, and clinical response to KI are not of much importance these days.[54]

Proteomic studies of tears[55,56] and lipidomics of serum and urine[57] have led to discovering a promising array of biomarkers; however, as these are not yet widely available, they remain of limited clinical use.

VISA CLASSIFICATION:

Date: Visit #:

Patient Label:

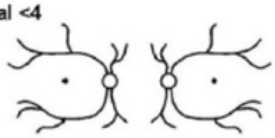
ORBITOPATHY
Time since onset:
Progress:
Tempo:
Symptoms:

Therapy:

THYROID
Time since onset:
Progress:
Status:
Symptoms:

Anti-thyroid meds:
Radioactive iodine:

GENERAL
Smoking:
Family Hx:
Medical Hx:
Allergies:
Meds:

SUBJECTIVE	OBJECTIVE	OD	OS	
VISION				**Refractions**
Vision: n / abn	Central vision: sc / cc / ph	20/___	20/___	Wearing _____ + _____ X _____
	with manifest	20/___	20/___	_____ + _____ X _____
				Manifest _____ + _____ X _____
Color vis: n / abn	Color vision errors (AO)			_____ + _____ X _____
	Pupils (afferent defect)	y / n	y / n	Normal <4
Fundus	Optic nerve: Edema	y / n	y / n	
	Pallor	y / n	y / n	
Progress: s / b / w				
INFLAMMATORY				**Inflammatory Index (worst eye/eyelid)**
Retrobulbar ache	Chemosis (0-2)			Chemosis (0-2):
At rest (0-1)	Conjunctival injection (0-1)			Conjunctival injection (0-1):
With gaze (0-1)	Lid injection (0-1)			Lid injection (0-1):
Lid swelling AM: y / n	Lid edema Upper (0-2)			Lid edema (0-2):
	Lower (0-2)			Retrobulbar ache (0-2):
Progress: s / b / w				**Total (8)**:
STRABISMUS/ MOTILITY				Prism Measure:
Diplopia:	Ductions (degrees):			
None (0)				
With gaze (1)				
Intermittent (2)				
Constant (3)	Restriction > 45°	0	0	
Head turn: y / n	30-45°	1	1	
	15-30°	2	2	
Progress: s / b / w	< 15°	3	3	
APPEARANCE/ EXPOSURE				Fat prolapse and eyelid position:
Lid retraction y / n	Lid retraction (upper): MRD-4	mm	mm	
	(lower scleral show):	mm	mm	
	Levator function	mm	mm	
	Lagophthalmos	mm	mm	
Proptosis y / n	Exophthalmometry (Hertel)	mm	mm	
Tearing y / n	Corneal erosions	y / n	y / n	
FB Sensation y / n	Corneal ulcers	y / n	y / n	Base:
	IOP -straight	mmHg	mmHg	
Progress: s / b / w	-up	mmHg	mmHg	

DISEASE GRADING		Grade	Progress / Response
V	(optic neuropathy)	y / n	s / b / w
I	(inflammation) 0-8	/8	s / b / w
S	(strabismus) 0-3	/3	s / b / w
	(restriction) 0-3	/3	s / b / w
A	(appearance/exposure)	mild / mod / severe	s / b / w

MANAGEMENT **FOLLOW-UP INTERVAL:**

Chart 2: Showing the VISA system of the classification of TED.

4.3. Radio-imaging

Ultrasonography of the thyroid can be performed to confirm hypo echogenicity or the presence of a nodule and a color Doppler for intense vascularity of Graves' disease. The preferred imaging modality is generally CT and soft helps in tissues and bone; it also helps evaluate the orbital walls, sinus, and orbital elements in orbital decompression planning. The radiological features consistent with severe cases of TED on CT scan are enlargement of the muscle belly , that can be classically described as "tendon sparing" (Coca-cola bottle sign), an increase in orbital fat content and volume, and crowding of the optic nerve at the level of orbital apex. There can be occurrence of stretch neuropathy manifested by a "taut" nerve which can be seen in severe cases. When there is associated vascular engorgement along with inflammation visibility of enlarged and anteriorly displaced lacrimal glands is appreciated. The difference in density of orbital tissues gives scope to high resolution imaging even without the use of intravenous (IV) contrast agent administration.[58,59] CT scan is a modality to evaluate the type of orbitopathy. There is CT scan-based classification which includes type 1 orbitopathy (lipogenic variant): which has involvement of only adipose tissue, type 2 orbitopathy (myogenic variant):with involvement of extraocular muscle, and type 3 orbitopathy (mixed): where there is enlargement of both orbital fat content in the compartment as well as extraocular muscle.[59,60]

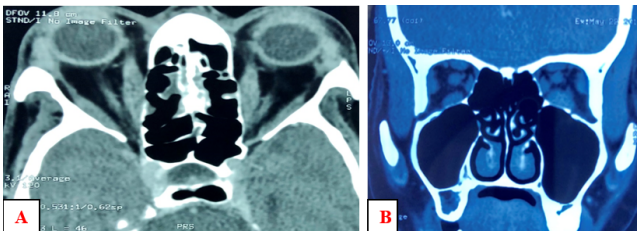


Fig. 4: CT Scan (**A**) Axial view and (**B**) Coronal view showing muscle enlargement and apical crowding.

The better option for the evaluation of soft tissue changes is MRI. Also, it can uncover details that may be important in the assessment of disease activity. In GO, to detect extraocular muscle edema, strongly T2-weighted and fat-suppressed images obtained using the turbo inversion recovery magnitude TIRM and STIR sequences are helpful.

Extraocular muscles have been described as the "shock organ" of GO.[61] In GO, only the non-tendinous portion of the muscle is involved, giving them a fusiform shape, with sharp borders. Muscle enlargement in the order of decreasing frequency occurs in the following muscles: inferior, medial, superior and lateral recti.[62] One study showed that nearly three-fourths of these patients (70%) showed involvement of two or more muscles.[62]

A significant component of the disease process is represented by expansion of the orbital fat compartment.[63] Abnormally increased orbital adipose tissue in a patient with exophthalmos is suggestive of GO, but obesity and Cushing's disease should be ruled out.[64] Other, less specific, less often seen observations are changes in bone, especially in the lamina papyracea, with bowing resulting from muscle pressure, displacement and enlargement of the lacrimal gland, exophthalmos, anterior soft tissue swelling and superior optic vein dilatation.[65] To determine the blood flow rates in the internal carotid artery, ophthalmic artery, and central retinal artery doppler ultrasound can be used and also it can detect early signs of TED.[66,67] Octreotide scintigraphy (octreoscan) uses octreotide, somatostatin (SM) analogue labelled with indium. A high uptake of radiolabeled octreotide may be correlated with orbital inflammation and active disease.[68] This is based on the assumption that orbital lymphocytes express SM receptors during the active phase of GO. Optical coherence tomography (OCT) can provide objective measurements of structures affected by TED, which has been seen to alter measurements of choroidal thickness,[69] peripapillary blood vessel density,[70] nerve fiber layer thickness and rectus muscles size .

5. Management

5.1. Immunosuppressive therapy

Currently, intravenous systemic glucocorticoid in high doses are first line of treatment for thyroid eye diseases with intravenous formulation being more efficacious than oral formulation. Higher cumulative doses (7.47 gm) of methylprednisolone renders short term advantage but without overall benefit on cost of major side effects affecting cardiovascular, cerebrovascular, and hepatic toxicity. Of now, a cumulative dose of 4.5–5 g of intravenous methylprednisolone is recommended for moderate-to-severe TED.[71] Kahaly et al recommended dose of IV methylprednisolone (500 mg weekly x 6 week then 250 mg weekly x 6 weeks for a total dose of 4.5g) for TED.[72]

Besides this, steroid-sparing agents like cyclosporine and MMF have also been shown to be effective in TED treatment in study conducted at Cambridge namely close endocrine control and it was observed that the early introduction of cyclosporin after initial systemic glucocorticoid immunosuppression has resulted in a 7-fold reduction in decompression surgery.[73]

In Oxford and Singapore, similar regimens but early addition of methotrexate after steroid based immunosuppression have shown good clinical efficacy and accelerated suppression of moderate-to-severe disease and accelerating visual recovery with a marked reduction in overall steroid requirement compared with the EUGOGO regime.[74,75]

Adding another drug to armamentarium of immunosuppressive drugs is Mycophenolate mofetil (MMF) which was found to be useful as an adjunct to intravenous methylprednisolone in moderate to severe active TED cases with incomplete response to corticosteroid . This drug can also be used as steroid sparing agent in reactivation cases. Mycophenolate mofetil (MMF) is an inhibitor of inosine monophosphate dehydrogenase involved in de novo purine synthesis which is potently cytostatic on both T and B cells.[76] In one single center trial conducted by Ye X et al 174 patients were included with active moderate to severe TED and they were randomized to either 3g IVMP followed by tapering oral prednisolone (60mg/day) or 1 gm daily MMF for 24 weeks. This was observed that the one group with MMF regimen had better overall outcomes at 12 and 24 weeks which included significant reduction in cases of proptosis and diplopia.[77] The proportion of patients with CAS reduction ≥2 was significantly greater in the MMF group at 24 weeks. The study also showed that the incidence of adverse events was more in those who were treated with steroids which was 28% when compared to those treated with MMF in which adverse events were 5%.[78]Thus, it was concluded from the study that MMF was having high efficacy and better safety profile than glucocorticoids in reducing the activity and severity in active, moderate-to-severe TED.[79] However the MINIGO trial showed that the efficacy results were not of the same magnitude as ye x et al study but this study also showed a favorable treatment outcome with MMF.[80,81]

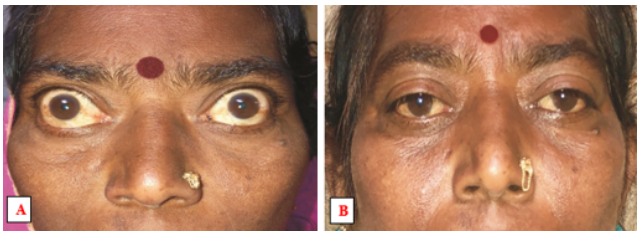


Fig. 5: (**A**) Middle aged female having bilateral both eyelids retraction and (**B**) compete response after corticosteroid therapy.

5.2. Smoking cessation

Cigarette smoking poses greater risk for development and progression of TED because of the oxidative damage it causes. IL-1β and IL-6 expression are upregulated significantly in intraorbital fat from smokers with TED.[82] Smoking cessation can go a long way in reducing further damage.

5.3. Antioxidants

Selenium is a trace mineral having antioxidant and immunomodulatory effects can be used in management of TED. One study was conducted to evaluate the role of Selenium (100 microgram sodium selenite twice per day for six months) as a therapeutic option on euthyroid patients with mild TED. The study showed that selenium-treated patients had a significant improvement in CAS and 61% patients had symptomatic improvement in those who were given the selenium-treatment. Only 7% of patients in the selenium group had disease progression, and selenium was not associated with any adverse effect.[83]

Allopurinol and Nicotinamide may also show improvement in visual acuity, reduction in differential pressure, and improvement in ocular motility in patients with TED , but because of lack of sufficient clinical data to demonstrate efficacy, they are currently not recommended for use in clinical practice.[84]

5.4. Orbital Radiotherapy

Radiation has a nonspecific anti-inflammatory effect; orbit-infiltrating lymphocytes are radiosensitive and vulnerable to OR,[85] and OR may target fibroblasts leading to reduced glycosaminoglycan synthesis and secretion.

Thus, despite OR being a well-tolerated and safe second-line treatment for patients with moderate-to-severe and active GO, OR is less effective than GCs. OR can possibly be used in combination with GCs in such patients whose GO has only partially responded to the first course of IV GCs alone and is still active.[85] The diabetes associated with hypertension and preexisting retinopathy is relative contraindication for OR. Low cumulative dose OR (<10 gray/Gy over 10 weeks) is recommended for active mild to moderate TED patients having diplopia or restricted motility.

5.5. Botulinum Toxin

Botulinum toxin type A (BTA) is neurotoxin which paralyses muscles by acting on motor end plate via inhibiting release of acetylcholine.[86] BTA has partial paralytic effect upon Muller's muscle and levator palpebrae superioris. Due to its ability to interfere with muscle contractions, botulinum toxin A has been studied in GO to decrease the upper eyelid retraction and was seen to be more effective in the inflammatory phase of TED.[87] The effect of BTA treatment is not permanent and this treatment is also not free from complications which besides causing bruising, oedema and other minor local occurrences, it can also lead ptosis (over correction) or diplopia.[86]

5.6. Hyaluronic Acid fillers

Hyaluronic acid can be injected either transcutaneously or transconjunctivally. The filler materials are injected in such a way that they are deposited near eyelid retractors to act properly and in upper eye lid they lengthen it and add weight to it while for lower lid the aim of filter deposition is to lengthen it and provide scaffolding support. Once the filters

are injected there, they last for 6-12 months. Their action can be reversed by injecting hyaluronidases in periocular region if needed. It represents an effective and minimally invasive alternative for eyelid malposition in the active phase of the diseases.

5.7. Biological therapy

Figure 6 showing mechanism of action of various biological therapeutic agents. Rituximab (RTX) is an anti- CD20 chimeric monoclonal antibody which has depleting action on both B lymphocytes (which are in the intermediate stage of maturation) and short-lived plasma cells. Moreover, it also has a blocking action on the B-cell proliferation and maturation[88] and has been used in patients with TED. The previous study results showed significant reduction in Clinical Activity Score (CAS) in patients treated with RTX, along with improvement in proptosis.[89,90] RTX is useful for treating TED at low doses (100mg) with steroid and as second-line steroid-sparing agent based on the kind of requirement[91] or at moderate doses (400mg) when the conventional therapy with steroid and radiotherapy has not shown adequate treatment response or failed.[92]

Tocilizumab is a monoclonal antibody against interleukin-6 receptor. The RCT conducted by perez et al had shown that tocilizumab is effective in reducing orbital inflammation in cases which are steroid-resistant along with a small disease-modifying effect.[93] The results of the study also showed that there was reduction in proptosis in 72% of cases with mean proptosis reduction was 3.92 mm but one patient showed reduction of 7 mm. Further more improvement was also noted in extraocular motility by >5 degree in 83%cases, and resolution of diplopia in primary gaze was seen in 53.9% cases with a minimum follow up of 9 months. Of now tocilizumab are recommended for treating active, severe TED cases refractory to steroid treatment. The adverse effects associated with use of tocilizumab were mostly minor and nonspecific such as tiredness, neutropenia, upper respiratory infection and reversible elevation of liver enzymes namely ALT and AST.[94,95]

Teprotumumab is a fully human monoclonal antibody against IGF-1R. It reduces the expression of IGF-1R and thyroid-stimulating hormone receptor (TSHR) on fibrocytes of Grave's disease patients along with reduced expression of IL-6 and IL-8 mRNA and protein induced by thyroid-stimulating hormone (TSH).[96] A study conducted on patients who had moderate-to-severe TED showed that teprotumumab was more effective than placebo in reducing the Clinical Activity Score (CAS) and improving proptosis.[97–100] This drug has very few adverse effect and one of them is hyperglycemia in patients with diabetes, which can be readily controlled by adjusting the diabetes medication.

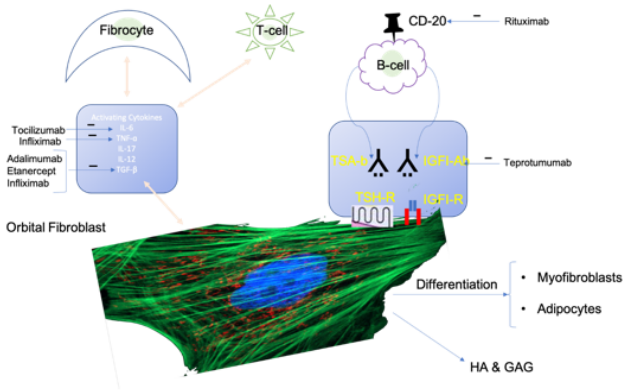


Fig. 6: Diagrammatic representation of mechanism of action of Biological therapy.

TNF specific monoclonal antibodies (infliximab and adalimumab) or TNF receptor-fusion molecule (etanercept) have shown promising usefulness in the treatment of TED.[101,102] Tocilizumab is a recombinant humanized monoclonal antibody against the interleukin-6 receptor, which has also shown effectiveness in small studies and recommended for the treatment of active moderate to severe corticosteroid resistant or intolerant TED.[102]

5.8. Orbital Decompression

Sometimes, enlargement of the bony orbit and fat resection may become necessary to prevent irreversible damage and reverse protrusion of orbital tissue. Indications for surgery are dysthyroid optic neuropathy, corneal breakdown, disfiguring proptosis, high intraocular pressure and pressure sensation. Computer-assisted tomographic imaging (CAT) with navigation markers should be performed before decompression to evaluate bony orbit and paranasal sinuses. At present, the medial and lateral orbital wall and the orbital floor are opened most commonly, while orbital roof removal has been abandoned due to low effect and possible intracranial complications. Surgical incisions for orbital decompression are coronal, upper skin crease, lateral canthus, inferior fornix, sub ciliary, direct via lower lid, transcaruncular, transnasal and transoral.[103] The choice of decompression procedure is based on individual case entity with careful clinical examination and radio imaging study. Orbital fat decompression is the first line of decompression procedure for patients with proptosis that results from expansion of the orbital fat volume. Fat decompression or single orbital wall decompression reduces an average of 2-3 mm of proptosis. Orbital fat in addition to one orbital bone decompression is known as two wall decompression results in greater effect on the reduction of Proptosis.[104,105] Removal of 1 ml of orbital fat is equal to reducing 0.7 mm proptosis.[106] Removal of orbital fat can be performed with endoscopic medial orbital wall decompression to reduce

proptosis; this is not a balanced decompression and risk of development of diplopia.[107] The endoscopic medial orbital wall decompression is done at the level of middle meatus involving medicalization of middle turbinate and ethmoidectomy from anterior to posterior. Orbital apex compression is the extended part of endoscopic medial wall decompression to improve the apical crowding in the cases of dysthyroid optic neuropathy. When the decompression is performed solely to improve the appearance from proptosis, the apex decompression is not needed.[108–113] The preferred techniques are combined ones either removal of medial wall and inferior wall (floor) or balanced decompression involving removal of medial and lateral orbital wall.[114] If you decompress on wall of the bone orbit, there is a chance to cause a greater degree of muscle imbalance.[110] There is Lateral orbital wall decompression with orbital fat excision are known as two wall decompression and indicated for mild to moderate proptosis (< 22 mm), additional medial wall decompression is needed for moderate to severe proptosis (22-25 mm), and 3-wall decompression with removal of the orbital floor for severe exophthalmos (>25 mm).[113] Rim-sparing deep lateral wall decompression is recent trend and produces aesthetic outcome than traditional lateral wall decompression.[114] The complication rate resulting from bone decompression is determined by which wall is removed. The removal of orbital roof is not advocated now days due to fewer effects on proptosis reduction and also causing for significant complications.

In mild cases, intraconal fat removal will suffice. Usually, superior nasal and inferior temporal orbital fat compartments are decompressed.[115]

5.9. Eyelid surgery in TED

Indications for surgical intervention include a significant upper lid retraction of >1 mm, asymmetry of palpebral apertures, or lateral (temporal) flare. For the upper lid, it can be performed via anterior approach (through an eyelid crease incision) or the posterior approach (through the conjunctiva and Müller's muscle).[107] Levator and/or muller muscles recession improves the condition of upper lid retraction that improves the appearance and also to protect the cornea from exposure keratitis.[52,96]

Graded mullerectomy is the preferred approach with 85% success rate for upper lid retraction. Anterior approach (Blepharotomy) is the good option, particularly for tight lids where difficult to evert the eylid over a Desmarres lid retractor or a spacer material is needed to lengthening the upper lid in severe eyelid retraction.[110] If the lid retraction is minimal (2-3 mm), mullerectomy alone is sufficient. Incision of the lateral aspect of levator muscle may require for lateral arching of the lid. Both Mullerectomy and levator muscle recession is the good option for moderate lid retraction (>3mm). Internal approach (transconjunctival) of Müller and levator muscles recession is safe and effective technique in correction of moderate or severe lid retraction in patients with thyroid eye disease. Second surgery may be addressed in 10% cases.[110,115]

Lower lid lengthening is indicated in lower lid retraction. A posterior approach is unanimously employed, and a spacer (auricular cartilage, hard palate mucosa, expanded polyethylene Medpor microplates, autogenous tarsus transplants, porcine acellular dermal matrix and donor sclera or pericardium) is placed between the retractors and tarsus.[116] The effect of lower lid lengthening can be increased by lateral tarsal strip or tarsorrhaphy.[117]

Blepharoplasty is frequently needed as the last step in the functional and cosmetic rehabilitation of GO patients. Redundant skin and fat can be excised, which should be modest in the lower lid to avoid lid retraction or ectropion. Preaponeurotic and subdermal fat should be removed, together with the orbicularis muscle.[118]

5.10. Strabismus Surgery in TED

Muscle fibrosis in GO causes reduced elasticity with preserved or even forced contractility, with impairment of motility, causing vertical or horizontal strabismus with diplopia. Diplopia and compensatory head tilt are the most common indications for eye muscle surgery. The fibrotic ocular muscle(s) is most commonly recessed. Forced duction test (FDT) has to be evaluated before every surgery to prove the fibrotic nature of the squint. The goal of surgery is to restore binocular-single vision in the primary gaze. Residual double vision may persist in secondary and tertiary gazes. Apart from being technically challenging, any restriction is likely to be aggravated if a muscle is shortened, inducing gaze limitation and a smaller field of binocular-single vision. In addition, any recurrence of the disease will result in further restriction. Therefore, muscle resection should be avoided.

5.11. Recent advances in surgical management

Due to the inflammatory nature of TED and resulting unpredictability of results, a staged surgical approach has classically been favored for TED for over three decades: first orbital decompression, then strabismus surgery followed by lid positioning and blepharoplasty[118]. Of late, 40 patients were treated with combined orbital decompression and aesthetic eyelid surgery, which resulted in high patient satisfaction and a reduced number of operations.[119]

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None.

7. Conflicts of interest

There are no conflicts of interest.

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