

Causes of proptosis and Thyroid Ophthalmopathy

Department of Ophthalmology

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Acknowledgement

- UptoDate: Graves' orbitopathy: Diagnosis and Treatment.
- Cummings Otolaryngology. Girod, Douglas A.; Wemer, Richard D.; Larsen, Christopher G.. Published January 1, 2015. © 2015.
- Endocrinology : Adult and Paediatric. Burch, Henry B.; Bahn, Rebecca S.. Published January 1, 2016. © 2016.
- Some of the images used were taken from eyetext.net

Learning Objectives

- **At the end of this class the students shall be able to :**
- Enumerate the common causes of proptosis
- Understand the pathogenesis and clinical features of thyroid eye disease.
- Enumerate and elicit the common eye signs of thyroid ophthalmopathy.
- Have a basic understanding of principles of management of the disease.

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Question

- A 44-year-old female patient presents with bilateral protrusion of the eyeball along with retraction of the eyelids and lid lag on downgaze. What is her most likely diagnosis?
- a. Grave's disease
- b. Orbital pseudotumor
- c. Orbital cellulitis
- d. Orbital varices

Proptosis

- Forward displacement or protrusion of eyeball.
- Protrusion of globe >21mm or atleast 2mm asymmetry between the two eyes is abnormal.
- Measured by Hertel's Exophthalmometer
- Differentiate from pseudoproptosis or apparent eyeball protrusion



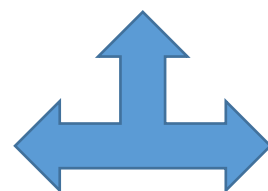
High myopia
Lid retraction



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Proptosis

- Axial and non-axial(Abaxial)
- Unilateral and Bilateral proptosis



Congenital: **Dermoid Cyst**
Traumatic: **Orbital hemorrhage**
Inflammatory: **Orbital cellulitis**
Orbital psudotumour
Vascular: **Orbital varix**
Cystic: Orbital **cysticercosis**
Tumours of the orbit

Inflammation: **Thyroid orbitopathy**
Sarcoidosis
Neoplasia: **Lymphoma**
Leukaemia
Vascular malformation:
Arterio-venous **shunts**
Lacrimal lesions: **Sjogren's syndrome**

Introduction of Thyroid eye disease

- Thyroid eye disease is an **autoimmune** disease producing symptoms related to **inflammation**, accumulation of fluid in the orbit and also to adipogenesis raising intra-orbital pressure.
- **Synonyms**
 - Graves' ophthalmopathy/orbitopathy (GO)
 - Thyroid eye disease (TED)
 - Thyroid associated ophthalmopathy (TAO)
 - Dysthyroid ophthalmopathy

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Epidemiology

- Prevalence of thyroid ophthalmopathy = 0.4%
- **Women > Men**
- But severity greater in men
- Bimodal age distribution – **Peak incidence in fourth and sixth decades of life**
- May be exacerbated by stress and smoking
- **Most common cause of exophthalmos**
- >50% of cases with Graves' disease have eye involvement

Etiology

- **Graves'** hyperthyroidism (90%)
- Hypothyroid **Hashimoto's** thyroiditis
- Euthyroid subjects with no current or past evidence of thyroid hyper or hypofunction (so called **euthyroid Graves'** disease).
- In patients with Grave's disease, eye signs may precede, coincide with or follow the hyperthyroidism

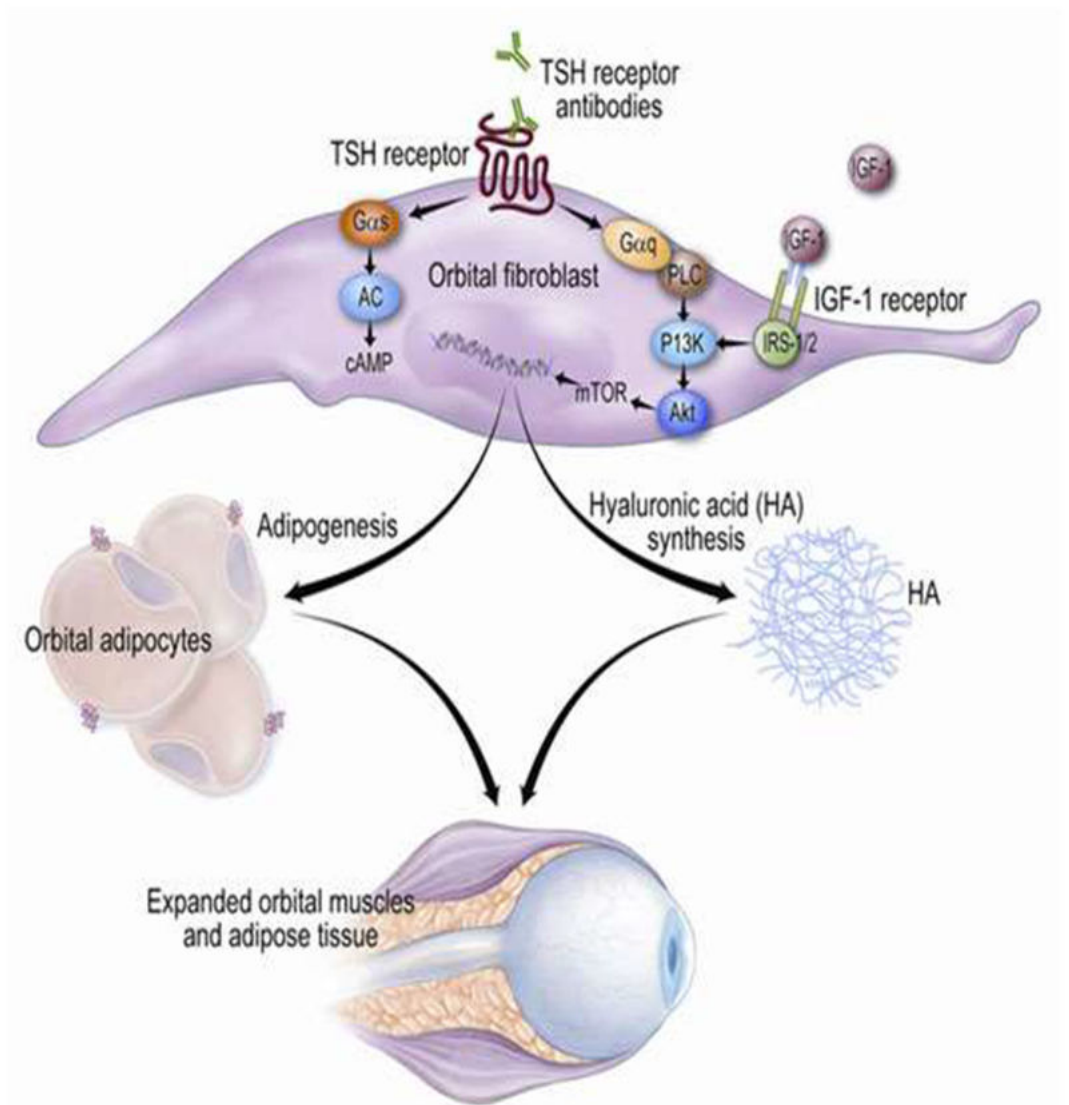
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Risk factors

- Smoking (strongest modifiable risk factor)
- Family history
- Monozygotic twins

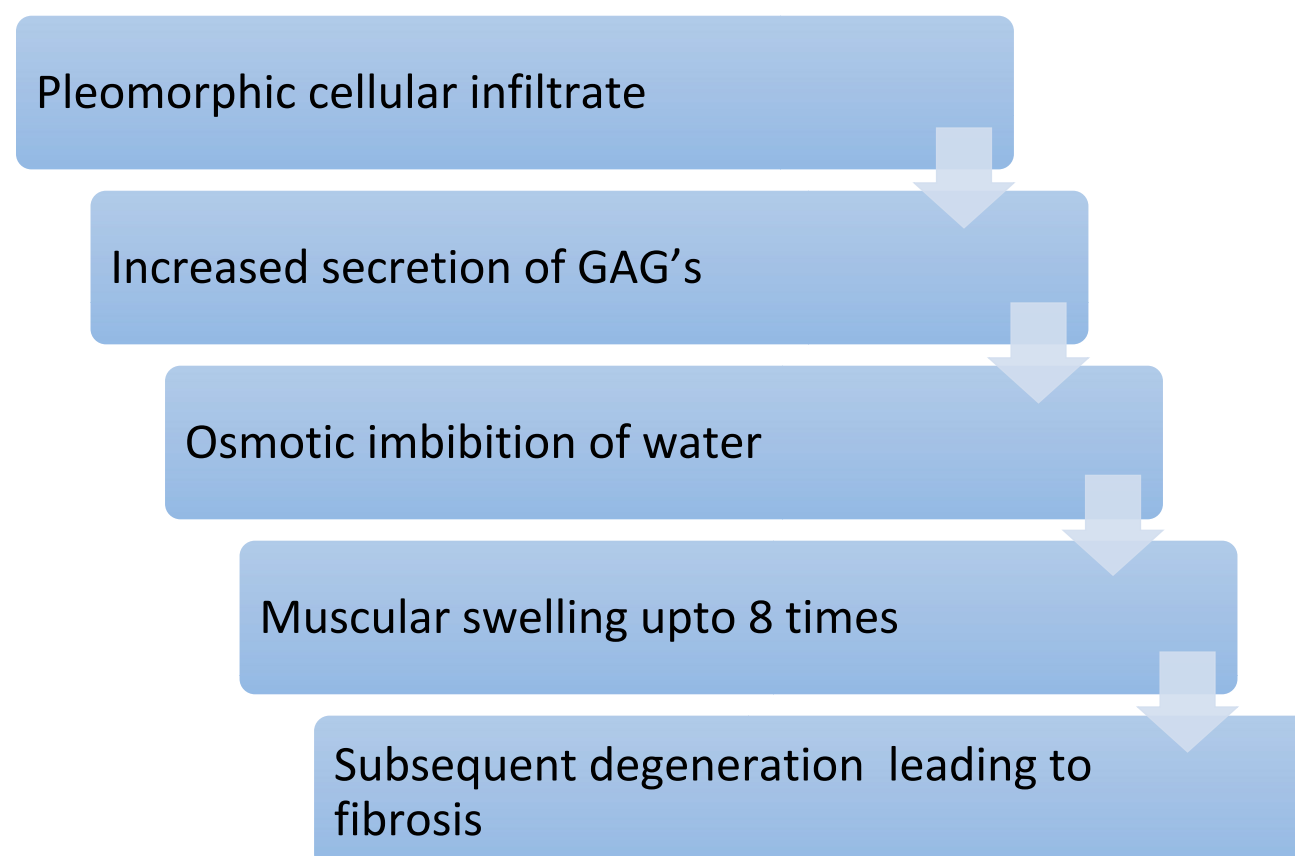
Pathogenesis

- **Autoimmune process** manifesting as:
- Extraocular muscle myositis
- T-cell inflammatory infiltrate
- Fibroblast proliferation
- Glycosaminoglycan overproduction
- **Increase in soft tissue mass** within bony orbit due to extraocular muscle enlargement, increased orbital fat and connective tissue
- Later in disease, inflammatory infiltrate replaced by widespread **fibrosis**
- “Inactive” phase occurs after 8 months to 3 years

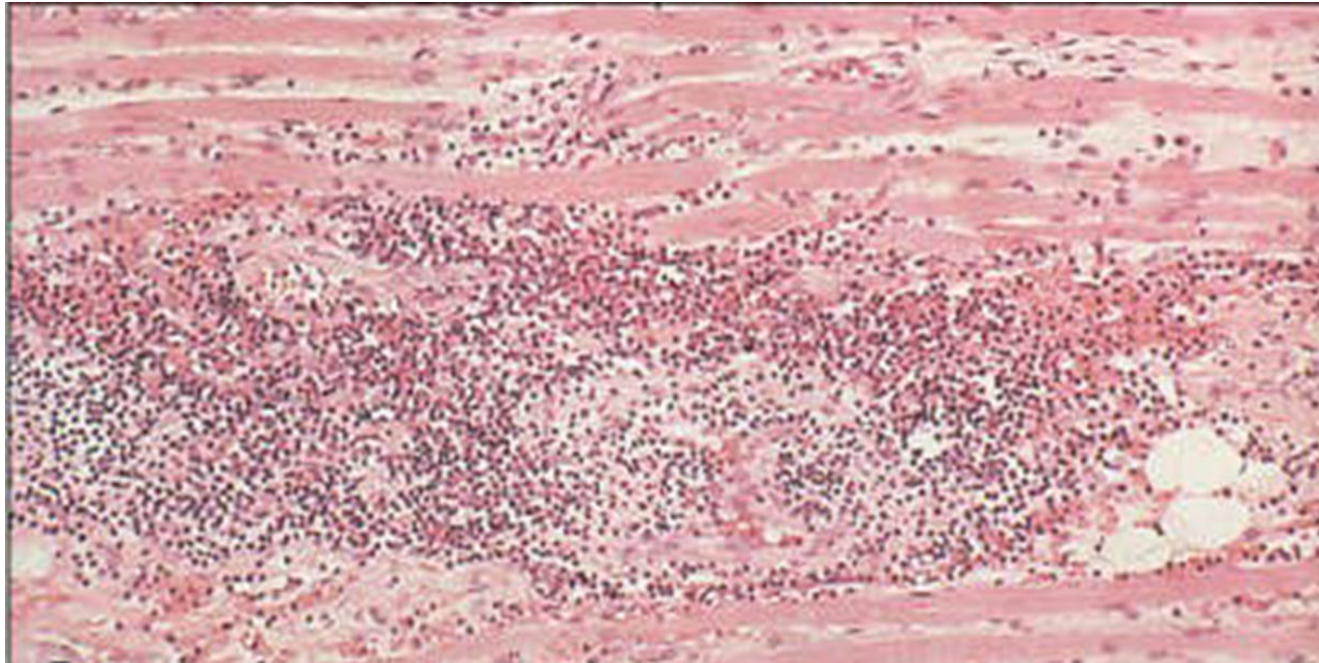


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Pathogenesis



Histology

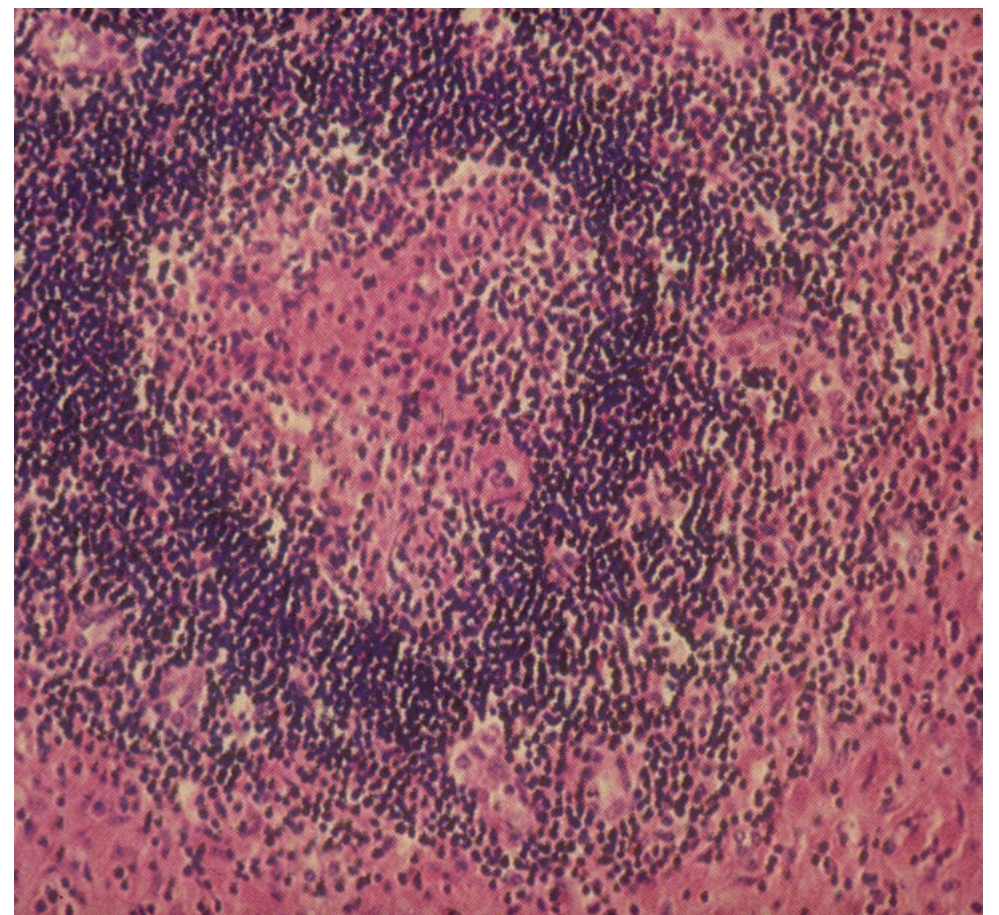


Fluid and inflammatory cells separate the muscle bundles of the extraocular muscles

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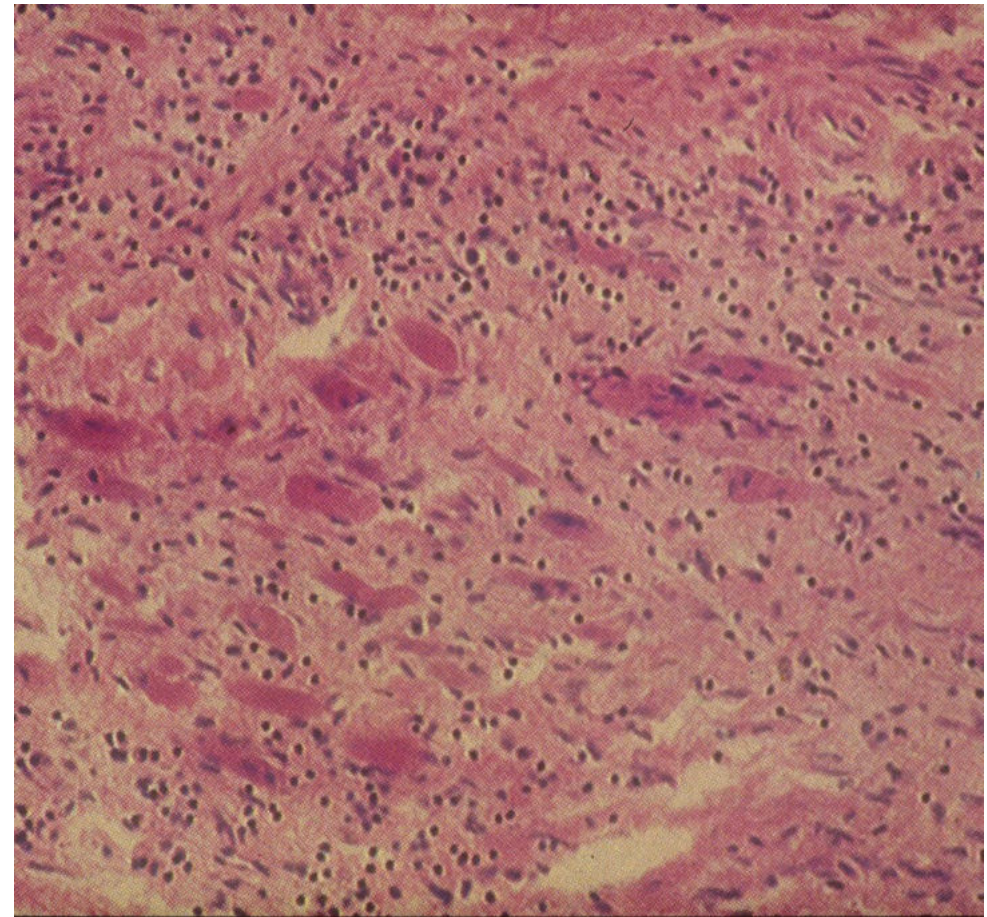
Histology

Lymphocytes, plasma cells, macrophages and mast cells infiltrate extraocular muscles, fat and connective tissue



Histology

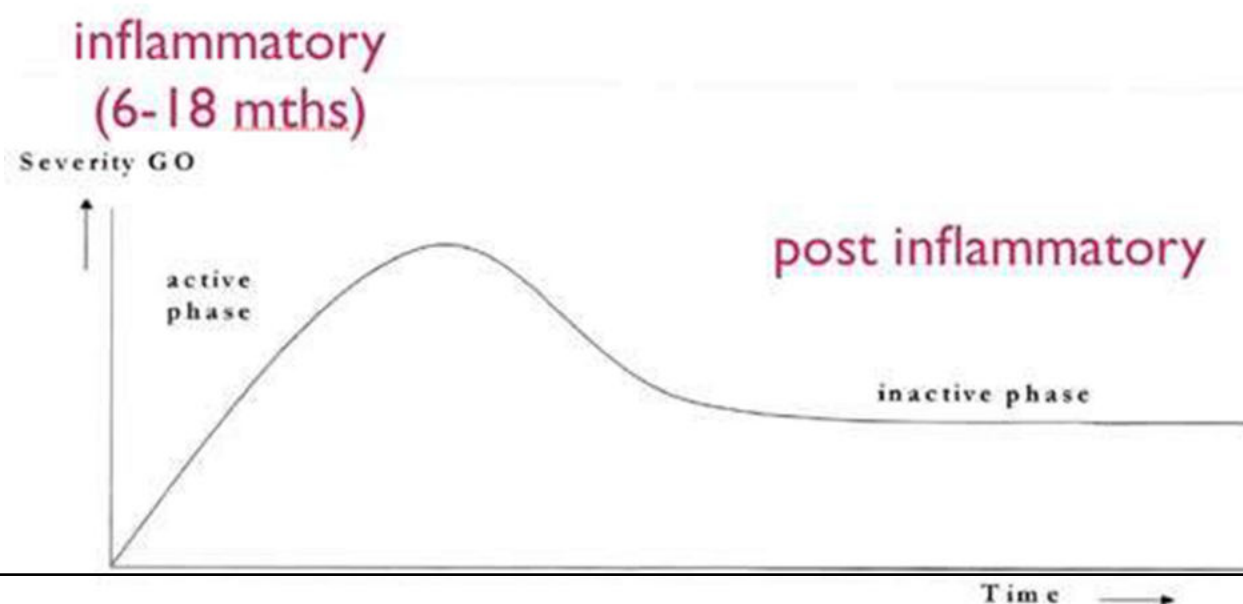
Degeneration
of muscle fibres
Leads to fibrosis
of the involved
muscle



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Natural History of Thyroid Eye Disease

- Progressive phase lasting for up to 18 months
- Stable (inactive) phase



Course of disease

- **Inflammatory/active phase**



- **Fibrotic/inactive phase**



Clinical course of orbital disease proceeds independently of thyroid gland dysfunction and treatment

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Symptoms

- Foreign body sensation
- Epiphora (tearing)
- Photophobia
- Bulging of eyes
- Puffiness of eye lids
- Diplopia
- Visual loss

Signs

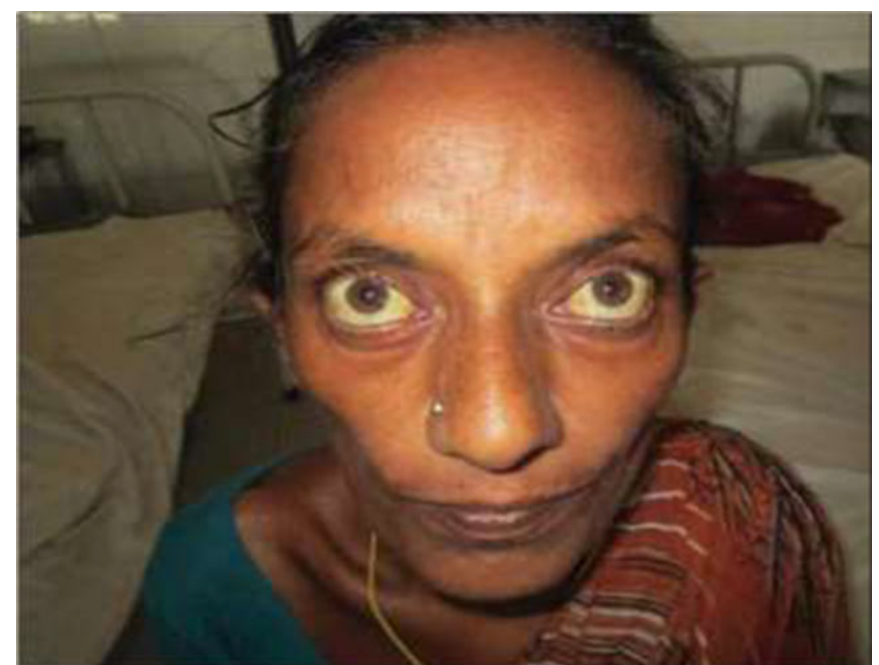
- Eyelid Retraction
- Proptosis
- Restrictive Myopathy
- Soft Tissue Involvement
 - Conjunctival hyperaemia, lid oedema and chemosis
- Optic Neuropathy



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Clinical signs in TED

- **Facial signs**
- **Joffroy's sign**-absent creases in the forehead on superior gaze



Clinical eye lid signs in TED

- Kocher's sign- staring appearance
- **Von Graefe's sign**- lid lag on downgaze
- Dalrymple's sign- lid retraction
- Stellwag's sign- incomplete & infrequent blinking
- **Enroth 's sign**- edema of lower lid
- Griffith's sign- lower lid lag on upgaze



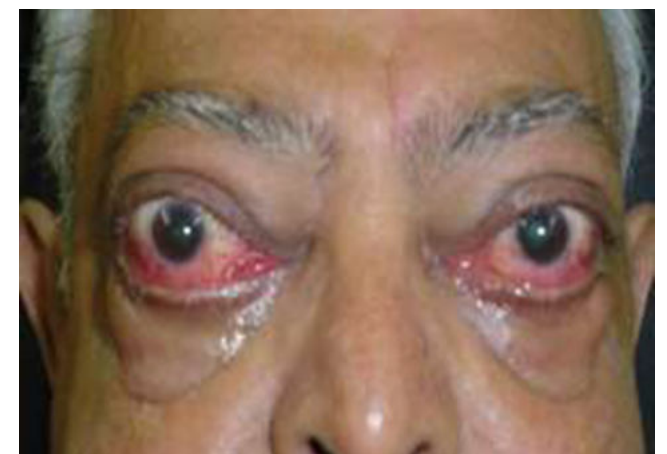
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Soft Tissue Inflammation

- Often the **earliest sign**.

Consists of

- periorbital edema
- conjunctival hyperemia
- chemosis



Eyelid retraction

- Also called Dalrymple's sign.
- Normally, upper eyelid- 2mm below limbus
- Lower eyelid-inferior limbus
- When retraction occurs, the sclera (white) can be seen

Occurs due to :

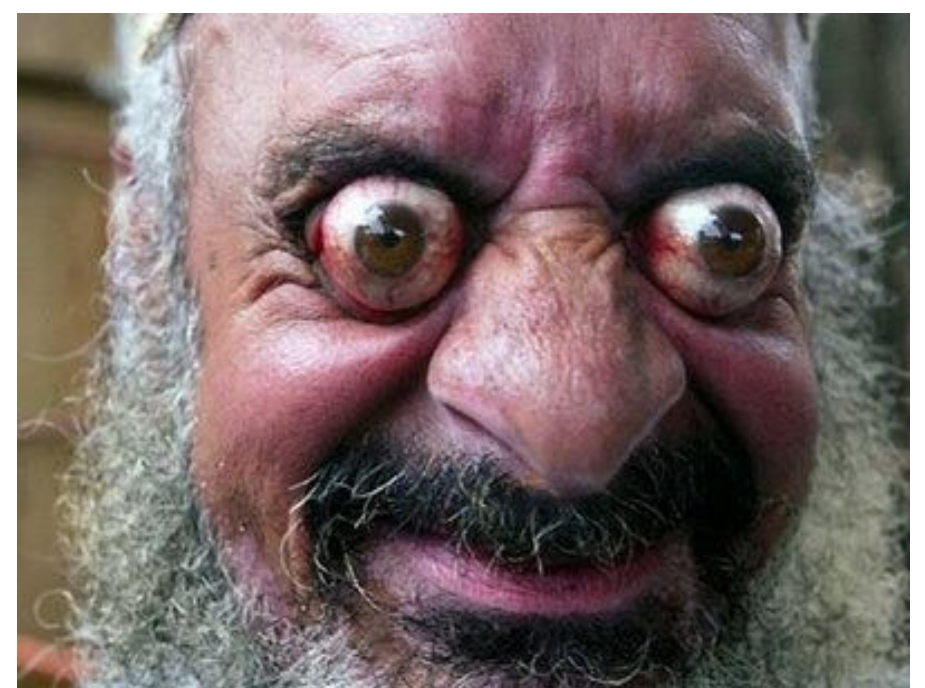
- Increased **sympathetic stimulation of Müller's** muscle by thyroid hormone
- Overaction of the levator muscle contracting against a tight inferior rectus



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Proptosis

- Usually (90%) bilateral
- Thyroid eye disease is the most common cause of unilateral and bilateral proptosis in adults
- Axial
- Resulting from enlargement of the extraocular muscles and adipose tissue, as well as orbital fat
- Infiltration of orbital tissues by GAGs and leukocytes



Proptosis

- It does not respond to hyperthyroidism treatment
- Is permanent in 70% of cases.
- Severe proptosis prevents adequate lid closure
- May lead to **severe exposure keratopathy** and **corneal ulceration**.

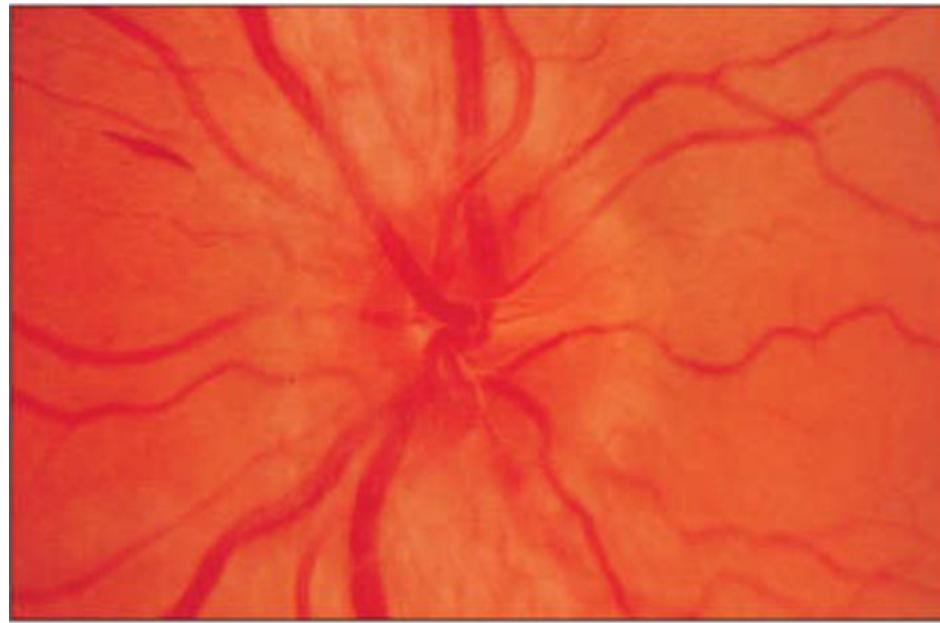


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Restrictive Myopathy

- Eye movements are restricted due to oedema in extraocular muscles during infiltrative stage and subsequent fibrosis.
- Despite expansion of the extraocular muscles , the muscle fibres themselves are normal.
- **IR>MR>SR>LR**
- Pressure exerted by a fibrotic inferior rectus muscle on the globe may cause a spike in intraocular pressure during upgaze.

Dysthyroid Optic Neuropathy (DON)



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Optic neuropathy as result of optic nerve compression from enlargement of extraocular muscles

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WERNER'S CLASSIFICATION - NOSPECS

- Class 0: **N**o signs or symptoms
- Class 1: **O**nly signs (lid retraction, stare \pm lid lag)
- Class 2: **S**oft tissue involvement
- Class 3: **P**roptosis
- Class 4: **E**xtraocular muscle involvement
- Class 5: **C**orneal involvement
- Class 6: **S**ight loss (optic nerve involvement)

EUGOGO classification

- **Mild** : eyelid swelling , lid retraction, proptosis
- **Moderate-Severe** : Active disease (EOM dysfunction, diplopia , proptosis >25 mm)
- **Very severe** : Compressive Optic Neuropathy , Corneal exposure (needs emergent surgery)

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VISA classification

- **V** (Vision) , **I** (inflammation), **S** (Strabismus) , **A** (Appearance)
- Vision/CON
- Inflammation/Congestion : based on documented change of inflammation rather than absolute value
- Strabismus/Motility : measuring ductions and alignments
- Appearance/Exposure
- Score of 5 or more —> Active disease or progression (Consider Steroids)

Differential Diagnosis

- Orbital tumors (primary or metastatic)
- Orbital pseudotumor
- Wegener's granulomatosis
- Orbital infection
- Carotid-cavernous sinus fistula

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Diagnosis

- **Characteristic eye findings**
- **Thyroid dysfunction**
- **Imaging**

Blood investigations

- Highly sensitive & specific -- **T4(thyroxine) + TSH or serum TSH**
- If eye findings associates with euthyroid Graves' disease –
- **Thyroid peroxidase antibody**
- **Antibody to thyroglobulin**
- Others
- **Free T4 index**
- **Thyroid-stimulating immunoglobulin**
- **Antithyroid antibodies**
- **Serum T3**

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Radiological Evaluation

- Usually employed if cause of exophthalmos is unclear (ie. normal thyroid lab studies, or history/physical examination inconsistent with thyroid disease)
- Also to determine optic nerve involvement if not obvious by fundoscopic examination.
- Distinct **sparing of muscle tendons** in thyroid ophthalmopathy.

Radiological Evaluation

- **CT scan** is currently the imaging study of choice.
- MRI is sensitive for showing compression of the optic nerve.
- Neuroimaging usually reveals
- **Thick muscle belly with tendon sparing**
- Usually IR & MR
- Bilateral muscle enlargement is the norm
- Unilateral cases usually represent asymmetric involvement rather than normality of the less involved side

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Axial and coronal C.T. scan in Thyroid eye disease



- Non-contrast enhanced coronal orbital CT scan most helpful to assess size of extraocular muscles.



A



B

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A

Axial CT of orbits
demonstrating
medial rectus
enlargement

Management

- **T** – Tobacco abstinence
- **E** – Euthyroidism
- **A** – Artificial tears
- **R** – Referral
- **S** – Self help groups

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Medical Management of Hyperthyroidism

- Anti-thyroid drugs : thionoamides (PTU) , carbimazole , methimazole.
- Thionamides inhibit synthesis of thyroid hormones.
- Need 6-8 weeks to achieve euthyroid state
- Side effects of anti-thyroid drugs
Skin rash , urticarial , arthralgia , fever

Treatment of mild Thyroid eye disease

Signs / Symptoms	Management Options
Peri-orbital oedema	Elevation head of the bed, anti-diuretics
Dryness, foreign body sensation	Artificial eye drops and ointment
Lagophthalmos	Nocturnal eye taping, eyes shield
Eyelid retraction	Topical Guanethidine or β -blockers eye drops
Diplopia	Prisms
Photophobia	Sunglasses

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Symptomatic treatment

- Artificial tears
- Eye shades
- Raise head of bed at night
- Diplopia can be managed with prism glasses
- Eventually may require strabismus surgery
- Conserve useful vision
- Minimize amount of exposed cornea
- May require lid surgery
- Treat optic neuropathy

Selenium

- 200 microgram/day for 6 months
- For Mild disease
- Antioxidant effect
- Immunomodulatory effect : reduce thyroid autoantibodies
- Reduces severity of disease and improve quality of life

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Corticosteroids

- Intravenous , Oral
- IV pulses are more effective and have less side effects
- IV dose (max 8 grams) : 500 mg weekly for 6 weeks and then 250 mg weekly for 6 weeks
- Relapse is common (20%)
- Steroid response is evident usually 2-4 weeks later
- Moderate to severe TED : 71% respond to IV steroid vs 51% with oral
- **IV steroids for compressive Optic Neuropathy**

Rituximab

- Chimeric mono-clonal antibody targets CD20
- CD20 is expressed on more than 95% of B cells and plasma cells
- RTX depletes 95% of mature B cells , blocks Ab production , and decreases inflammatory cytokine release
- For **steroid-refractory disease**
- Side effects : Allergic reaction (mild) PML (severe)

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Orbital Radiation

- Mechanism : lymphocyte sterilization, destruction of tissue monocytes
- 20 Gy in 10 divided sessions over 2 weeks
- May have a role in patients with TED who have restricted ocular motility or active disease
- Some studies have shown benefit (controversial)
- More suited for patients > 35 years of age
- Contra-indicated in pre-existing retinopathy (diabetes , hypertensive)

Botulinum Toxin

- Neurotoxin , inhibits acetylcholine release
- For upper lid retraction (transconjunctival , transcutaneous route)
- Effect on Muller's muscle and LPS
- Side effects of Botox : bruising , ptosis and diplopia

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Orbital Decompression for TED

- Decompression **usually in stable phase** of disease.
- Indications
- compressive optic neuropathy
- severe exposure keratopathy
- Post-operative complications (diplopia, vision loss)
- Outcome is variable : degree of fibrosis , fat expansion , bone available, duration of optic neuropathy.
- **Decompression —> Muscle Surgery —> Lid surgery**

Strabismus Surgery for TED

- In the stable phase with **stable alignments for 6 months**
- Aim is **single binocular vision in primary and reading position**
- Typically involves release of the restricted muscle by **recession** rather than resection
- Conjunctival dissection is challenging
- Use of **adjustable sutures** is strongly recommended due to the variability in fibrosis, resulting in unpredictable results.
- Oblique surgery can increase area of single binocular vision

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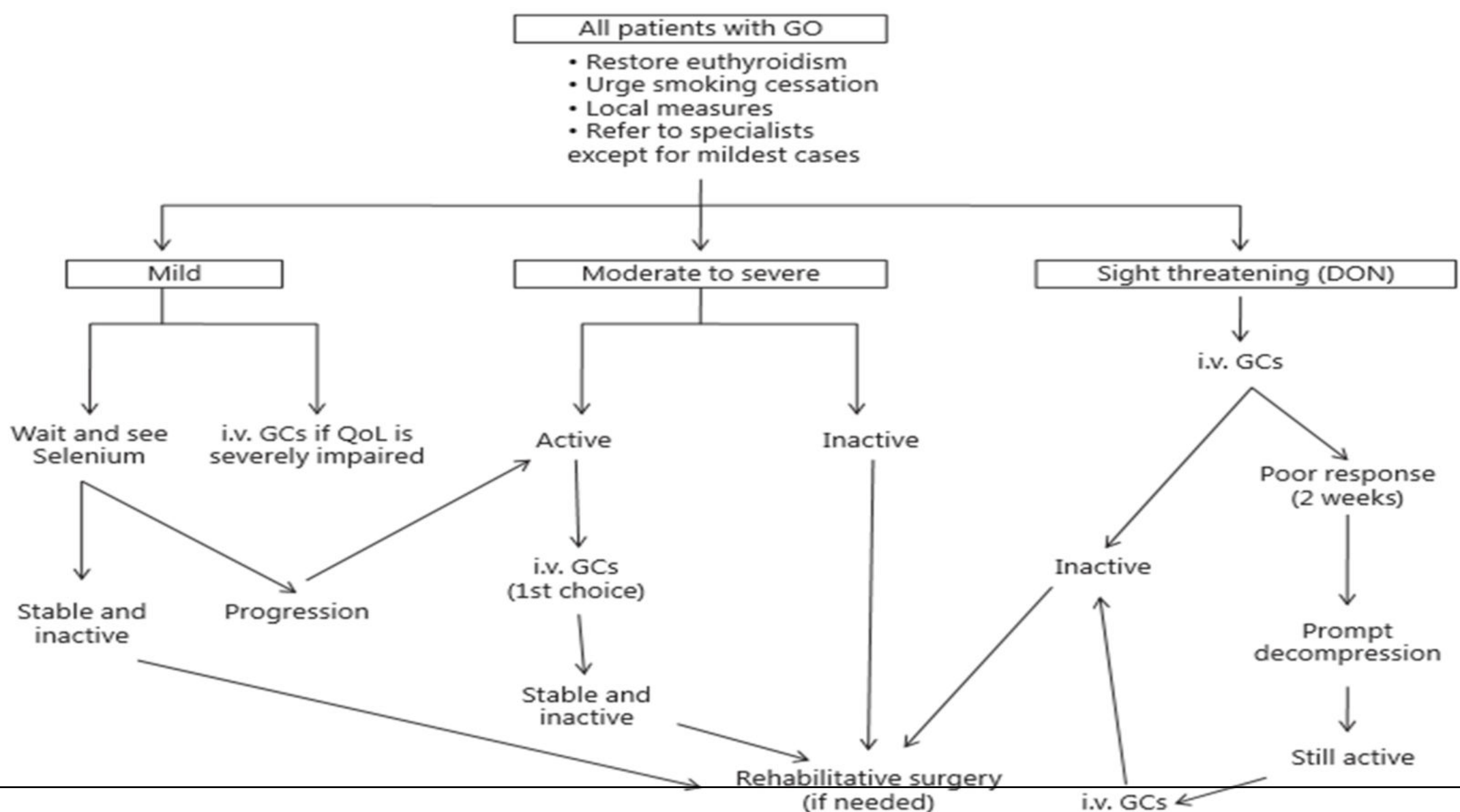
Eye lid surgery

- The most common indication for lid surgery is upper lid retraction.
- Graded Muller's and levator aponeurosis weakening.
- Lower lid lengthening is indicated in lower lid retraction.

Psychological Impact of TED

- Disfigurement/altered facial appearance
- Misinterpretation as hostile or angry
- Almost 50% of TED suffer depression and/or anxiety
- 90% of TED have appearance concerns (young females)
- 44% have self-confidence issues
- Multidisciplinary approach (psychiatric included)
- Support groups

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Conclusion

- Activation of thyrotropin receptor on orbital fibroblast by circulating autoantibodies plays a primary role in development of thyroid ophthalmopathy.
- Management is based on accurate assessment of both severity and activity of disease.
- Immunosuppressive therapy is reserved for patients with clinically active moderate to severe disease

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Question

- Which of the following statement is correct regarding Thyroid eye disease?
- a. It cannot be present in the euthyroid patient.
- b. The earliest sign is loss of sight due to optic neuropathy
- c. The lateral rectus muscle is least commonly involved.
- d. There is only unilateral involvement in the disease.

Thank You