Thyroid associated orbitopathy (or Graves' orbitopathy)

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Introduction

- Most common extrathyroidal manifestation of Graves
- an auto-immune entity
- Can also occur in
  - less frequently occur in patients with Hashimoto's thyroiditis
  - without thyroid abnormalities (so-called Euthyroid Graves' disease)
- Women > Men
- **Cigarette smoking, thyroid dysfunction, and in few cases radioiodine therapy for Graves' hyperthyroidism can cause GO**

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Smoking and GO

- Smoking can predispose
- In **children who are smokers or passive smokers it can cause GO**
- Mechanisms whereby smoking may affect the development and course of GO are unclear
- There is increase in orbital connective tissue and increased adipogenesis and hyaluronic acid production in smokers

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RI therapy and GO

- Radioiodine therapy for Graves' hyperthyroidism is associated with GO progression in about 15% of cases, although this effect may be transient
- Seen in
  - Patients who already have GO prior to radioiodine therapy,
  - Smoker
  - Who have high TRAb levels
  - whose post-radioiodine hypothyroidism is not promptly corrected by L-thyroxine replacement therapy
- Lower doses of oral prednisone (0.2 mg/Kg bw) for 6 weeks are as effective in preventing RAI-associated progression of GO

Risk factor of GO	Preventive measure
Cigarette smoking	Refrain from smoking
Hyperthyroidism	Restore euthyroidism by antithyroid drugs and/or obtain a permanent control by thyroid ablation (thyroidectomy, radioiodine, both)
Hypothyroidism	Restore euthyroidism by L-thyroxine replacement therapy
Radioiodine therapy for hyperthyroidism	Give oral prednisone concomitantly with radioiodine administration. Avoid leaving the patient with untreated post-radioiodine hypothyroidism
High TSH-receptor antibody levels	Control hyperthyroidism as soon as possible
Oxidative stress	Give a 6-month selenium course in mild GO

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Pathogenesis

- Autoimmune inflammatory disorder
- Triggered by the migration of **autoreactive T-helper cells, CD4+ T cells into the orbit**
- Less extend CD8+ T cells, B cells, fibrocytes, mast cells, and macrophages are also involved
- **Orbital fibroblasts** are the main target for this cells
- Fibroblasts proliferate, may differentiate into myofibroblasts and adipocytes, **accumulate and secrete hyaluronic acid (HA)**
- HA attracts water and causes edema of the extraocular muscles and orbital tissue
- They may synthesize and secrete chemoattractants (interleukin-16, RANTES, CXCL10) and a number of cytokines (interleukins) etc

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Role of TSH Receptors

- The TSH receptor (TSH-R), the ultimate cause of hyperthyroidism due to Graves' disease
- It also have a role in GO
- **TSH-R expression is found in orbital tissue of GO patients, in molecular levels (mRNA and Protein levels)**
- **This causes fibroblast , lymphoblast, macrophages stimulation**
- But this TSH-R are expressed normally also in orbital tissues in small quantity, and also in many other tissues not involved in Graves' disease and orbitopathy
- TSH Receptors are blocking type and stimulating type.
- Blocking type can cause hypothyroid state and stimulating type (commonly seen) causes hyperthyroidism

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TRAb are independent risk factors for GO and can help to predict severity and outcome of eye disease

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IGF-1 receptor and GO

- Increased IGF-1 receptor levels are found in orbital fibroblasts as well as in B and T lymphocytes from **few** Graves' patient
- But IGF-I Receptors are also involved in other autoimmune diseases, such as rheumatoid arthritis

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Other autoantibodies that may be found

- Several Eye Muscle Antigens,
- Acetylcholine Receptor,
- Thyroperoxidase,
- Thyroglobulin,
- Alpha-fodrin,

- **Their true role uncertain**

Clinical manifestation

- Clinical manifestations of GO IS MAINLY DUE TO orbital space related ISSUES
- Orbital tissue are infiltrated by inflammatory cells, including lymphocytes, mast cells, and macrophages
- Increase in **retroocular fibroadipose tissue and swelling of extraocular muscles**
- increased production of glycosaminoglycans which causes edematous changes both in the connective tissue and the muscles

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Effects of GO

- Forward displacement of the globe (proptosis or exophthalmos)
- Severe proptosis can cause subluxation of the eye may occur.
- Incomplete eyelid closure (lagophthalmos)
- Lagophthalmos and Proptosis is responsible for corneal exposure keratopathy
- usually measured by Hertel exophthalmometer;
- normal values are usually less than 20 mm. More than 21 is proptosis

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IOP

- Increase intraorbital pressure
- Particularly in upward gaze
- but this rarely progresses to true glaucoma

EOM

- Extraocular muscle dysfunction causing **diplopia and/or strabismus**
- It can be
  - intermittent (i.e., present only when fatigued or when first waking),
  - inconstant (i.e., present only at extremes of gaze),
  - constant (i.e., present also in reading positions and primary gaze);
- Objective assessment is done by **measurement of duction in degrees**

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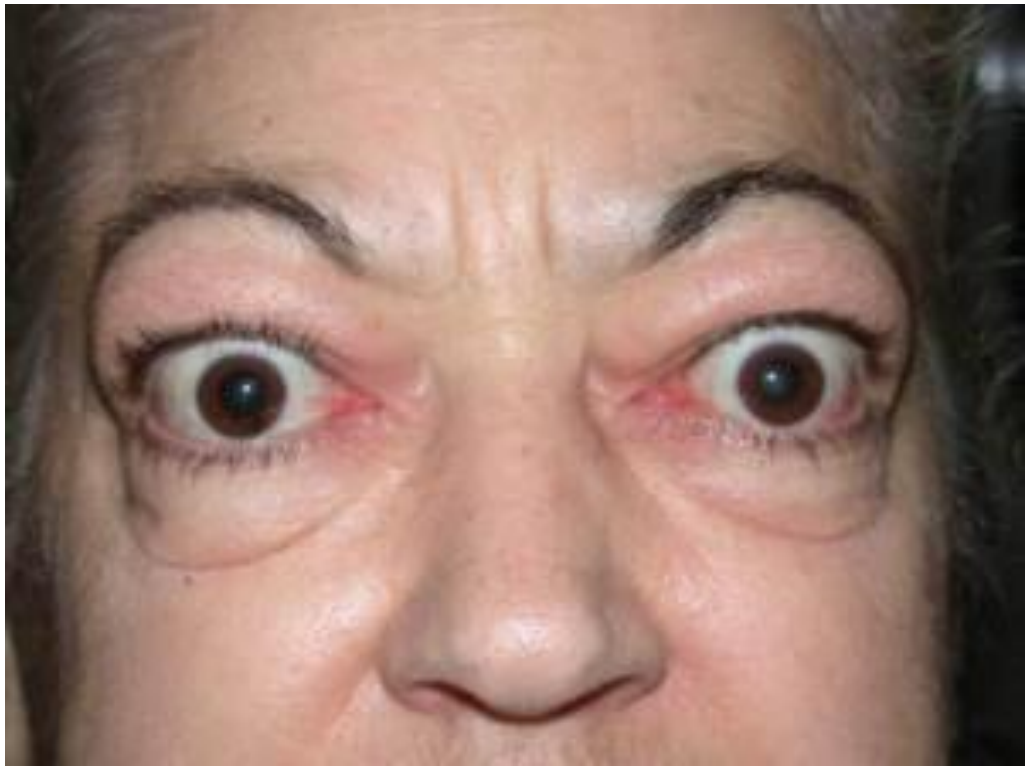
Soft tissue changes

- **Soft tissue changes are**
  - **eyelid edema and periorbital swelling,**
  - **eyelid erythema,**
  - **conjunctival hyperemia and chemosis,**
  - **inflammation of the caruncle or plica**
- Orbital inflammation and related anatomical changes may cause venous and lymphatic congestion that contribute to periorbital edema and chemosis.



Moderately severe GO. Periorbital swelling, injection of conjunctival vessels, proptosis, marked lid retraction, and proptosis.

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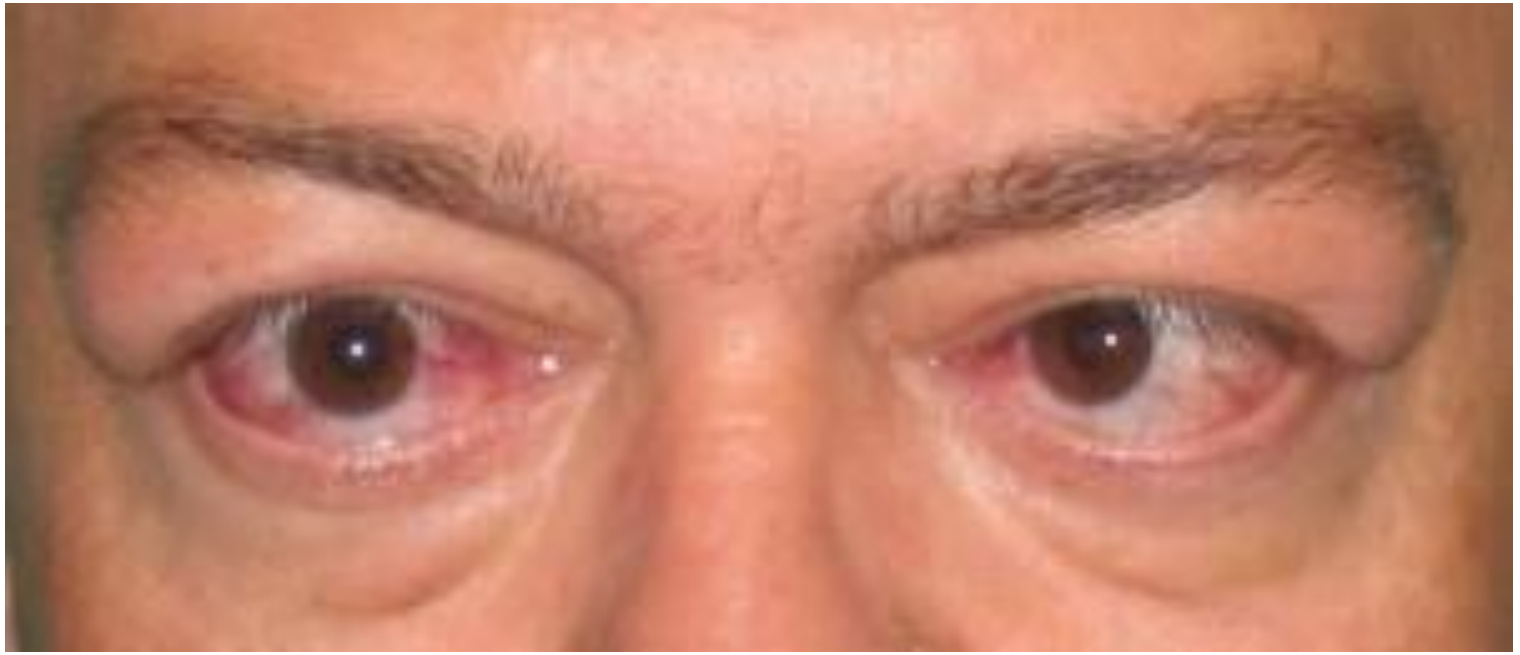

Moderately severe GO. Note marked periorbital swelling, conjunctival hyperemia, esotropia (strabismus) in the left eye.

moderately severe GO. Note the superior eyelid edema, mild conjunctival vessel injection, marked proptosis, and marked upper lid retraction.

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Dysthyroid optic neuropathy

- Reason :
  - Mainly due to - Enlarged muscle volume may cause optic nerve compression
  - optic nerve stretching in cases of marked proptosis or eye subluxation
- It is more in orbital apex
- It causes sight loss
- Dysthyroid ON is more common if the **orbital septum is tight and proptosis is minimal**
- **Clinically**
  - Pupillary responses
  - Reduced visual acuity,
  - abnormal color vision test, contrast sensitivity,
  - Fundoscopy showing disc swelling,
  - Perimetry changes
  - visual-evoked potentials abnormality

Severe GO.

marked periorbital swelling, palpebral hyperemia, conjunctival hyperemia, proptosis (particularly in the left eye), caruncle edema.

Eye motility was markedly reduced, lagophthalmos was present, there were two corneal ulcers in the left eye, and corneal punctate staining in the right eye, reduced visual acuity in the left eye (5/10).

CT scan showed enlargement of extraocular muscles (particularly medial rectus and inferior rectus) in both eyes, but no relevant compression of the optic nerve at the orbit apex.

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Late cases

- With time inflammation subsides
- But the muscle fatty degeneration and fibrosis may contribute to further extraocular muscle restriction and strabismus
- At this stage, it can be corrected only be corrected by surgery.

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Basic NOSPECS Classification of eye changes of Graves' disease

- N = No symptoms or signs
- O = Only signs
- S = Soft tissue involvement
- P = Proptosis
- E = Extraocular muscle involvement
- C = Corneal involvement
- S = Sight loss due to optic nerve compression

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Modified NOSPECS Classification

Class		
	Grade	Symptoms and Signs
0	**No symptoms or signs**	
1	**Only signs (upper lid retraction, without lid lag or proptosis)**	
2	**Soft tissue involvement with symptoms (excess lacrimation, sandy sensation, retrobulbar discomfort, and photophobia, but not diplopia);objective signs as follows:**	
	0	absent
	a	minimal (edema of conjunctivae and lids, conjunctival injection, and fullness of lids, often with orbital fat extrusion, palpable lacrimal glands, or swollen extraocular muscles beneath lower lids)
	b	Moderate (above plus chemosis, lagophthalmos lid fullness)
	c	marked

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3	**Proptosis associated with classes 2 to 6 only (specify if inequality of 3 mm or more between eyes, or if progression of 3 mm or more under observation)**	
	0	absent (20 mm or less)
	a	minimal (21-23 mm)
	b	moderate (24-27 mm)
	c	marked (28 mm or more)

4	**Extraocular muscle involvement (usually with diplopia)**	
	0	absent
	a	minimal (limitation of motion, evident at extremes of gaze in one or more directions)
	b	moderate (evident restriction of motion without fixation of position)
	c	marked (fixation of position of a globe or globes)

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5	**Corneal involvement (primarily due to lagophthalmos)**	
	0	absent
	a	minimal (stippling of cornea)
	b	moderate (ulceration)
	c	marked (clouding, necrosis, perforation)

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6	**Sight loss (due to optic nerve involvement)**	
	0	absent
	a	minimal (disc pallor or choking, or visual field defect, vision 20/20 to 20/60)
	b	moderate (disc pallor or choking, or visual field defect, vision 20/70 to 20/200)
	c	marked (blindness, i.e., failure to perceive light; vision less than 20/200)

Severity of GO

EUGOGO definition- European Group on Graves' Orbitopathy

- **Mild, Mod-severe, Sight threatening**
- Assessment of severity is to decide on whether to be
  - **Treated by aggressive treatments (either medical or surgical) or**
  - **Simply by local or**
  - **General supportive measures**

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Mild GO - (one or more of below)

- **Minor Lid Retraction (<2 Mm),**
- **Mild Soft Tissue Involvement,**
- **Exophthalmos <3 Mm Above Normal For Race And Gender,**
- **Transient Or No Diplopia, And Corneal Exposure;**

The above features usually have a minor impact on daily life

No need immunosuppression

Only General measures needed

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Moderate-to-severe GO

one or more of the following

- **lid retraction ≥2 mm,**
- **moderate or severe soft tissue involvement,**
- **exophthalmos ≥3 mm above normal for race and gender,**
- **inconstant or constant diplopia;**

- Patients in this category have an impact on daily life

- **They need immunosuppression (if GO is active) or**
- **surgical intervention (if GO is inactive**)

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Sight-threatening GO

- Dysthyroid optic neuropathy (DON) or corneal breakdown
- They need immediate intervention

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GO -activity

- **Active Phase-** progressive exacerbation of ocular manifestations
- **Plateau phase**
- **Spontaneous Partial Remission**
- **Inactive phase (burnt-out GO)** –
  - Only residual ocular manifestations are present (e.g., proptosis, strabismus due to muscle fibrotic changes),
  - Inflammation has subsided
  - Unlikely that it may flare up.
- **It takes between 6 months and two years for reaching inactive phase**
- **In active phase or if inflammation present they respond to** immunosuppressive treatments
- **In Burnt out phase immunosuppressive have no role**

Assessment of GO activity,

- **Clinical Activity Score (CAS)- Best**

- **Other tools are: -- not accurate**
  - Short Duration Of Treatment (<18 Months)
  - Positivity Of Octreoscan,
  - Decreased Extraocular Muscle Reflectivity At Orbital Ultrasound,
  - Prolonged T2 Relaxation Time At MRI
  - Increased Urinary Glycosaminoglycan Levels

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Clinical Activity Score (CAS)

- **1. Spontaneous retrobulbar pain**
  2. Pain on eye movements
  3. Eyelid erythema
  4. Conjunctival injection
  5. Chemosis
  6. Swelling of the caruncle
  7. Eyelid edema or fullness

In its original formulation it had 10 items , which were subsequently reduced to 7

- **O**ne point is given to each item, if present.
- CAS is the sum of all scores
- ranging from 0 (no activity) to 7 (maximal activity).
- **Active GO : CAS≥3 → Need Immunosuppression**

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Original CAS Score with 10 items- not used now

- Symptoms
  - Pain or pressure in a periorbital or retroorbital distribution
  - Pain with upward, downward, or lateral eye movement
- Signs
  - Swelling of the eyelids
  - Redness of the eyelids
  - Conjunctival injection
  - Chemosis
  - Inflammation of the caruncle or plica
- Changes
  - Increase in measured proptosis $\geq$ 2 mm over 1-3 months
  - Decrease in eye movement limit of $\geq$ 8º over 1-3 months
  - Decrease in visual acuity (2 Snellen chart lines) over 1-3 months

Diagnosis of GO

- Usually clinical grounds and by careful ophthalmological examination
- MRI of the orbit confirm diagnosis by showing enlarged extraocular muscles (without involvement of the tendon) and/or increased orbital fibroadipose tissue
- MRI helps to detect optic nerve compression

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Asymmetrical or unilateral GO

- Rule out other causes like
  - primary or metastatic orbital tumors,
  - carotid-cavernous sinus fistula,
  - carotid aneurysm,
  - cavernous sinus thrombosis,
  - subarachnoid hemorrhage,
  - subdural hematoma
  - Granulomatous disorders
  - IgG4-related ophthalmic disease
- **MRI is very useful in such cases**

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Octreoscan

- Octreoscan may be useful to identify patients with active GO
- Also useful to find treatment effectiveness
- But its high cost limits its use
- It is SPECT scintigraphy using octeriotide.
- It is also used for carcinoid tumours, Pancreatic tumor imagings

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Management

- multidisciplinary approach - endocrinologists, ophthalmologists, orbit surgeons, radiologists and radiotherapists
- Control of thyroid dysfunction is fundamental, because progression often is associated with hyper- or hypothyroidism
- refrain from smoking

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Mild GO - (one or more of below)

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Only General measures needed

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1. Mild GO.

- If GO activity is <3 , symptomatic relief until GO is burnt-out
  - **Selenium 100 µg twice a day for 6 months**
- **Photophobia** -sunglasses;
- **Grittiness** due to corneal exposure - artificial tears and topical lubricants
- **Lagophthalmos**- taping the eyelids shut at night;
- **Eyelid retraction** - b-blocking drops (useful for the increased intraocular pressure) or by botulinum toxin injections
- **Elevation of the bed** - reduce periorbital swelling due to congestion;
- **Mild diplopia** - by prisms (if they are tolerated).

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Moderate-to-severe GO

one or more of the following

- **lid retraction ≥2 mm,**
- **moderate or severe soft tissue involvement,**
- **exophthalmos ≥3 mm above normal for race and gender,**
- **inconstant or constant diplopia;**

- Patients in this category have an impact on daily life

- **They need immunosuppression (if GO is active) or**
- **surgical intervention (if GO is inactive**)

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2. Moderate-to-severe GO.

- **Management not only on severity, but also on activity and inflammation of the orbitopathy**
- **Medical treatment** is likely to be beneficial in patients with **active GO** with
  - signs of inflammation ,
  - recent-onset extraocular muscle dysfunction,
  - recent progression of the ocular abnormalities
- **Surgical, rehabilitative approach is preferable**
  - Long-standing GO,
  - chronic proptosis and residual, stable diplopia and/or strabismus,
  - No evidence of inflammation

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2.A Medical Management

1st line

- **IV Methyl Prednisolone 0.5g (low dose) once weekly for 6 weeks,**
- Followed by **0.25g once weekly for 6 weeks**
- cumulative dose is 4.5g
- Glucocorticoids **are most effective** on
  - soft tissue,
  - inflammatory changes,
  - recent-onset extraocular muscle dysfunction,
  - dysthyroid optic neuropathy
- **Proptosis and long-lasting eye muscle impairment are less responsive**
- Intravenous glucocorticoid treatment of Graves' ophthalmopathy is not associated with secondary adrenocortical insufficiency. presumably because it is given for a limited period and intermittently.

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2nd line:

- Second course of intravenous GC, if cumulative dose of 8g is not exceeded.
- **Rituximab**: **Single injection 500 mg of Rituximab** in cases that have had suboptimal response to GC can be tried and response reassessed.
  - Rituximab is contraindicated in patients with overt or impending dysthyroid optic neuropathy
- **Orbital radiation** (20Gy: 2 Gy per day for 10 days over 2 weeks or 1 Gy per week for 20 weeks) along **with oral steroids** (0.3 – 0.5mg/kg body weight of oral prednisolone for 6 weeks to 3 months)
- **Cyclosporin with oral GC:** Cyclosporin 5mg/kg/day for up to 12 months with oral prednisolone 100mg in decreasing doses for 3 months. Complications include renal toxicity, hepatic toxicity and gingival hyperplasia

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2.B Surgical Treatment of inactive disease:

- An inactive disease for **more than 6 months with stable proptosis and strabismus**
- Do surgical procedures aimed for symptomatic and cosmetic rehabilitation
- The procedures are
  - Orbital Decompression
  - Rehabilitative surgery

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Orbital decompression

- It involve removing part of one, two, three or four orbital walls (floor, roof, lateral wall, medial wall) as well as part of the **retroorbital fibroadipose tissue**
- Posterior decompression of the optic canal is best for ON than wall
- It is indicated in patients who have impending sight loss due to optic neuropathy
- do not respond promptly to intravenous glucocorticoids
- corneal damage due to eyeball exposure in patients with marked proptosis
- Recurrent subluxation of the globe, which may stretch the optic nerve and cause sight loss

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Rehabilitative surgery

- Includes surgery for strabismus or eyelid retraction
- Timing of surgery **- it should not be performed when GO is active,** but when it has been inactive for 6 months
- Multiple operations may be required to correct the strabismus and eye ball positioning
- Eyelid surgery is for exposure keratitis and corneal ulcerations
- Eyelid surgery usually constitutes the last step of rehabilitation

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Sight-threatening GO

- Dysthyroid optic neuropathy (DON) or corneal breakdown
- They need immediate intervention

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3. Dysthyroid optic neuropathy

- Requires immediate treatment
- If there is no response to medical treatment (high-dose intravenous glucocorticoids), orbital decompression is warranted
- **Intravenous GC 1g (high dose) per day for 3 days**
- Repeated after 1 week if needed
- pulses continued weekly as described for moderate severe disease (should not exceed 12 weeks; cumulative dose should not exceed 8g)
- Orbital decompression: If there is worsening in spite of GC,
- Apex decompression should be done within 2 weeks

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Reference

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