Updates on Thyroid eye disease

B.Eshraghi M.D

Associate professor of ophthalmology

Ophthalmic plastic and reconstructive surgeon

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Original Article

Epidemiological Status of Thyroid Eye Disease in Central Iran

Bahram Eshraghi[1], Mojgan Nikdel[2], Maryam Abbasi[1]

[1]Isfahan Eye Research Center, Department of Ophthalmology, Isfahan University of Medical Sciences, Isfahan, Iran, [2]Private Practice, Rasht, Iran

Abstract

Purpose: To focus on clinical manifestations and epidemiology of thyroid eye disease (TED) in Central Iran's population.

Methods: In this retrospective case study, we analyzed all patients with TED who were referred to our oculoplastic clinic from 2015 to 2019. The patients' epidemiological characteristics and clinical presentation were compared between different thyroid disease groups and genders.

Results: Overall, 383 patients (155 male; 40.5% and 228 female; 59.5%) were included. The mean age was 39.55 years (standard deviation ± 13.45, range 10–72). Most patients (89%) were hyperthyroid with the highest duration of ocular involvement among all categories (25.6 months). The most common signs on ophthalmic examinations were proptosis (80.4%), followed by eyelid retraction (72.3.0%). TED was classified as mild in 24.5%, moderate to severe in 67.6%, and sight-threatening in 7.9%. Thirty patients (7.8%) had active TED.

Conclusions: This series with a relatively more significant number of TED cases in Central Iran found similar epidemiological and clinical characteristics of TED compared to other studies from Iran. Most of our patients were hyperthyroid, with more females compared to males. Proptosis and eyelid retraction were the most common manifestations. Most TED patients were classified as moderate to severe.

Keywords: Graves' disease, Proptosis, Thyroid eye disease, Thyroid orbitopathy, Thyroid-associated ophthalmopathy

Address for correspondence: Maryam Abbasi, Isfahan Eye Research Center, Department of Ophthalmology, Isfahan University of Medical Sciences, Isfahan, Iran.
E-mail: mdr.abbasi86@gmail.com
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RESEARCH Open Access

Hypo vs. hyperthyroid eye disease: is there any difference?

Bahram Eshraghi, Mohsen Pourazizi, Maryam Abbasi and Iman Mohammadbeigy*

Abstract

Background Thyroid-eye disease (TED) is the most common extra-thyroidal presentation of graves' disease. We performed this study to compare clinical characteristics of TED in hypothyroid vs. hyperthyroid patients.

Methods This was a retrospective analytical cross-sectional study in which we compared demographics, severity (EUGOGO classification) and activity (clinical activity score) of TED, thyroid disease duration, TED duration and clinical signs between hypothyroid eye disease (Ho-TED) and hyperthyroid eye disease (Hr-TED). To minimize the effect of selection bias and potential confounders, 1:1 propensity score matching (PSM) was also performed.

Results Three hundred and seventy-four patients (341 Hr-TED and 33 Ho-TED) with a female to male ratio of 1.4:1 were identified in our study. Female to male ratio was 1.3:1 in hyperthyroid and 4.5:1 in hypothyroid group ($P=0.005$). The duration of thyroid disease was longer in Ho-TED ($P=0.002$) while the duration of eye disease was not significantly different between the Hr-TED (mean = 24.33 ± 41.69, median = 8) and Ho-TED (mean = 19.06 ± 33.60, median = 12) (P = 0.923). Most of the patients in hypothyroid group developed eye involvement after thyroid disease (80.0% in hypo vs. 48.1% in hyper, $P=0.003$). Severity ($P=0.13$) and activity ($P=0.11$) was not different between Hr-TED and Ho-TED patients. After PSM analysis, no clinical characteristics were significantly different between the two groups ($P>0.05$).

Conclusion The results of our study showed several differences between the Hr/Ho TED patients including sex, duration of thyroid disease and pattern of eye involvement. After matching the two groups with statistical methods, no clinical characteristics were different between Hr-TED and Ho-TED patients.

Keywords Thyroid-eye disease, Graves' orbitopathy, Hypothyroidism, Hyperthyroidism

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ORIGINAL PAPER

A comparison between bilateral and unilateral thyroid eye disease

Bahram Eshraghi · Mohsen Pourazizi · Maryam Abbasi · Iman Mohammadbeigy

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OCULOPLASTICS AND ORBIT

Decreased Bell's phenomenon after inferior and medial orbital wall decompression in thyroid-associated ophthalmopathy: a double-edged sword in management of the patients

Bahram Eshraghi[1] · Maryam Moayeri[2] · Mohsen Pourazizi[1] · Mohammad Taher Rajabi[2] · Mohsen Rafizadeh[2]

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BMC Ophthalmology

CASE REPORT Open Access

Nonspecific orbital inflammation and thyroid eye disease, a rare comorbidity: report of two cases and review of literature

Bahram Eshraghi[1], Amin Dehghan[2], Niloofar Javadi[2] and Mohammadreza Fazel[1*]

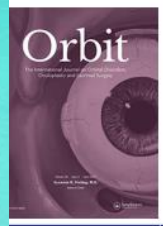
Abstract

Background: To present the very rare comorbidity of developing non-specific orbital inflammation (NSOI) in two patients with histories of definite thyroid eye disease (TED).

Case presentation: Both patients complained of new-onset progressive proptosis although their thyroid disease was controlled and computed tomography scan revealed an intraorbital inflammatory mass. The pathological assessment indicated that both patients had developed fibrosing NSOI. Therefore, intravenous corticosteroids were administered. The mass regressed and the amount of proptosis was decreased in both patients.

Conclusions: We reviewed all related cases in the literature and extracted their clinical and radiological characteristics for this paper. Ophthalmologists should consider TED and NSOI in patients with a new-onset complaint of proptosis. Despite rare comorbidity of TED and NSOI, it should be considered especially in patients with refractory proptosis, and lead to its further evaluation and prompt management.

Keywords: Non-specific orbital inflammation, thyroid eye disease, comorbidity, orbital mass, prednisolone



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Orbit

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Orbital decompression during coronavirus disease 2019 pandemic: A shared experience

Bahram Eshraghi & Hamed Radmehr

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Strabismus Surgery in Thyroid-Associated Ophthalmopathy; Surgical Outcomes and Surgical Dose Responses

Mohammadreza Akbari , Reza Bayat , Arash Mirmohammadsadeghi , Raziyeh Mahmoudzadeh , Bahram Eshraghi & Mirataollah Salabati

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ORIGINAL RESEARCH
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Mycophenolate Mofetil (CellCept®) in Combination With Low Dose Prednisolone in Moderate to Severe Graves' Orbitopathy

Mohammad Taher Rajabi[1], Seyed Mohsen Rafizadeh[1], Abbas Mohammadi[1], Bahram Eshraghi[1], Nader Mohammadi[1], Seyedeh Simindokht Hosseini[1], Mohammad Bagher Rajabi[1], Mohammad Mohsen Keshmirshekan[1], Mansoor Shahriari[1], Seyedeh Zahra Poursayed Lazarjani[1,2] and Mohammad Mehdi Parandin[1]*

[1] Eye Research Center, Farabi Eye Hospital, Tehran University of Medical Sciences, Tehran, Iran, [2] Department of Eye, Eye Research Center, Amiralmomenin Hospital, School of Medicin, Guilan University of Medical Science, Rasht, Iran

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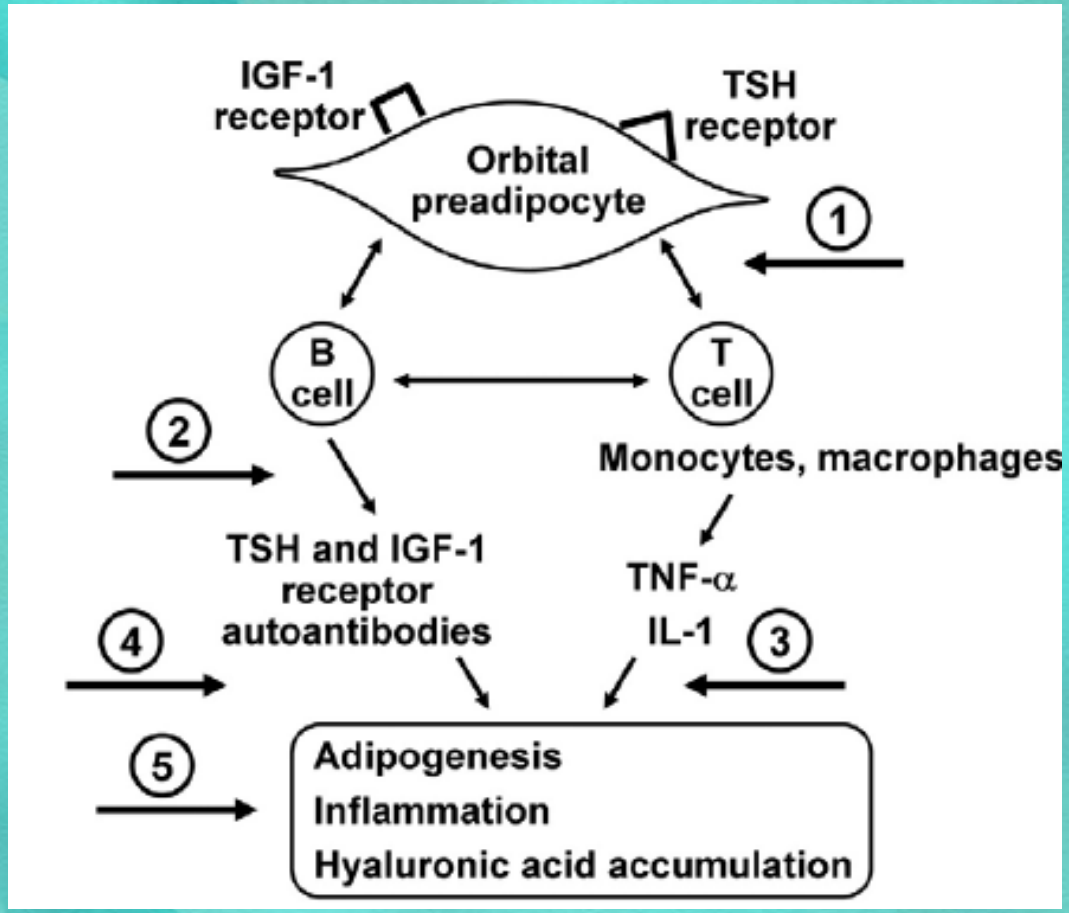
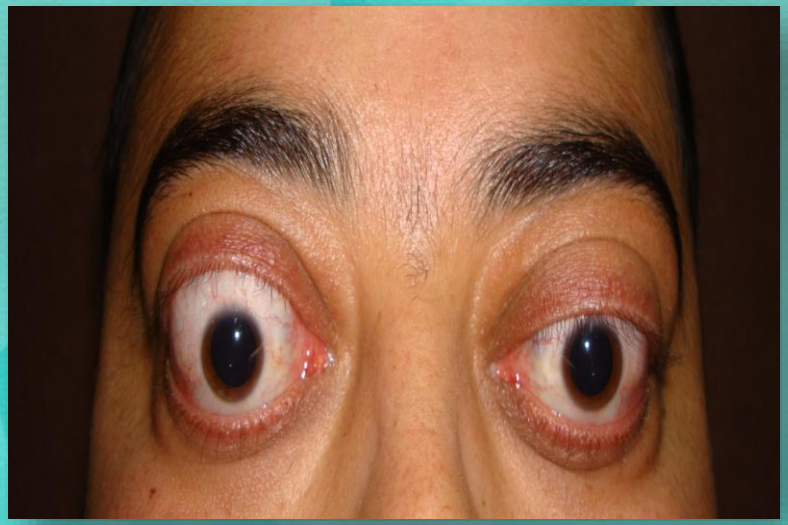

IGF-1 receptor
TSH receptor
Orbital preadipocyte
1
B cell
T cell
2
Monocytes, macrophages
TSH and IGF-1 receptor autoantibodies
TNF-α
IL-1
4
3
5
Adipogenesis
Inflammation
Hyaluronic acid accumulation

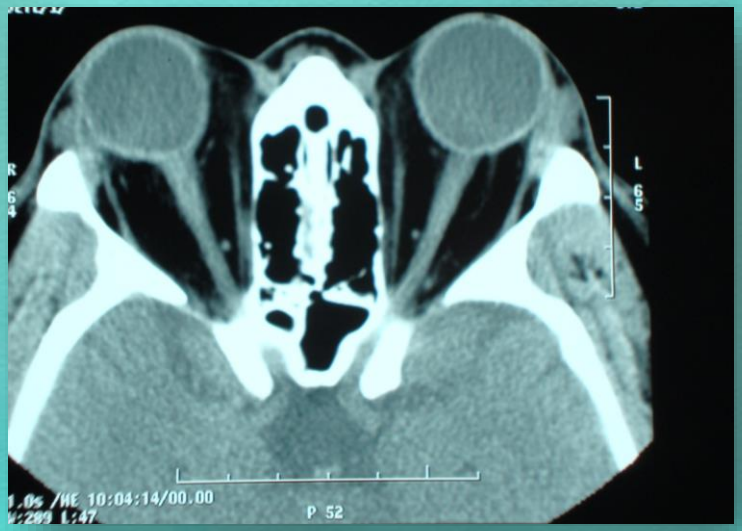
Pathological findings

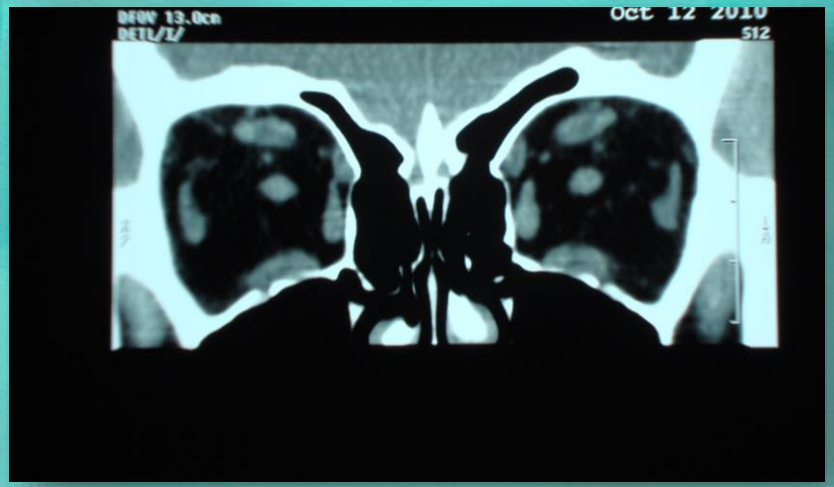
- Many of the clinical symptoms and signs of GO can be explained on a **mechanical basis** by an increase in the volume of both：

1. Orbital fatty connective tissues
2. Extraocular muscle bodies

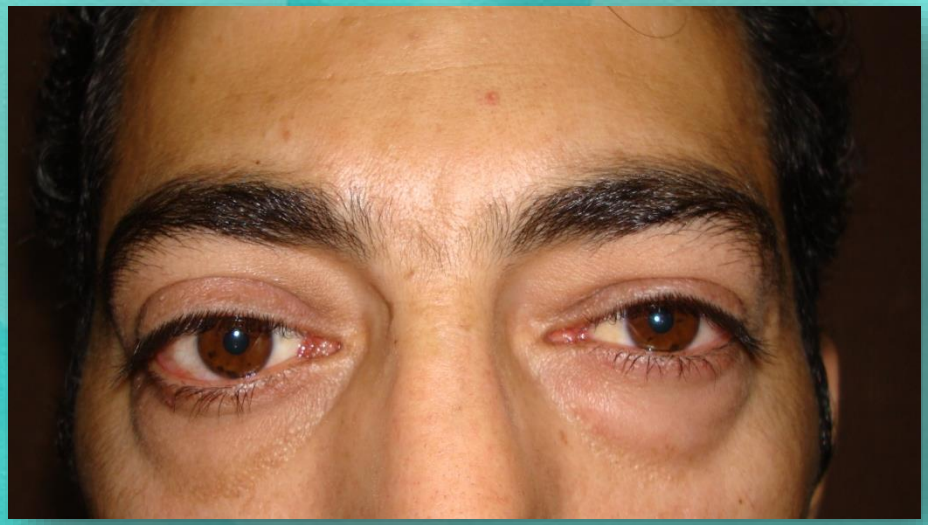
Sever proptosis with increased orbital adipose tissue

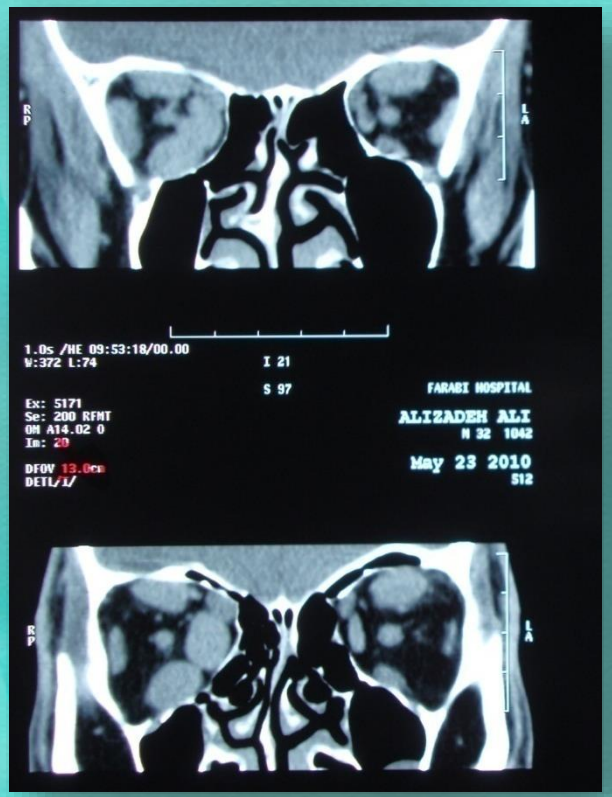




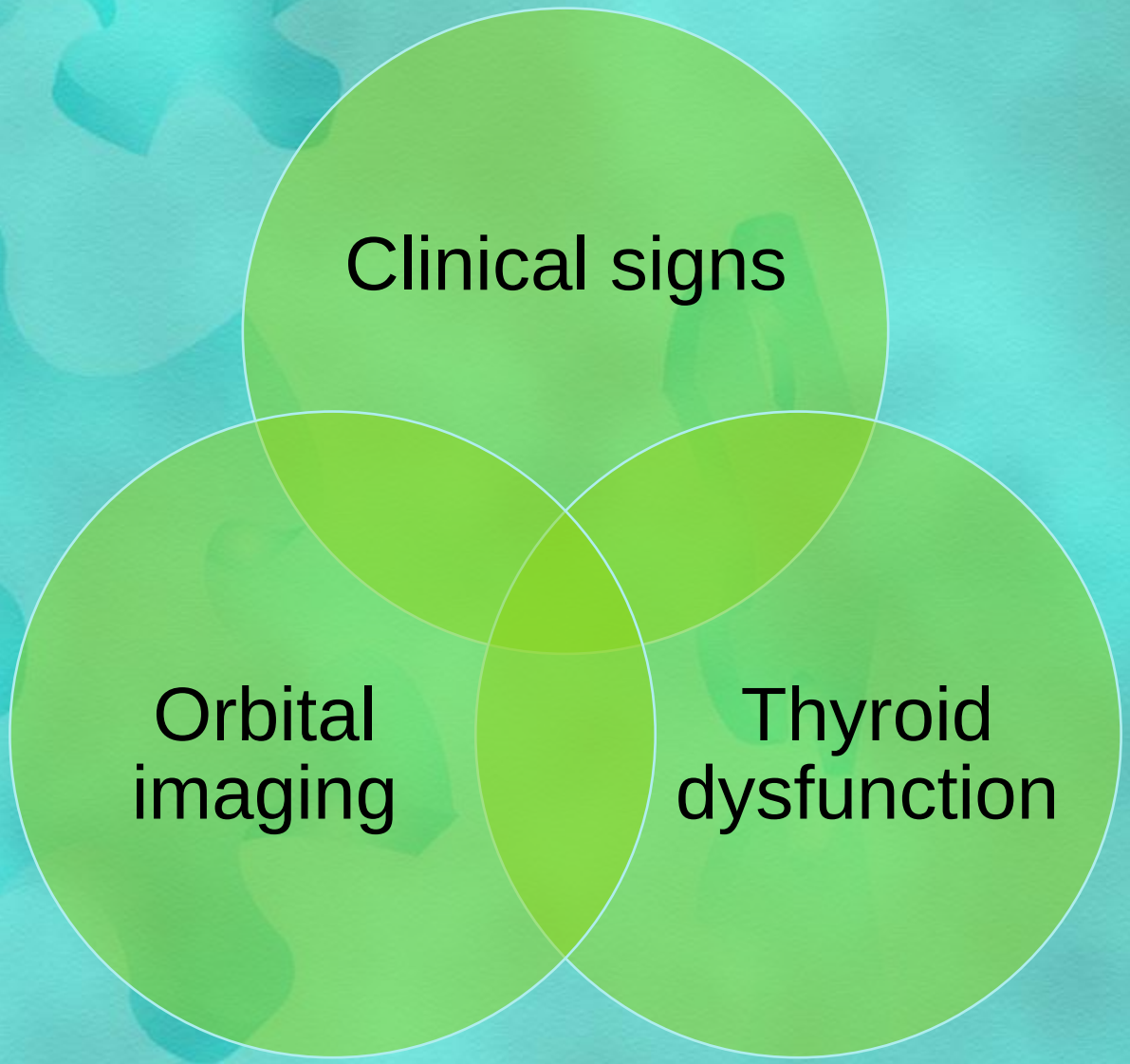


TED with large muscles





Diagnosis of TED



Clinical features

- **Blurred vision**
- **Orbital pain**

- **Diplopia**
- **Lid edema**

- **Lacrimation**

- **Ocular discomfort**

- **Photophobia**

- **Lid edema**
- **Chemosis**

- **Conjunctinal injection**
- **SLK**

- **Keratopathy**
- **Proptosis**

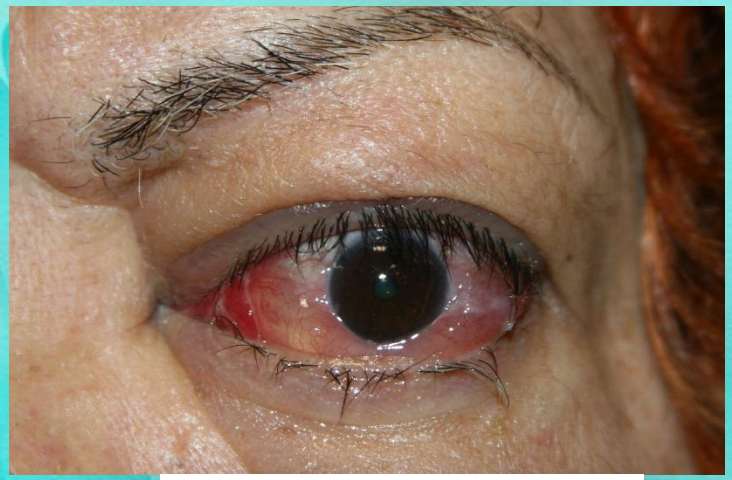
- **Lid retraction**
- **Lagophthalmos**

- **High IOP**
- **Abnormal disc**

- **Choroidal folds**
- **Extraocular muscle dysfunction**

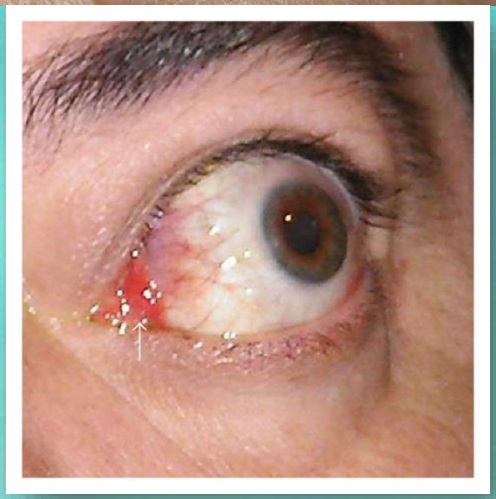
Activity measures

- Activity measures based on the classical features of inflammation (it consists of two symptoms and five signs):



- 1. Spontaneous retrobulbar pain
- 2. Pain on attempted up or down gaze

- 3. Redness of the eyelids
- 4. Redness of the conjunctiva
- 5. Swelling of the eyelids
- 6. Inflammation of the caruncle and/or plica
- 7. Conjunctival edema



- ***A CAS ≥3/7 indicates active GO***

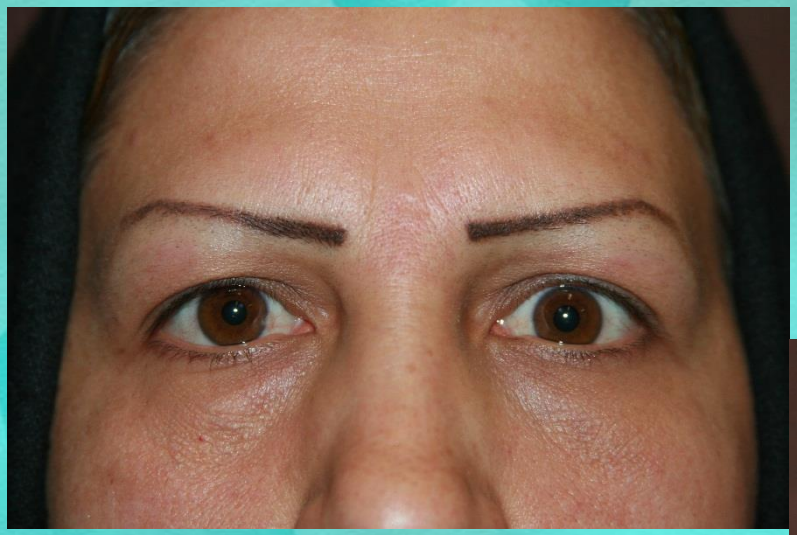
- Patients assessed after follow-up (1–3 months) can be scored out of 10:

- 8- Increased of >2mm proptosis
- 9- Decrease in uniocular ocular excursion in any one direction of >8°
- 10- Decrease of acuity equivalent to 1 Snellen line

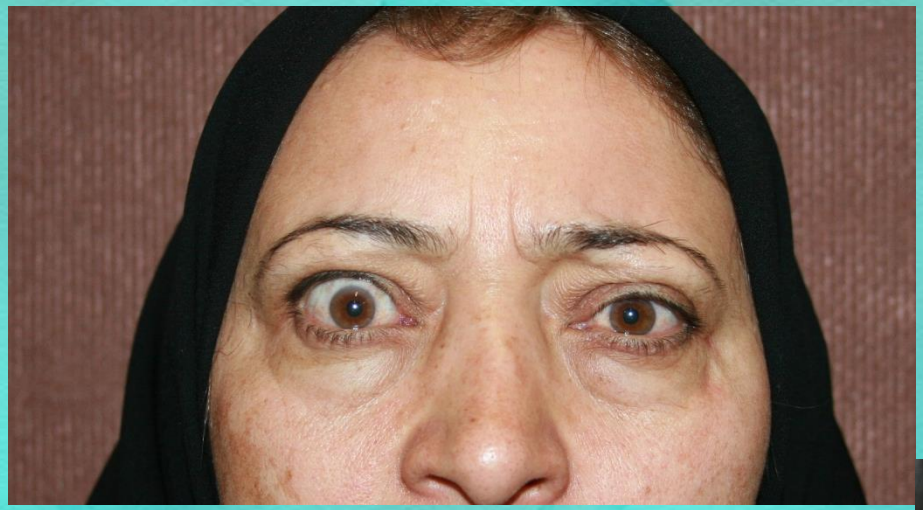
Severity classification:

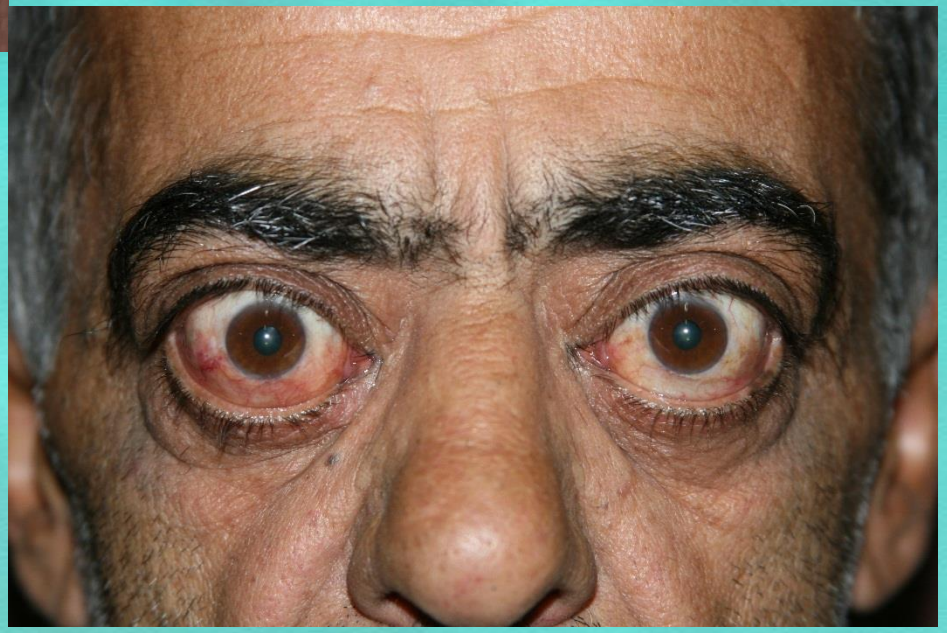
- Mild TED
- Moderate to sever TED
- Sight threatening

Mild inactive TED

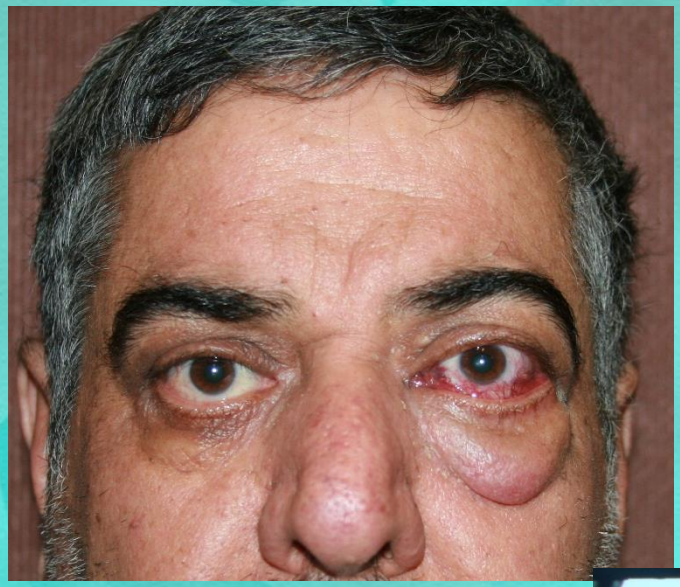


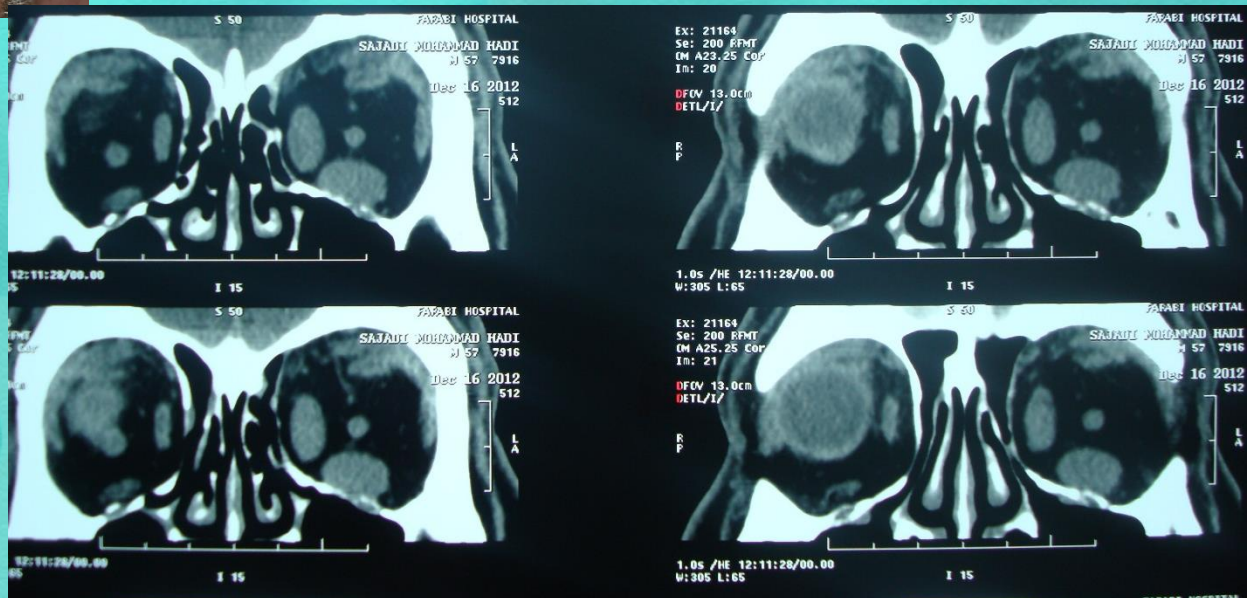
Moderate to severe inactive TED



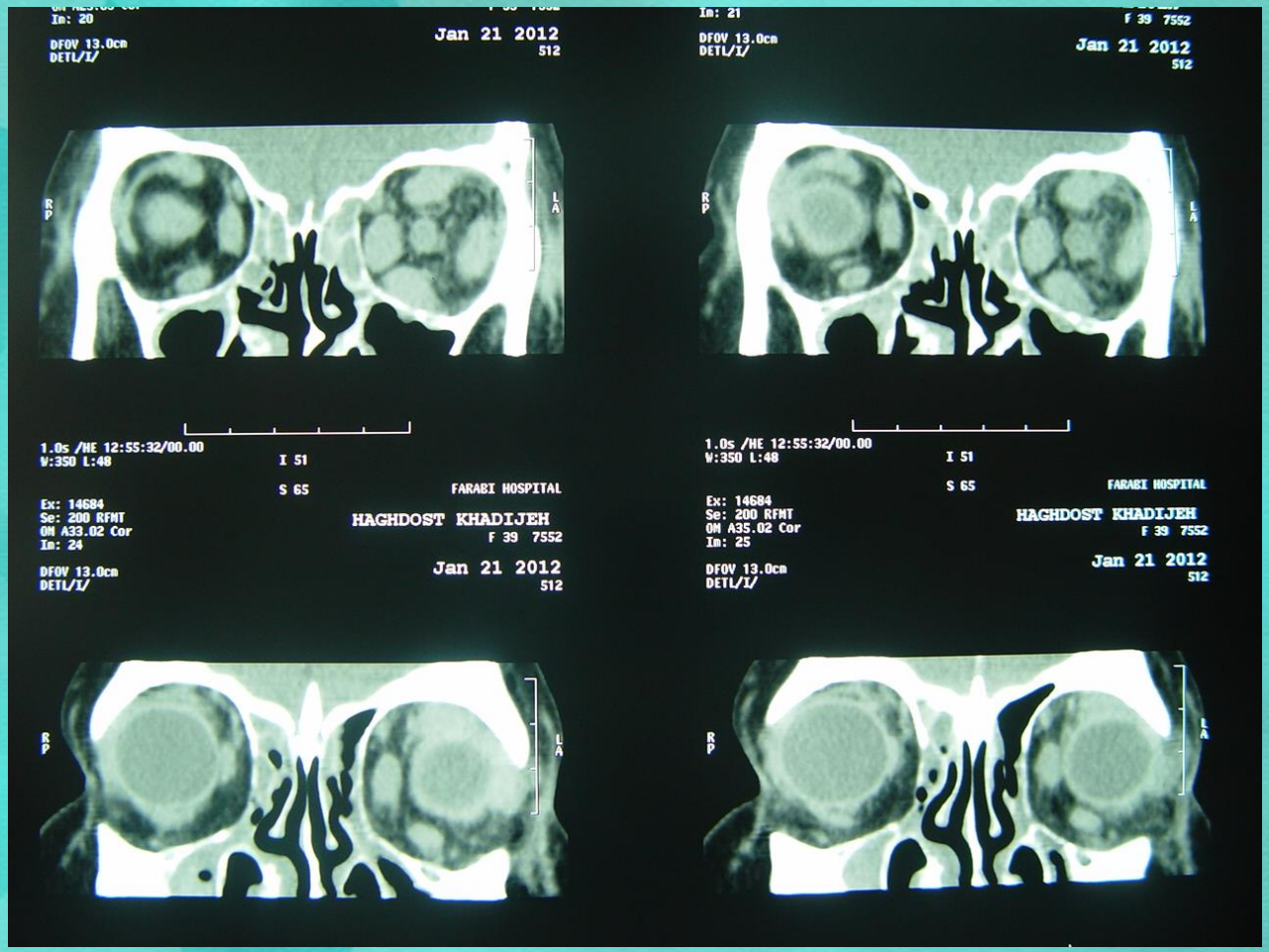


Active Mod to sever TED

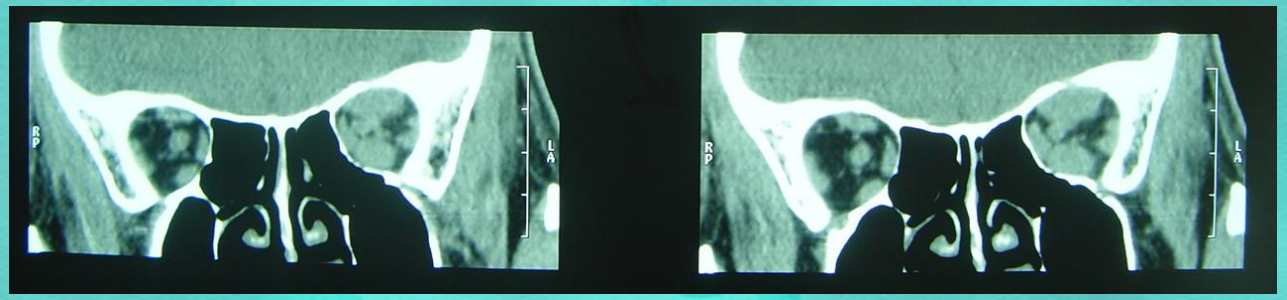




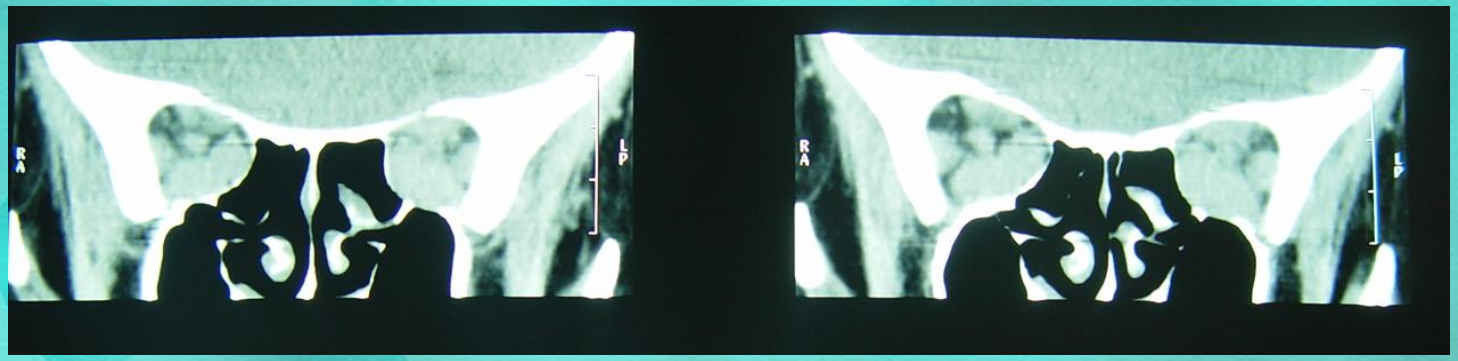
Active TED &Sinus opacification

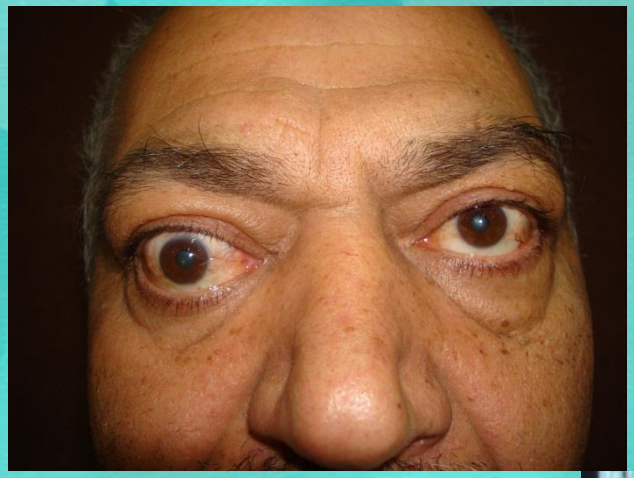


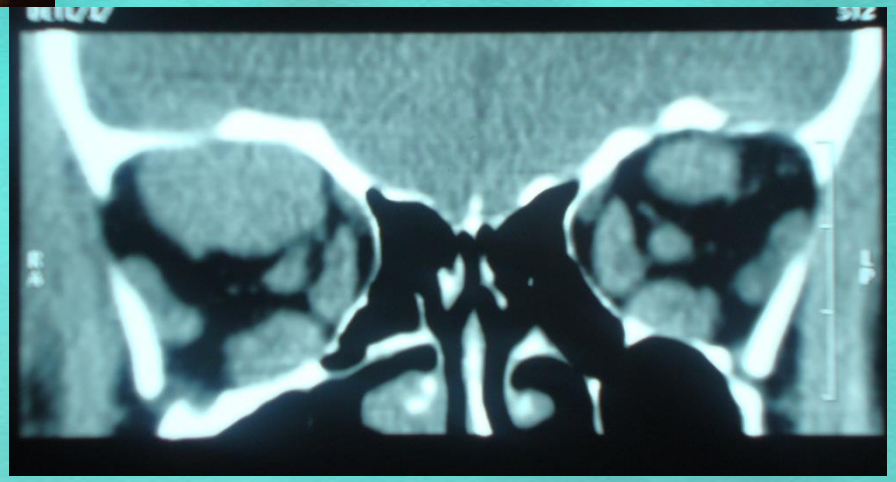
Orbital apex crowding



Strabismus







Management:

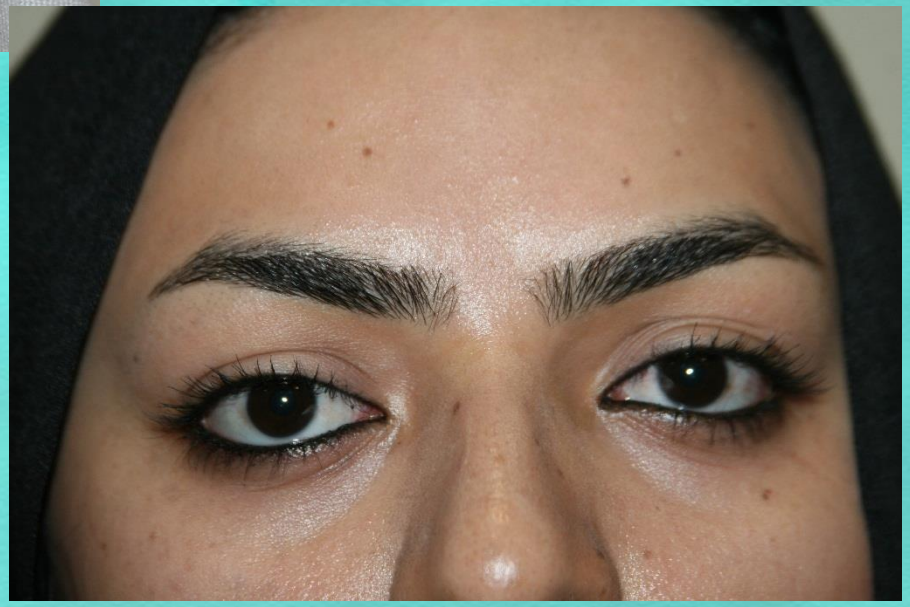
- **TED is often mild and self-limiting**
- **Active inflammation usually lasts between 6 months to 2 years**
- **Reactivation can occurs in 5% even after 7 years**

- All patients with GO, except for the mildest cases, should either be managed by a physician with particular expertise in managing GO or better be referred to a combined thyroid eye clinics for further assessment and management

General consideration

- Elevation of head
- Low salt diet
- Lubrication (dry eye is common because of evaporation and lacrimal gland inflammation)
- Sunglasses
- Patching
- Prism
- Botulinum toxin

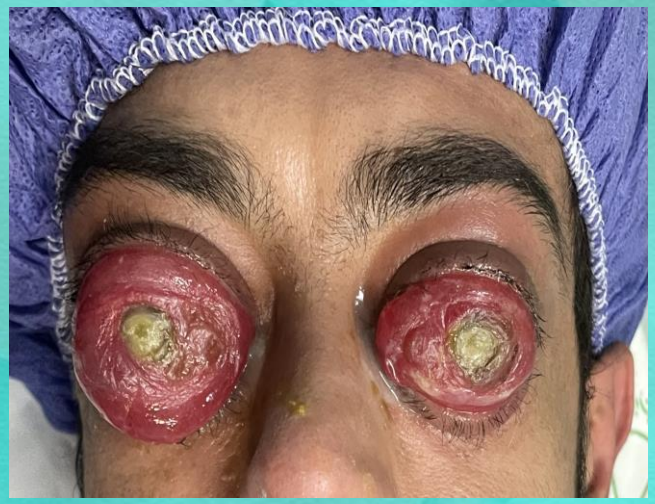
Botulinum toxin injection in upper lid retraction

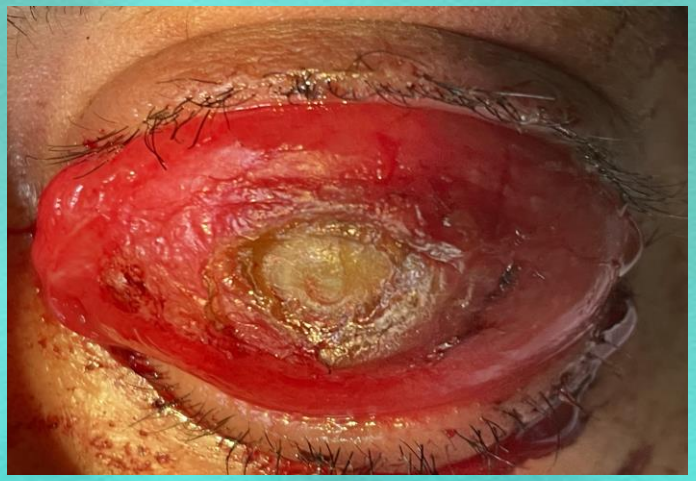


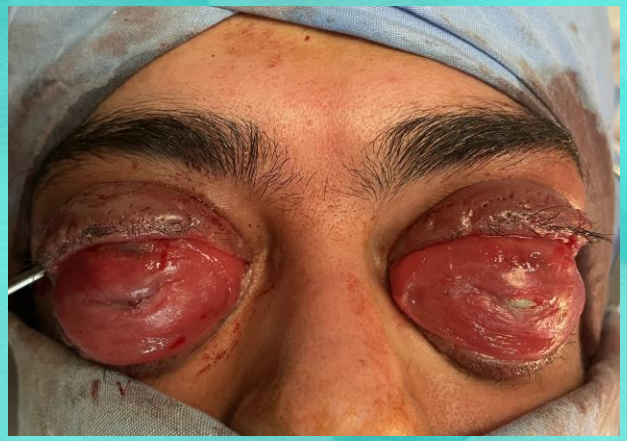
Smoking

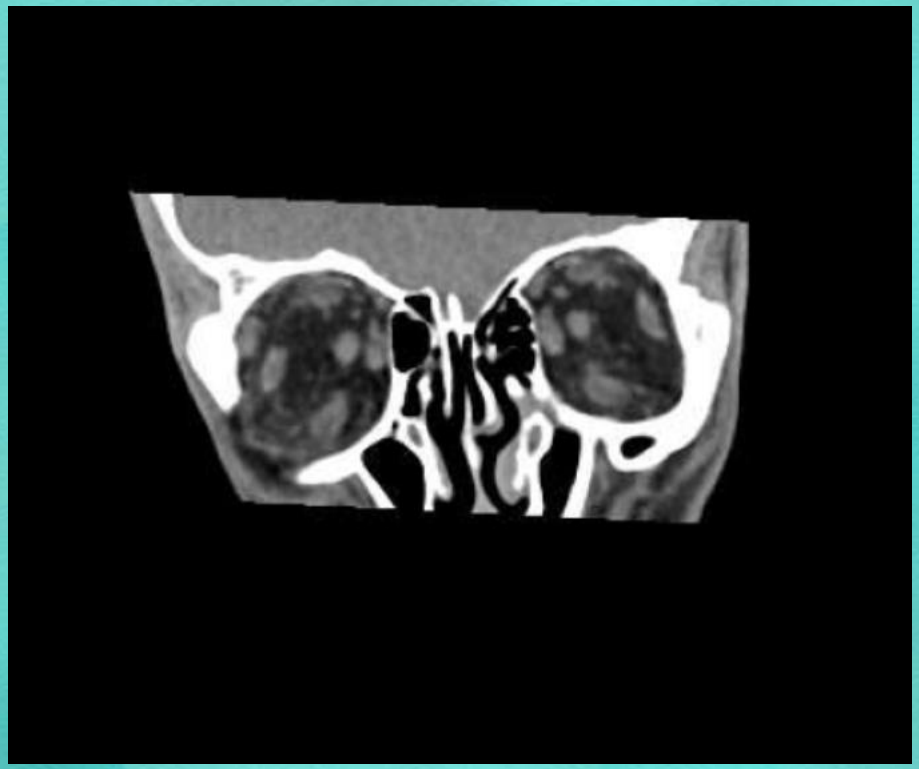
- The mechanisms involved in the association between smoking and GO are unclear
- Smoking is the most important risk factor amenable to modification in patients with GO
- The odds ratio, relative to controls, has been reported to be as high as 20.2 for current smokers

- Development of GO
- Deterioration of pre-existing disease
- Effectiveness of treatment
- More sever disease
- Progression after radioiodone









RAI:

- In a large RCT, progression of GO occurred in 23 of 150 patients given RAI (15%), being persistent in 8 (5%), hence requiring immunosuppressive treatment for GO
- The original regimen used a starting daily dose of 0.3–0.5 mg/kg/bodyweight, gradually tapered and withdrawn after 3 months .
- Lower doses of oral prednisone (0.1–0.2 mg/kg/bodyweight as starting dose, gradually tapered and withdrawn after 6 weeks
- The 0.3–0.5 mg dose should be used in patients who are at risk for progression and/or de novo development of GO (smokers, high TSHR-Ab levels, severe hyperthyroidism, preexisting GO).

Selenium:

- A randomized, doubleblind, placebo-controlled trial of patients with mild GO, performed in Europe, reported a higher rate of improvement in both GO-QoL and overall ophthalmic outcome and a lower rate of progression to more severe GO in patients receiving sodium selenite (200 µg (91.2 µg selenium) daily for 6 months), compared to the placebo group

- There is no evidence of a beneficial adjuvant effect of selenium in patients with moderate-to-severe and active GO

Statins:

- High cholesterol is an emerging and potential risk factor for GO
- The use of statins was associated with a reduced risk of GO occurrence in two large cohort retrospective studies
-
- A study published in 2020 showed that statins have anti-fibrotic activity in Graves' orbitopathy orbital fibroblasts
- The effects of statins might be related to their cholesterol lowering mechanism, pleiotropic actions, interaction with methylprednisolone

- Atorvastatin, a dose of 20 mg per day

- There was a trend to a better outcome of clinical activity score and diplopia in the atorvastatin group.

Statins for Graves' orbitopathy (STAGO): a phase 2, open-label, adaptive, single centre, randomised clinical trial

Giulia Lanzolla, Elena Sabini*, Marenza Leo, Francesca Menconi, Roberto Rocchi, Angela Sframeli, Paolo Piaggi, Marco Nardi, Claudio Marcocci, Michele Marinò*

Summary

Background A protective action of statins on development of Graves' orbitopathy suggests that statins might be used for treatment of the disease. We aimed to assess the efficacy of the addition of a statin, atorvastatin, to intravenous glucocorticoids (ivGCs) on Graves' orbitopathy outcomes in patients with hypercholesterolaemia.

Lancet Diabetes Endocrinol 2021; 9: 733–42

Published Online September 27, 2021

Medical treatment

Clinical Practice Guideline

L Bartalena, G J Kahaly and others | Guidelines for medical management of GO | **185**:4 | **G43**–G67

The 2021 European Group on Graves' orbitopathy (EUGOGO) clinical practice guidelines for the medical management of Graves' orbitopathy

L Bartalena[1,*], G J Kahaly[2,*], L Baldeschi[3], C M Dayan[4], A Eckstein[5], C Marcocci[6], M Marinò[6], B Vaidya[7] and **W M Wiersinga[8] on behalf of EUGOGO[†]**

[1]Department of Medicine and Surgery, University of Insubria, Varese, Italy, [2]Department of Medicine I, Johannes Gutenberg-University (JGU) Medical Center, Mainz, Germany, [3]Department of Ophthalmology, Cliniques Universitaires Saint Luc, Catholic University of Louvain, Brussels, Belgium, [4]Thyroid Research Group, Cardiff University School of Medicine, Cardiff, UK, [5]Clinic for Ophthalmology, University Clinic, Essen, Germany, [6]Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy, [7]Department of Endocrinology, Royal Devon & Exeter Hospital and University of Exeter Medical School, Exeter, UK, and [8]Amsterdam University Medical Center, Amsterdam, the Netherlands

*(L Bartalena and G J Kahaly contributed equally to this work and share first authorship)

[†](List of EUGOGO members who collaborated for this Guideline is provided in the Acknowledgements section)

Correspondence should be addressed to G J Kahaly
Email
gkahaly@uni-mainz.de

		GO spectrum	
13	Glucocorticoid withdrawal	Clinicians should monitor each individual patient receiving glucocorticoid therapy for response to treatment and adverse events. When drug-induced side effects outweigh benefits, clinicians should consider withdrawing glucocorticoid treatment in favor of another modality, or watchful monitoring	2,ØØOO
14	Local injections of triamcinolone	Local subconjunctival/periocular injections of triamcinolone acetate may be considered when systemic glucocorticoids are absolutely contraindicated	2, ØØOO
15	Mycophenolate	Mycophenolate has a positive efficacy/safety profile in patients with moderate-to-severe and active GO, both as monotherapy and in combination with i.v. glucocorticoids	1, ØØØØ
16	Orbital radiotherapy	Orbital radiotherapy is considered an effective second-line treatment for moderate-to-severe and active GO, in combination with glucocorticoids, particularly in the presence of diplopia and/or restriction of extraocular motility	1, ØØØO
17	Cyclosporine	The combination of cyclosporine and oral glucocorticoids is a valid second-line treatment for moderate-to-severe and active GO	1, ØØØØ
18	Azathioprine	Consideration can be given to azathioprine as a second-line and glucocorticoid-sparing agent in combination with oral glucocorticoids	1, ØØOO
19	Teprotumumab	Very promising drug with a strong reduction of exophthalmos, diplopia, and improvement of QoL. Currently, second-line option as longer-term data, availability, affordability, costs, and need for subsequent rehabilitative surgery are pending	1, ØØØ0
20	Rituximab	Rituximab can be considered a second-line treatment for patients with moderate-to-severe and active GO of recent onset (<12 months) if refractory to i.v. glucocorticoids, as long as dysthyroid optic neuropathy (DON) is excluded. We strongly recommend that such treatment be applied in experienced centers only that manage potentially serious adverse events	1, ØØOO
21	Tocilizumab	Tocilizumab may be given consideration as a second-line treatment for moderate-to-severe and active glucocorticoid-resistant GO	1, ØØOO
22	First-line treatment for moderate-to-severe and active GO	Intravenous methylprednisolone in combination with oral mycophenolate sodium (or mofetil) represents the first-line treatment for moderate-to-severe and active GO	1, ØØØO
23	First-line treatment for moderate-to-severe and active GO	In the more severe forms of moderate-to-severe and active GO, including constant/inconstant diplopia, severe inflammatory signs and exophthalmos > 25 mm, i.v. methyl-prednisolone at the highest cumulative dose (7.5 g per cycle) as monotherapy represents an additional valid first-line treatment	1, ØØØO

Table 1 Continued.

Number		Recommendations	Strength of recommendation and level of evidence
24	Second-line treatments for moderate-to-severe and active GO	If response to primary treatment is poor and GO is still moderate-to-severe and active, subsequent to careful ophthalmic and biochemical (liver enzymes) evaluation, the following second-line treatments should be considered: • Second course of i.v. methylprednisolone monotherapy, starting with high single doses (0.75 g) and a maximal cumulative dose of 8 g per cycle • Oral prednisone/prednisolone combined with either cyclosporine or azathioprine • Orbital radiotherapy combined with oral or i.v. glucocorticoids • Teprotumumab • Rituximab • Tocilizumab	1, ØØØO
25	Combination of orbital radiotherapy and i.v. glucocorticoids	Based on expert opinion only (as randomized trials are not available), the task force suggests combination of orbital radiotherapy and i.v. methylprednisolone as a potential second-line treatment for moderate-to-severe and active GO	2, ØØOO
26	Treatment of sight-threatening GO	Optic neuropathy should be treated immediately with high single doses of i.v. methylprednisolone (0.5–1 g of methylprednisolone daily for either three consecutive days or more preferably on every second day), and urgent orbital decompression should be performed if response is absent or poor within 1–2 weeks. Recent eyeball subluxation should undergo orbital decompression as soon as possible	1, ØØØO
27	Treatment of sight-threatening GO	Severe corneal exposure should be urgently treated medically or by means of progressively more invasive surgeries in order to avoid progression to corneal breakdown; the latter should be immediately surgically addressed	2, ØØOO
28	Thyroid treatment in patients with GO	Mild and inactive GO: any treatment for hyperthyroidism can be used based on standardized criteria and patient choice	1, ØØOO
29	Thyroid treatment in patients with GO	Mild and active GO: antithyroid drugs (ATDs) or thyroidectomy is preferred and prednisone/prednisolone prophylaxis should be used if RAI treatment is selected	1, ØØØO
30	Thyroid treatment in patients with GO	Moderate-to-severe, longstanding and inactive GO: as for mild and inactive GO, but consideration should be given to prednisone/prednisolone prophylaxis if RAI treatment is selected and risk	1, ØØOO

Intravenous glucocorticoids therapy in the treatment of Graves' ophthalmopathy: a systematic review and Meta-analysis(Int J Ophthalmol 2019)

3Department of Ophthalmology, Shanghai General Hospital, Shanghai Jia*Li-Quan Zhao1, Dan-Yang Yu2, Jin-Wei Cheng3*
1Department of Ophthalmology, Shanghai Pudong New Area People's Hospital, Shanghai 201200, China
2Department of Ophthalmology, 920th Hospital of Jiont Logistics Support Force, Kunming 6500032, Yunnan Province, Chinao Tong University School of Medicine, Shanghai 200080, China

- Ten RCTs were included in the Meta-analysis.
- Intravenous Glucocorticoids Versus Placebo: The finding was compatible with significantly increased chance of composite outcome improvement for IVGC, suggesting that for patients using placebo with a response rate of 11%, the response rate using IVGC would be between 12.5% and 100%.
- Intravenous Versus Oral Glucocorticoids: Participants receiving IVGC achieved significantly higher response compared to participants receiving OGC, assuming approximately 53% overall response of participants receiving OGC, the anticipated overall response of participants receiving IVGC would be between 66.3% and 97.0%.

Network Meta-Analysis of Different Intravenous Glucocorticoid Regimes for the Treatment of Graves' Orbitopathy(*Frontiers in Pharmacology 2022)*

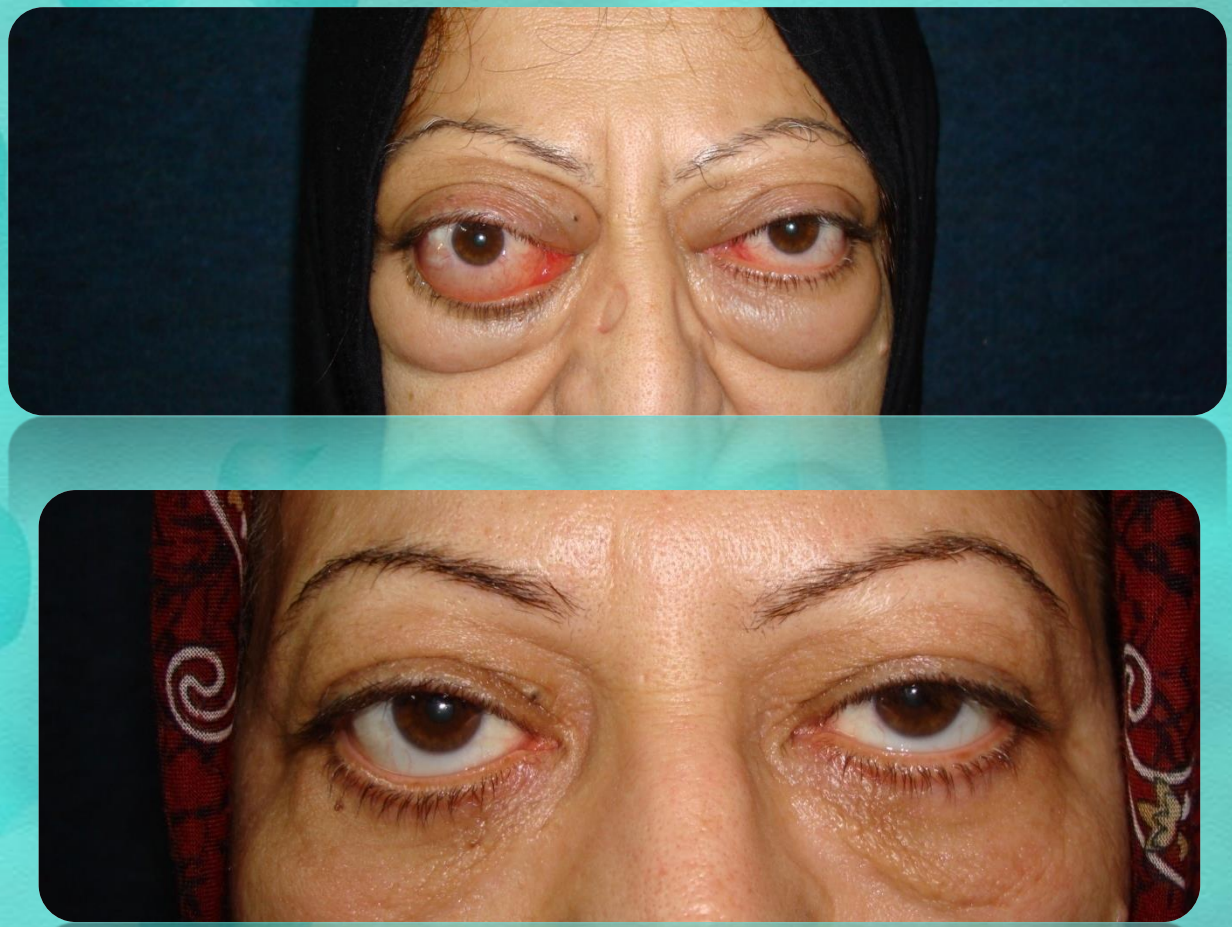
J

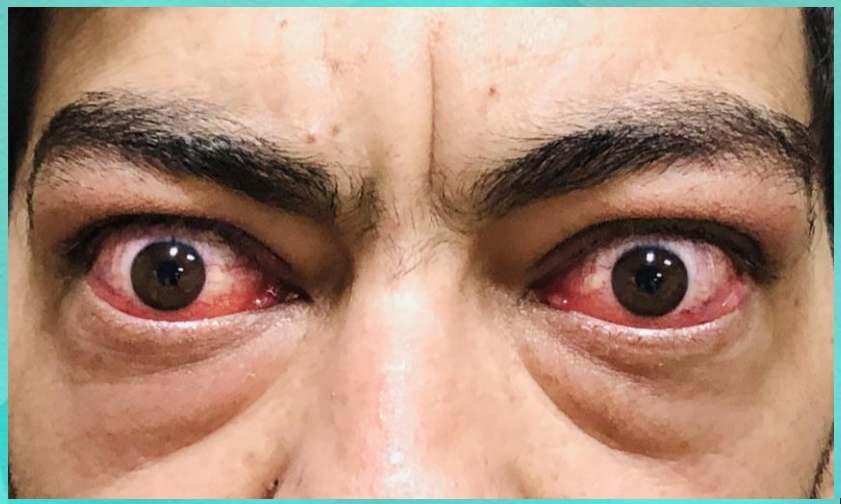
1Department of Ophthalmology, The Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China, 2Department of Endocrinology, The Central Hospital of Wuhan, Tongji Medical College, Htotal of 10 studies involving 593 patients uazhong University of Science and Technologyun Jia 1†, Jingjian Dong2† and Lin Deng2*, Wuhan, China

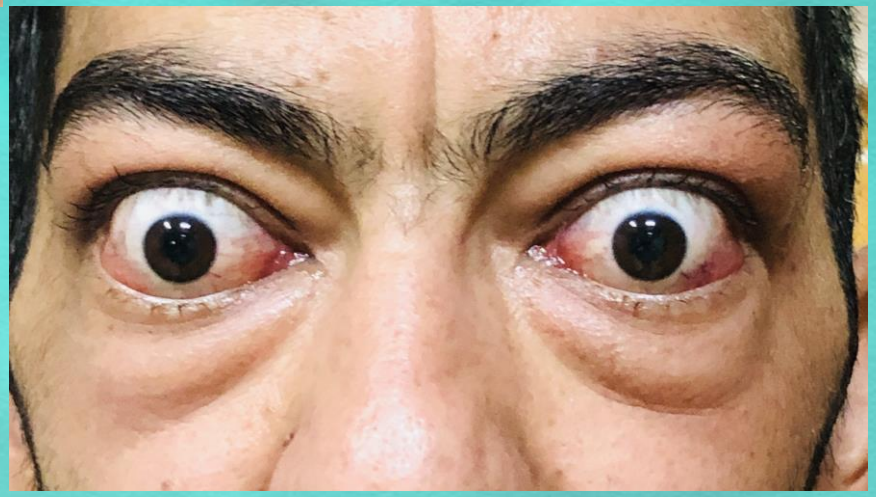
- A met the selection criteria.

- Based on the best available evidence, we conclude that the WR(weekly intravenous regimen) or MR(monthly regimen) should be preferentially prescribed to treat moderate-to-severe GO because the WR or MR is significantly associated with improved response, reduced CAS, and lower adverse effect than the OGC regime.

Prednisolone:







Rituximab

- two double-blind, but low-powered single-center RCTs have evaluated rituximab in patients with moderate-to-severe and active GO with conflicting results.
- The US : no additional advantage of rituximab over placebo was found in reducing CAS or severity of GO at 24 or 52 weeks
- The Italian study demonstrated better ophthalmic and QoL outcomes with rituximab as compared to i.v. glucocorticoids: At 24 weeks, all patients treated with rituximab showed inactivation of GO as compared to 69% in the i.v. glucocorticoid group.

Rituximab for thyroid-associated ophthalmopathy *(Cochrane Database Syst Rev 2022)

Swan Kang [1], Shirin Hamed Azzam [1], Neda Minakaran [2], Daniel G Ezra [3]
Moorfields Eye Hospital NHS Foundation Trust, London, UK.\
[2]Department of Ophthalmology, Moorfields Eye Hospital NHS Foundation Trust, London, UK.
[3]Moorfields and UCL Institute of Ophthalmology BMRC, Moorfields Eye Hospital NHS Foundation Trust, London, UK.

- This review update assesses the efficacy and safety of using RTX for the treatment of TAO.

- CONCLUSIONS: There is currently insufficient evidence to support the use of RTX in people with TAO. Future studies investigating RTX in people with active TAO may need to be multi-centre in order to recruit enough participants to make an adequate judgement on the efficacy and safety of this novel therapy.

Tocilizumab:

- Tocilizumab: is a humanized monoclonal anti-IL-6 antibody.

- The Tocilizumab for Graves' Orbitopathy study group conducted a masked randomized control trial of 32 patients randomized to intravenous tocilizumab 8 mg/kg at 0, 4, 8, and 12 weeks versus placebo.

- All patients had moderate to severe disease that did not respond to corticosteroids. There was a significant difference in the number of patients who achieved the primary outcome, a change in CAS score of at least 2, with 93.3% of patients in the tocilizumab group achieving this endpoint compared to only 58.8% of controls.

- In addition, there was a 1.5 mm reduction in proptosis in tocilizumab patients compared to no change in proptosis in controls. Thus, there are promising data supporting the use of tocilizumab to treat TAO

Teprotumomab:

- The insulin-like growth factor-1 (IGF-1) receptor is overexpressed in GO orbital fibroblasts and lymphocytes
- The safety and efficacy of teprotumumab were evaluated sequentially in two RCTs, which comprised 170 patients with moderate-to-severe and active GO
- The pooled ITT population consisted of 84 patients assigned teprotumumab and 87 assigned placebo
- Seventy-three percent in teprotumumab groups (vs 14% in placebo groups) were overall responders with both CAS and proptosis improvement.
- CAS of 0–1 (62% vs 22%) and proptosis response (77% vs 15%)
- Proptosis response occurred early at week 6 in most patients. The mean reduction in proptosis by week 24 ranged from 2.9 to 3.3 mm.
- One year after the final dose, integrated proptosis, diplopia, and composite responses were 67, 69, and 83%

- Teprotumumab side effects included muscle spasms (25%), nausea (17%), alopecia (13%), diarrhea (13%), fatigue (10%), hearing impairment (10%), and hyperglycemia (8%).

- the number of diplopia responders was also significantly higher with teprotumumab for all subgroups except tobacco users and patients with TBII less than 10 IU/L at baseline. I

- Teprotumumab is contraindicated for those with inflammatory bowel disease and in pregnancy

Teprotumumab for patients with active thyroid eye disease: a pooled data analysis, subgroup analyses, and off-treatment follow-up results from two randomised, double-masked, placebo-controlled, multicentre trials

George J Kahaly, Raymond S Douglas*, Robert J Holt, Saba Sile, Terry J Smith*

Lancet Diabetes Endocrinol 2021; 9: 360–72

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See Comment page 323

*Contributed equally to this manuscript and share first authorship

Department of Medicine I, Johannes Gutenberg University Medical Center, Mainz, Germany (Prof G J Kahaly MD); Cedars-Sinai Medical Center, Los Angeles, CA, USA (Prof R S Douglas MD); Horizon Therapeutics, Deerfield, IL, USA (R J Holt PharmD, S Sile MD); Kellogg Eye Center-Michigan Medicine and University of

Summary

Background Thyroid eye disease manifests inflammation and treatment-resistant proptosis and diplopia. Teprotumumab, an insulin-like growth factor-1 receptor inhibiting monoclonal antibody, was approved in the USA on Jan 21, 2020, on the basis of two randomised trials. In this analysis we evaluated the short-term and long-term aggregate response to teprotumumab from the two trials, focusing on proptosis and diplopia.

Methods We analysed integrated outcomes and follow-up data from two randomised, double-masked, placebo-controlled, multicentre, trials done at a total of 28 academic referral tertiary specialised centres offering joint thyroid eye clinics, or orbital clinics or practices, or both, in Europe and the USA. Participants were adult patients with a diagnosis of Graves' disease and active moderate-to-severe thyroid eye disease (clinical activity score [CAS] ≥4). Patients received eight intravenous infusions of either teprotumumab (10 mg/kg body weight for the first infusion, 20 mg/kg for subsequent infusions) or placebo every 3 weeks. The final study visit was at week 24, 3 weeks after the final infusion. In our analysis, the prespecified primary outcome was the between-group difference from baseline to week 24 in the proportion of patients with a proptosis response (≥2 mm reduction in the study eye without similar deterioration in the fellow eye at week 24) stratified by tobacco non-use and current use. Secondary endpoints at week 24 were the proportion of patients with improved diplopia (≥1 Bahn–Gorman grade), an overall response (reduction of ≥2 mm in proptosis and reduction of ≥2 points in CAS), mean change from baseline in proptosis measurement in the study eye, mean change from baseline in Graves' ophthalmopathy quality of life (GO-QOL) questionnaire scores (overall, visual functioning, and appearance), and the proportion of patients with disease inactivation (ie, a CAS score of 0 or 1). We also assessed data

TSHR antagonist

- Small molecule antagonists targeting TSHR have been developed and tested in preclinical studies. These antagonists selectively inhibit TSH-stimulated signaling. They have been found to reduce serum free T4 levels by 44% and lower mRNAs for thyroperoxidase by 83%.TSHR antagonists present a promising option for targeted therapy.

Adalimumab

- Adalimumab, an antitumor necrosis factor-alpha (TNF-α) agent, was evaluated for the treatment of active TED in a small retrospective study. Four out of 10 patients reported subjective improvements in diplopia, pain, and swelling; however, there were no significant objective improvements in proptosis or extraocular movement restriction

Infliximab

- Infliximab is a monoclonal antibody that targets TNF-α. Its use in cases of steroid-resistant, severe TED has been reported with improvement in VA and CAS after one dose in one case report and complete resolution in three cases after three doses

Table 2. Summary of biologic therapies for TED.

Small Molecule Therapies	Target	Dosing	Findings	Side Effects
Rituximab	CD20	Two infusions of 1000 mg each two weeks apart	Mixed results in improvement of clinical activity score (CAS), proptosis, and motility[65,66]	Exacerbation of inflammatory bowel disease, arthralgias, hypotension
Adalimumab	TNF-α	Subcutaneous injections of initial 80 mg dose, then biweekly 40 mg doses for a total of 10 weeks	6/10 showed decrease in inflammation, no changes in proptosis or extraocular motility[67]	Sepsis (1/10)
Infliximab	TNF-α	Infusions at 5 mg/kg each dose over 2 h	Case reports showed improvement in visual acuity and CAS after 1 dose and complete resolution in three cases after 3 doses[68,69]	Infections, malignancies (especially lymphoma), drug-induced lupus
Tocilizumab	IL-6	Three infusions at 8 mg/kg given every 4 weeks	93% with ⩾2-point improvement in CAS, mean proptosis reduction of 1.5 mm, no change in diplopia[70]	High recurrence rate, transaminitis, pyelonephritis
Teprotumumab	IGF-1R	Initial infusion at 10 mg/kg, followed by seven infusions at 20 mg/kg given every 3 weeks	Reduced proptosis in 79–83% of patients, improved CAS in 69%, reduced diplopia in 68%[71,72]	Most common: muscle spasms fatigue, nausea, diarrhea, hyperglycemia, hearing impairment, and alopecia. 5–12% with serious adverse events requiring early withdrawal.
Emerging Therapies				
IMVT-1401 (Phase II clinical trials)	FcRn	Subcutaneous injections of two weekly 680 mg doses followed by four weekly 340 mg doses	4/7 with ⩾ 2-point improvement of CAS, 3/7 with improved proptosis, 65% reduction in IgG levels (ASCEND-GO 1 clinical trial, NCT03922321)	No serious adverse events
TSHR Antagonist (Preclinical)	TSHR	N/A	N/A	N/A

Mycophenolate :

- Mycophenolate competitively and reversibly inhibits inosine monophosphate dehydrogenase, resulting in:
- Decreased antibody production by B cells and dual antiproliferative effect on both B- and T-cells
- Mycophenolate induces apoptosis of activated T-cells
- Mycophenolate inhibits fibroblast proliferation and functions

- In the EUGOGO's observer-masked multicenter trial the combination group displayed statistically significant superior response rate at week 24 (71% vs 53%) and a sustained response rate at week 36 (67% vs 45.5%).

- Overall, combination treatment demonstrated more significant improvements in CAS, swelling of eyelids and caruncle, orbital pain, chemosis, downgaze duction and elevation, as well as GO-QoL visual functioning score.

- In addition, the mycophenolate sodium+glucocorticoid group of the EUGOGO trial performed better than mycophenolate alone

- The combination treatment did not increase the risk of infection and hepatotoxicity when compared to i.v. methylprednisolone monotherapy

Efficacy and safety of mycophenolate mofetil in the treatment of moderate to severe Graves' orbitopathy: a meta-analysis*

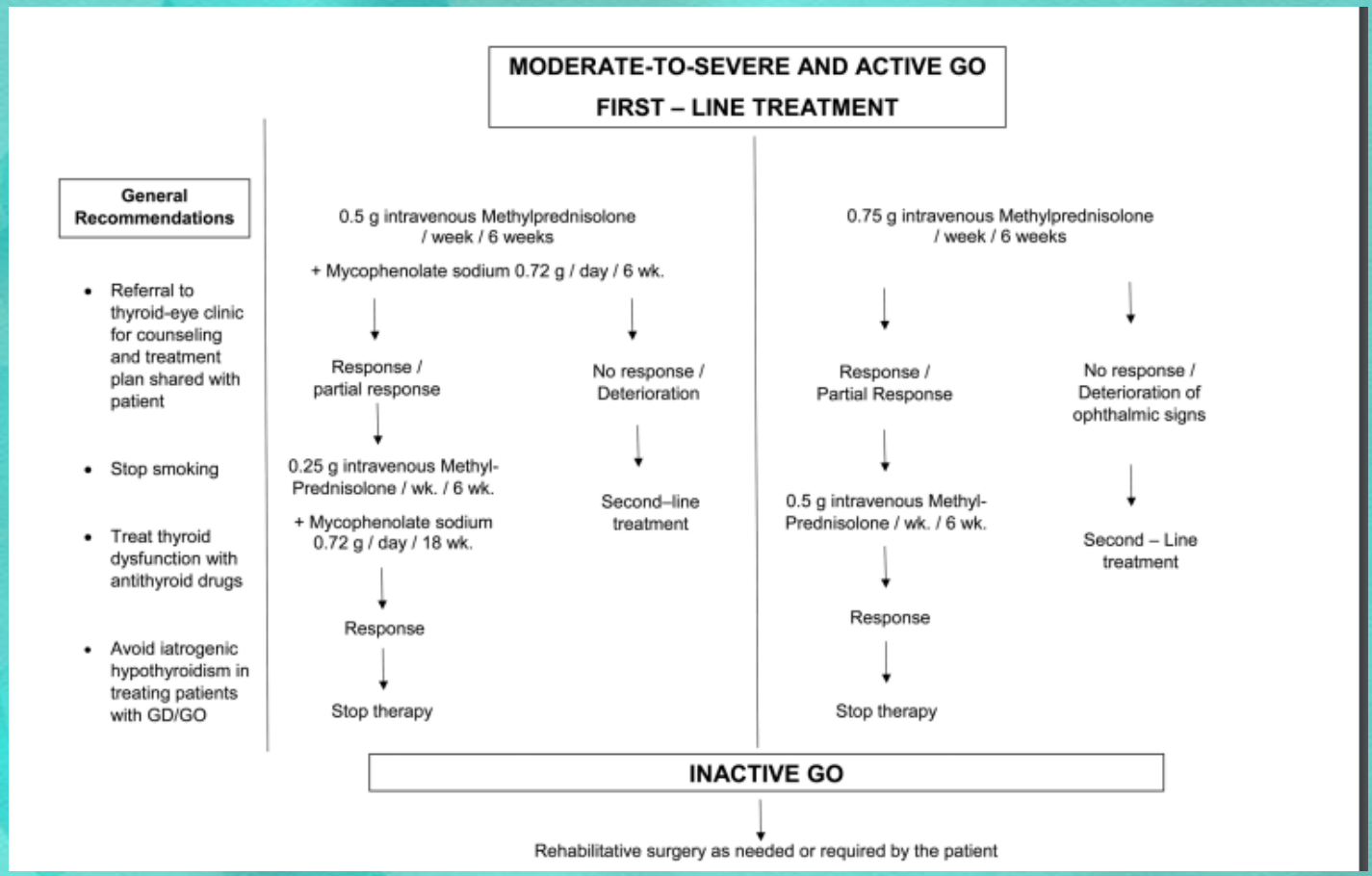
(*BIOENGINEERED 2022*)

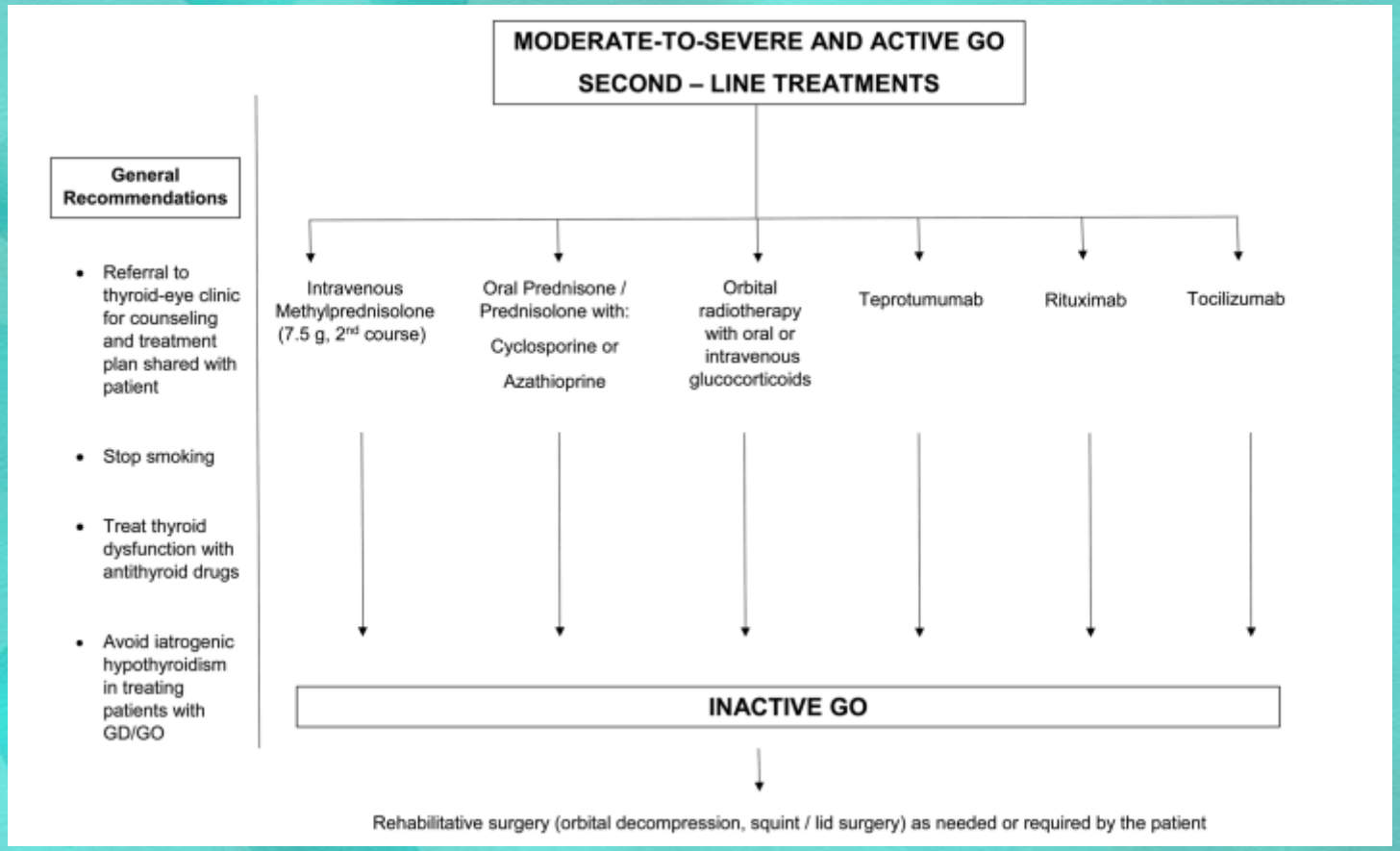
Wenwen Fenga,*, Yifang Hua,b,*, Chengzhou Zhanga,c,*, He Shid, Peng Zhange, Yanli Yanga, Shiying Chena, Weijiang Cuie, and Dai Cui

Department of Endocrinology, the First Affiliated Hospital of Nanjing Medical University, Nanjing, China; bDepartment of Geriatric Endocrinology, the First Affiliated Hospital of Nanjing Medical University, Nanjing, China; cDepartment of Internal Medicine, Maternal and Child Health Hospital of Yancheng, Yancheng, China; dDepartment of Nuclear Medicine, the First Affiliated Hospital of Nanjing Medical University, Nanjing, China; eDepartment of Ophthalmology, Ili & Jiangsu Joint Institute of Health, the Friendship Hospital of Ili Kazakh Autonomous Prefecture, Ili, China

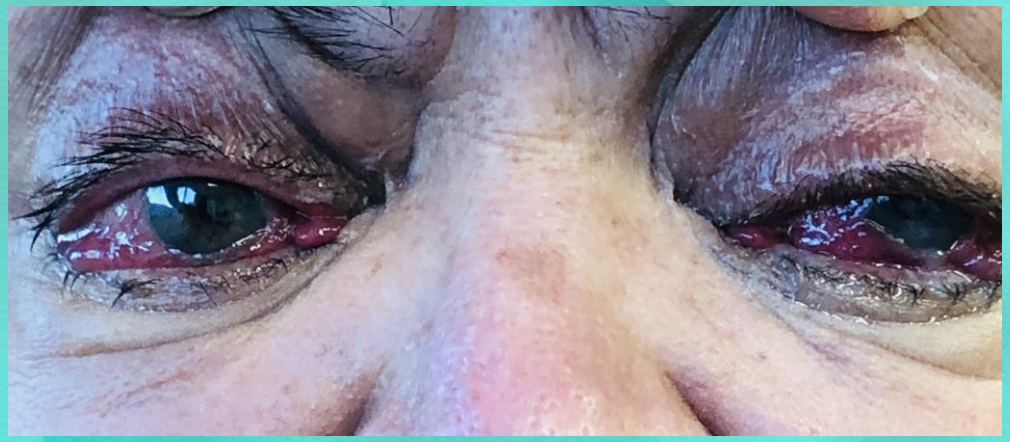
- A meta-analysis of clinical control trials comparing MMF (with or without glucocorticoid (GC)) for the treatment of GO with GC was conducted.

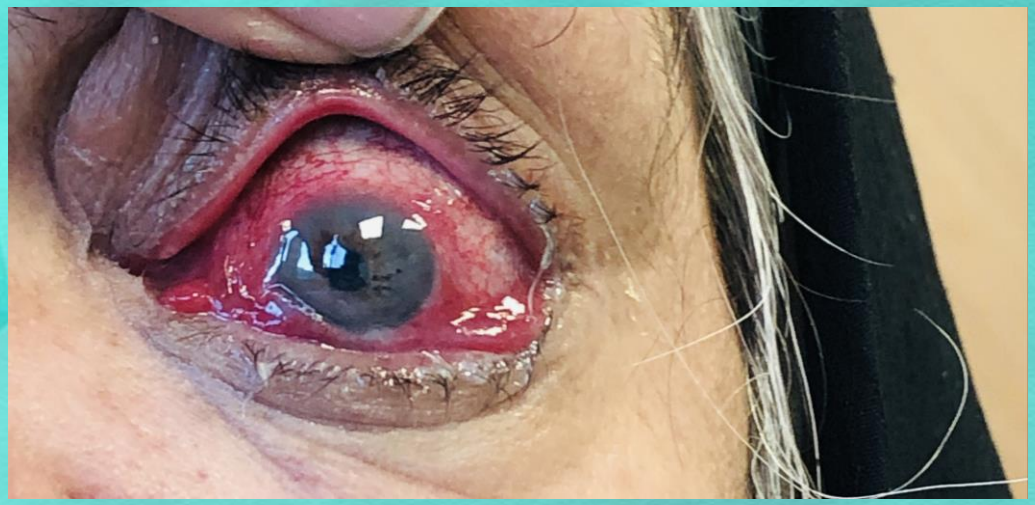
- The results showed that MMF (with or without GC) was superior to GC in the treatment of GO. Subgroup analyses also showed that MMF monotherapy was more effective than GC. Compared to methylprednisolone (MP) monotherapy, a combination of MP and MMF was more effective. CAS decreased even more significantly and fewer AEs occurred in patients receiving MMF. Compared with GC therapy, MMF is safer and more effective. However, more large-sample and high-quality studies targeting MMF use in GO patients and long-term surveillance of prognosis are urgently needed.

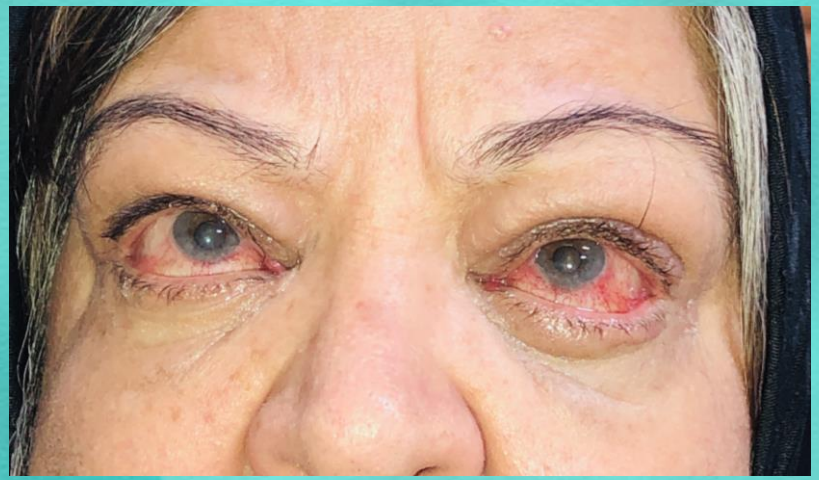

MODERATE-TO-SEVERE AND ACTIVE GO
FIRST – LINE TREATMENT
General Recommendations
Referral to thyroid-eye clinic for counseling and treatment plan shared with patient
Stop smoking
Treat thyroid dysfunction with antithyroid drugs
Avoid iatrogenic hypothyroidism in treating patients with GD/GO
0.5 g intravenous Methylprednisolone / week / 6 weeks
+ Mycophenolate sodium 0.72 g / day / 6 wk.
Response / partial response
0.25 g intravenous Methyl-Prednisolone / wk. / 6 wk.
+ Mycophenolate sodium 0.72 g / day / 18 wk.
Response
Stop therapy
No response / Deterioration
Second–line treatment
0.75 g intravenous Methylprednisolone / week / 6 weeks
Response / Partial Response
0.5 g intravenous Methyl-Prednisolone / wk. / 6 wk.
Response
Stop therapy
No response / Deterioration of ophthalmic signs
Second – Line treatment
INACTIVE GO
Rehabilitative surgery as needed or required by the patient

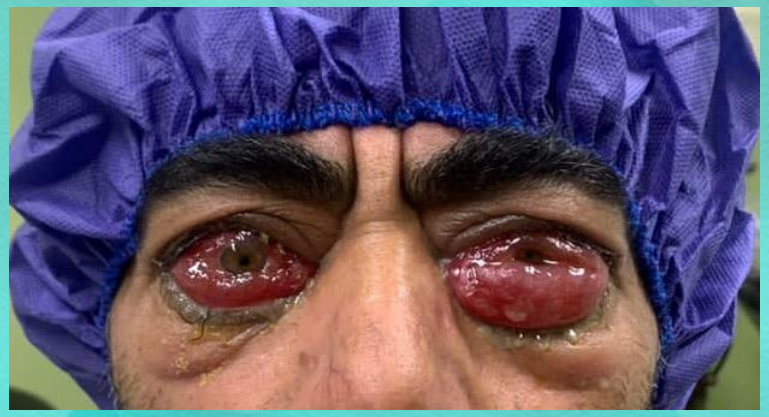

MODERATE-TO-SEVERE AND ACTIVE GO
SECOND – LINE TREATMENTS
General Recommendations
• Referral to thyroid-eye clinic for counseling and treatment plan shared with patient
• Stop smoking
• Treat thyroid dysfunction with antithyroid drugs
• Avoid iatrogenic hypothyroidism in treating patients with GD/GO
Intravenous Methylprednisolone (7.5 g, 2nd course)
Oral Prednisone / Prednisolone with:
Cyclosporine or
Azathioprine
Orbital radiotherapy with oral or intravenous glucocorticoids
Teprotumumab
Rituximab
Tocilizumab
INACTIVE GO
Rehabilitative surgery (orbital decompression, squint / lid surgery) as needed or required by the patient

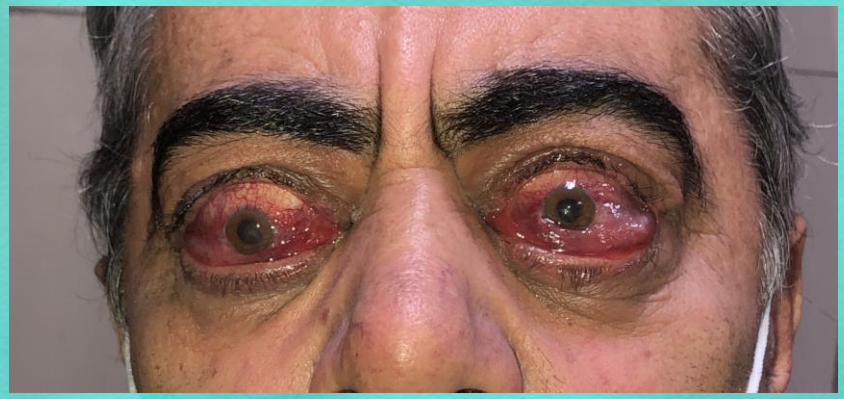
Congestive orbitopathy

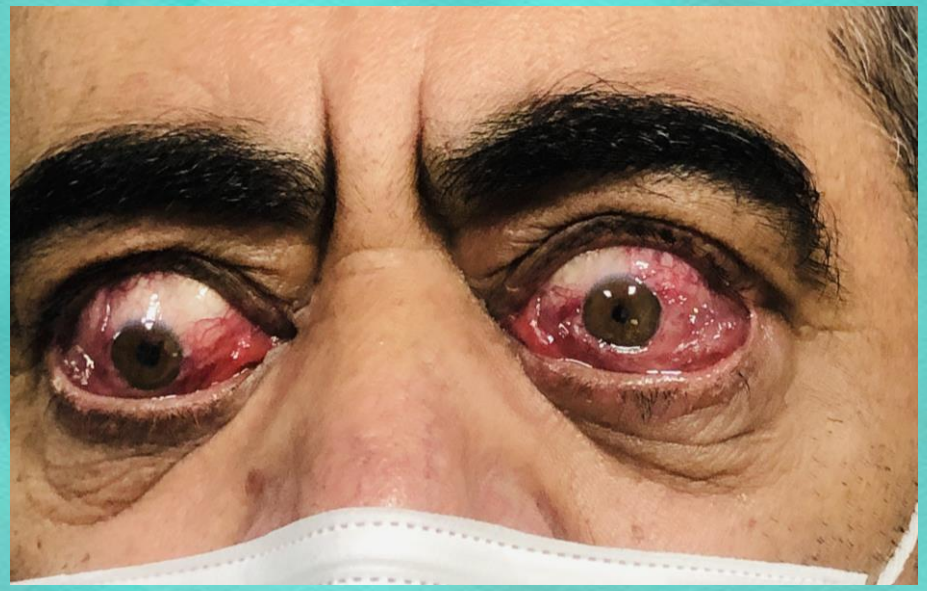












The role of thyroidectomy

Brammen *et al. Trials* (2018) 19:495
https://doi.org/10.1186/s13063-018-2876-0

Trials

STUDY PROTOCOL Open Access

Total thyroidectomy (Tx) versus thionamides (antithyroid drugs) in patients with moderate-to-severe Graves' ophthalmopathy – a 1-year follow-up: study protocol for a randomized controlled trial

Lindsay Brammen[1], Philipp Riss[1,6*], Julius Lukas[2], Alois Gessl[3], Daniela Dunkler[4], Shuren Li[5], Asha Leisser[5], Sandra Rezar-Dreindl[2], Katharina Eibenberger[2], Andreas Selberherr[1], Christian Scheuba[1] and Andrea Papp[2]

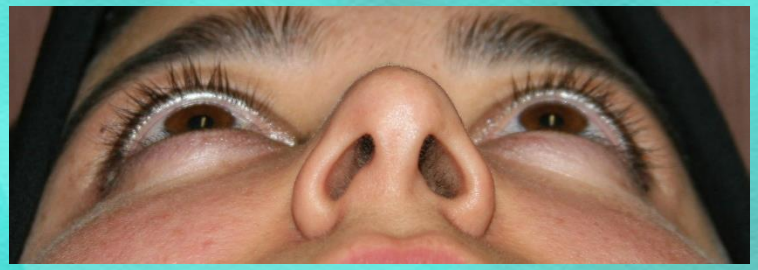
- Elsayed YA, Abdul-Latif AM, Abu-Alhuda MF, et al. Effect of near-total thyroidectomy on thyroid orbitopathy due to toxic goiter. World J Surg 2009; 33: 758–766

- Clinical activity evaluation, exophthalmometry and extraocular muscles measurement by MRI revealed that the majority of the cases experienced improvement of their ophthalmopathy [65%]

Surgical rehabilitation

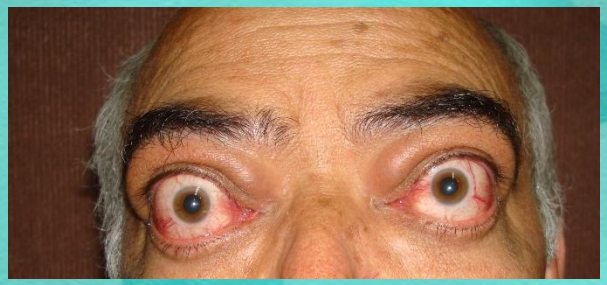
- Orbital decompression (Fat, lateral wall, medial wall, inferior wall)
- Strabismus surgery
- Eyelid surgery (retraction, blepharoplasty)

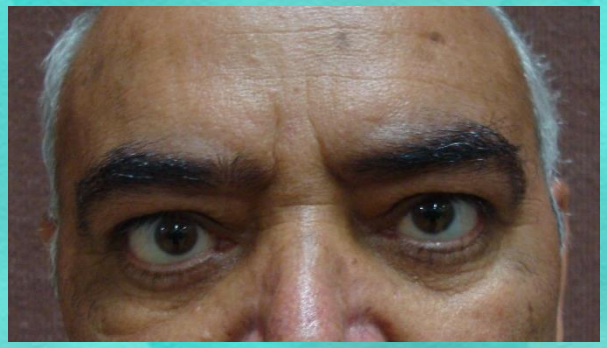
Fat and medial wall decompression , levator recession



Muller recession

1-before surgery
2-medial and inferior wall decompression (arrow)
3- lateral wall decompression and levator recession





Medial wall decompression, retractor recession and spacer