

Graves' Orbitopathy

Hengameh Abdi, MD

Endocrine Research Center

Research Institute for Endocrine Sciences

Shahid Beheshti University of Medical Sciences

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Tehran

No Disclosures

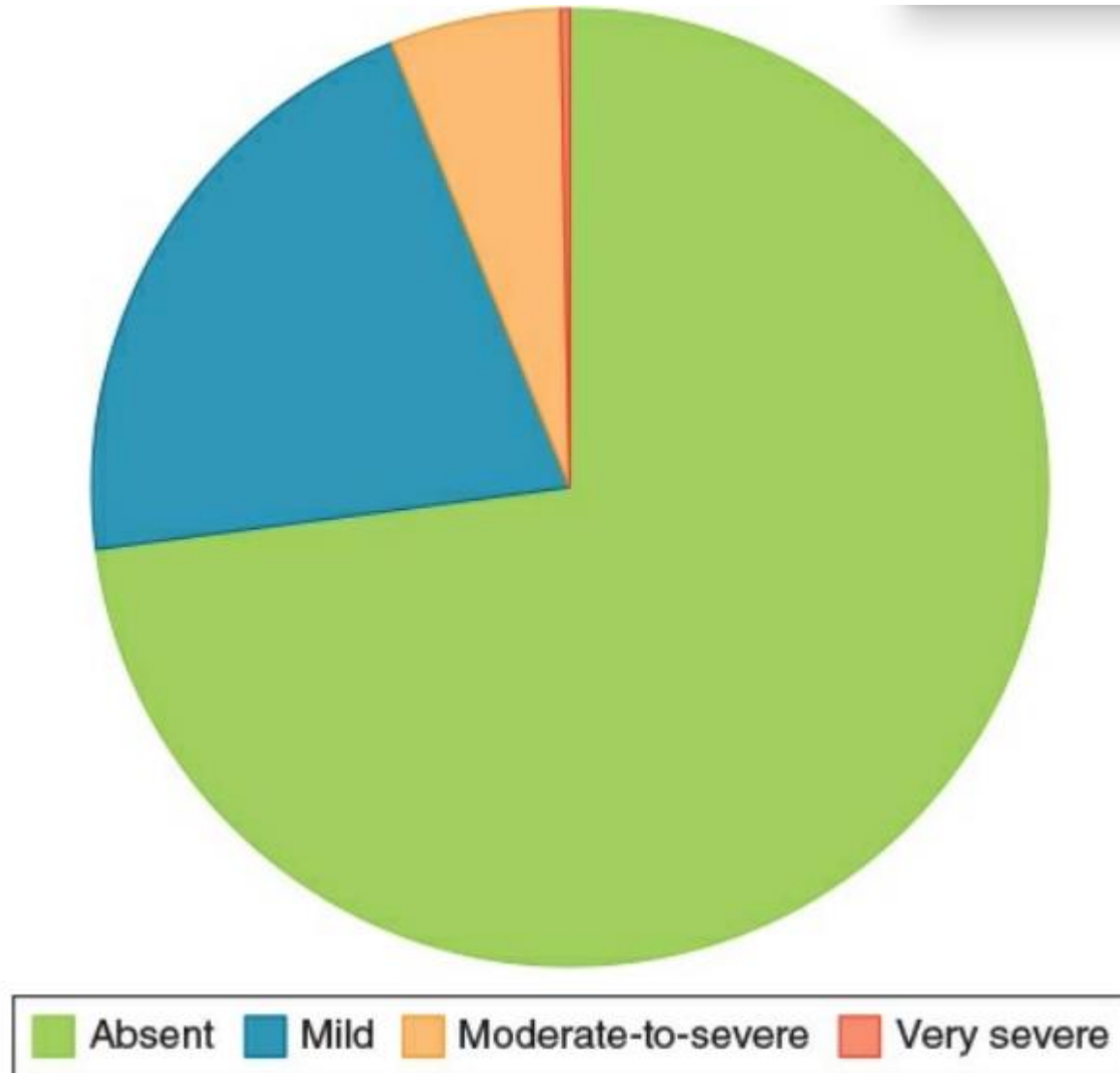
Outlines

- Epidemiology
- Pathogenesis
- Natural history
- Risk factors
- Classification
- Conclusion

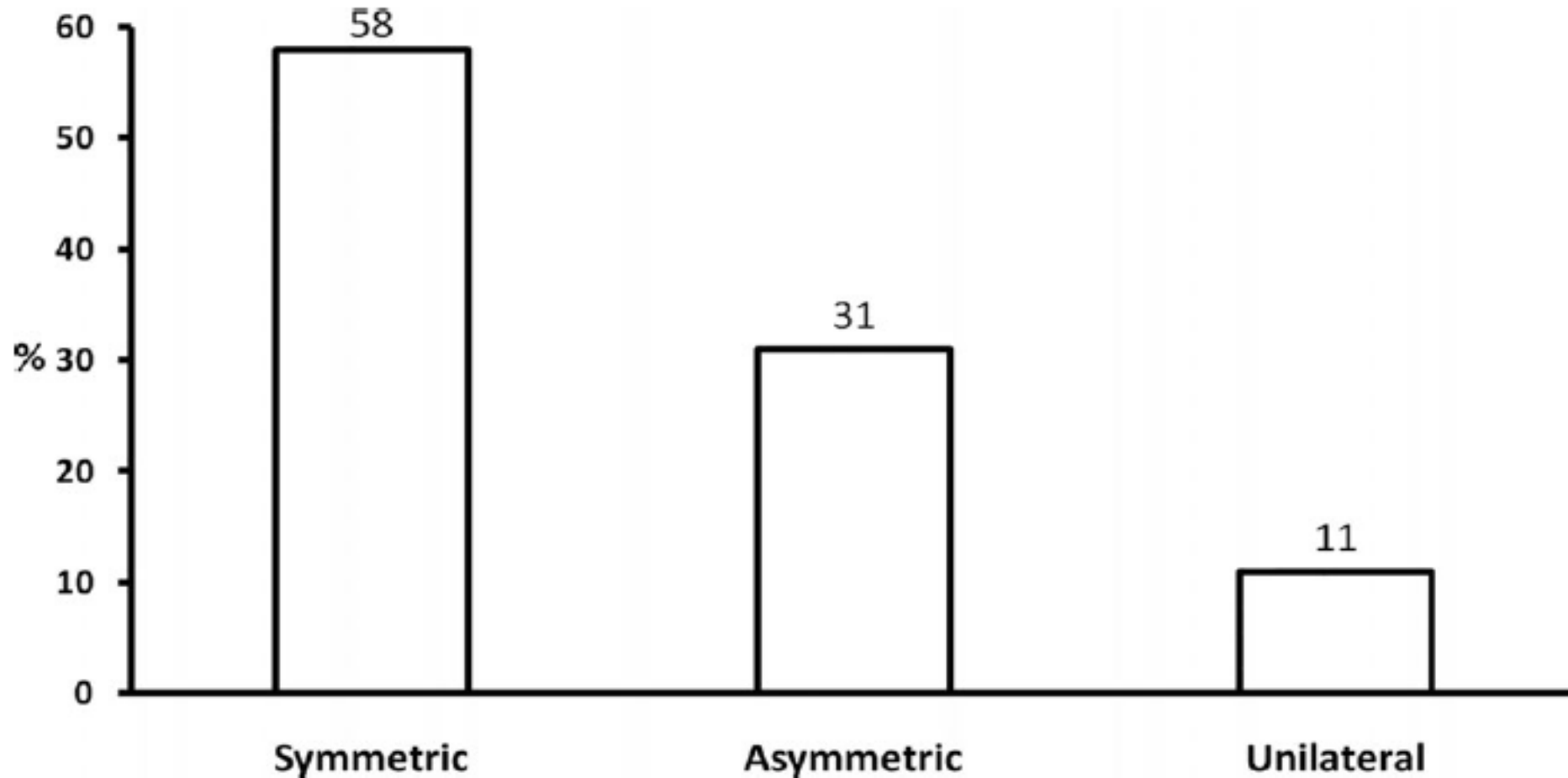
Graves' orbitopathy-Epidemiology

- Thyroid eye disease or thyroid-associated orbitopathy
- A relatively rare autoimmune disorder
- The major extrathyroidal manifestation of Graves' disease
- Sometimes in patients with euthyroid or hypothyroid chronic autoimmune thyroiditis
- Incidence: 0.54-0.9/100,000/year in men
2.67-3.3/100,000/year in women
- More commonly mild and nonprogressive
- Moderate-to-severe forms: 5-6% of cases

Prevalence and severity of GO in patients with newly diagnosed and recent-onset GD



Presentation of Graves' orbitopathy in a series of 269 patients referred to EUGOGO tertiary centers



EUGOGO, European Group on Graves' orbitopathy

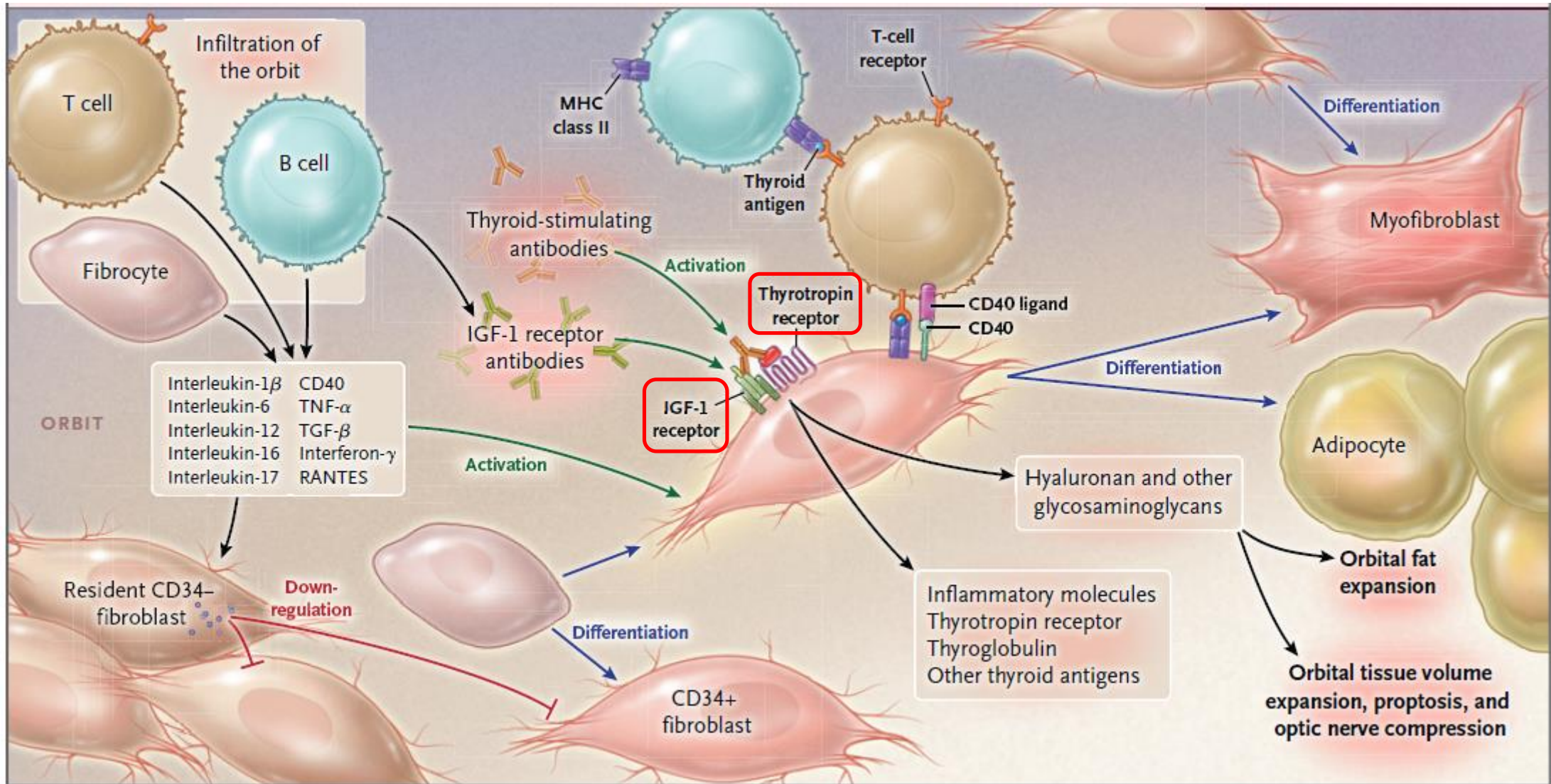
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Pathogenesis

- Failure of T cells to tolerate the thyrotropin receptor and development of autoimmunity directed against this receptor-TSH receptor antibodies
- Immunological cross-reactivity of thyroid and orbital antigens in muscular, connective, and adipose tissues-“shared antigen” hypothesis
- The IGF-1 receptor and related autoantibodies
- Increased volume of both extraocular muscles and retroocular connective tissue

Theoretical model of the pathogenesis of Graves' orbitopathy



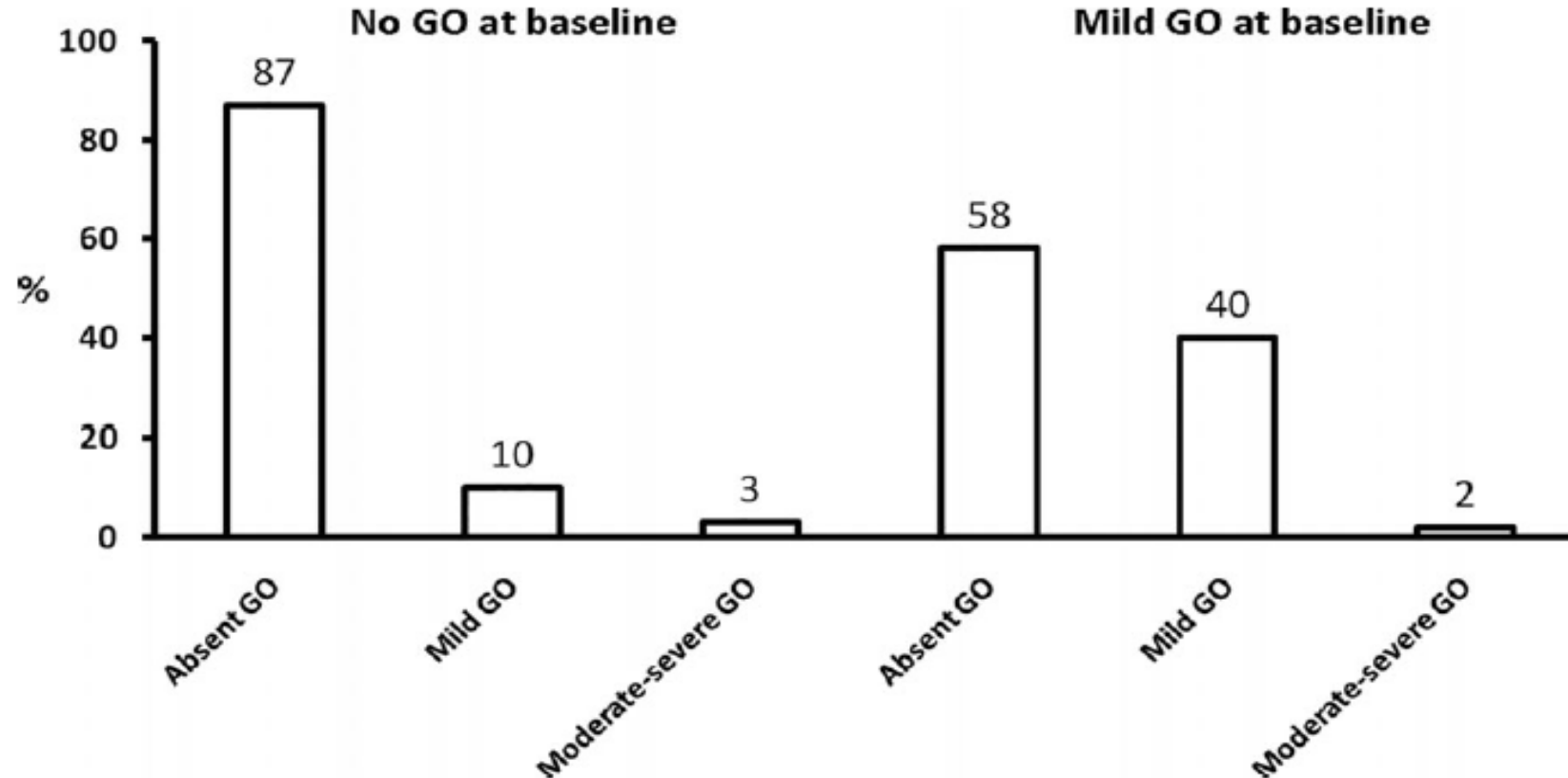
Clinical features of Graves orbitopathy

Feature	Cause
Exophthalmos	Increase in orbital tissue volume (enlargement of extraocular muscle and/or expansion of fibroadipose tissue)
Lacrimation, photophobia, grittiness, conjunctival hyperemia, chemosis, lagophthalmos	Ocular surface involvement due to exophthalmos and eyelid retraction
Pain at rest and/or with eye movements	Extraocular muscle inflammation
Diplopia, strabismus	Extraocular muscle involvement
Blurred vision	Excessive lacrimation Dysthyroid optic neuropathy
Decreased visual acuity, impaired color sensitivity	Dysthyroid optic neuropathy

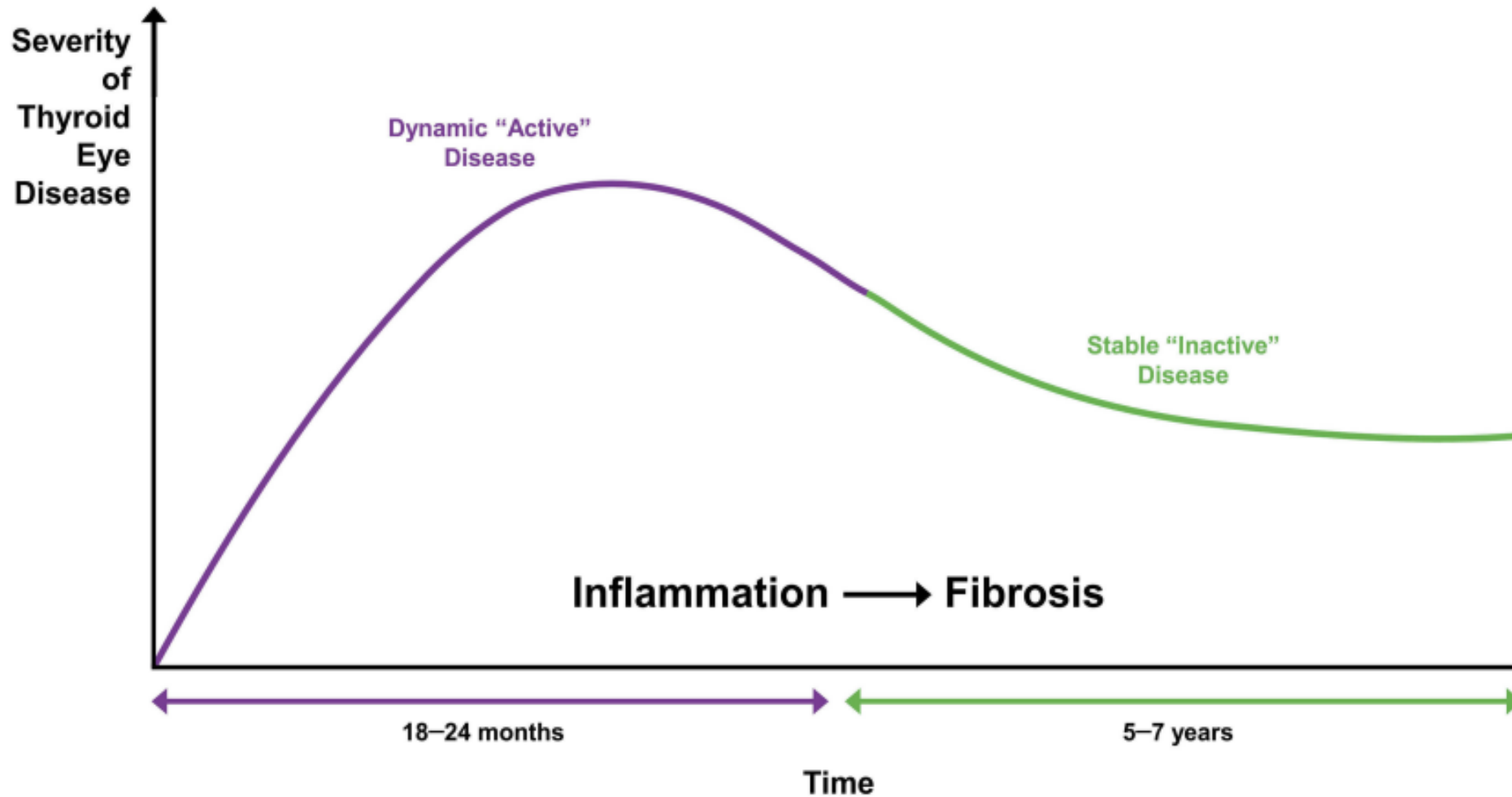
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Natural history of Graves' orbitopathy at the end of antithyroid drug treatment



Severity of thyroid eye disease over time-Rundle curve



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Graves' orbitopathy-Risk factors

- **Unmodifiable:**

- Age
- Gender
- Genetic (?)

- **Modifiable:**

- Smoking
- Radioactive iodine therapy for hyperthyroidism
- Thyroid dysfunction
- Oxidative stress
- Hypercholesterolemia

Graves' orbitopathy-Risk factors *(continued)*

- Age is a relevant factor affecting severity of GO, and the disease tends to be more severe in older patients.
- GO tends to be relatively more severe in men, in whom it occurs at a more advanced age.
- Ethnicity: controversial

Graves' orbitopathy-Risk factors *(continued)*

- Smoking increases the risk of GO in patients with GD.
- Smokers have more severe GO.
- Development or progression of GO after radioactive iodine treatment is more frequent in smokers.
- Smokers have a delayed or worse outcome of immunosuppressive treatments.
- Smoking cessation is possibly associated with a better outcome of GO.
- All patients with GD, irrespective of the presence of GO, should be urged to quit smoking.

Graves' orbitopathy-Risk factors *(continued)*

- Radioactive iodine bears a consistent risk of causing progression and/or de novo occurrence of GO.
- Both de novo occurrence and progression of GO following radioactive iodine are more likely in smokers, in patients with duration of GD <5 years, and less likely in patients with long-standing and inactive GO.

Graves' orbitopathy-Risk factors *(continued)*

- TSH receptor antibodies strongly correlate with the clinical activity and severity of GO.
- 85% of cases GO develops within 18 months before or after the onset of hyperthyroidism.
- Both hyperthyroidism and hypothyroidism have a negative impact on the occurrence/progression of GO.
- Euthyroidism should be promptly restored and stably maintained in all patients with GO.

Graves' orbitopathy-Risk factors *(continued)*

- High cholesterol is an emerging and potential risk factor for GO.
- Serum total and LDL cholesterol levels correlate the presence and activity of GO.
- Based on the findings of a US cohort study, the use of statins was associated with a decreased risk of developing GO.
- Oxidative stress and a trial of 6-month supplementation of selenium in mild active GO of recent onset

Bartalena L, Kahaly GJ, et al. Eur J Endocrinol 2021;185:G43-G67.

Bartalena L, et al. Front Endocrinol 2020;11:615993.

Stein JD, et al. JAMA Ophthalmol 2015 Mar;133(3):290-6.

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Clinical activity score (CAS)

Painful, oppressive feeling on or behind the globe, during the past 4 weeks

Pain on attempted up, side, or down gaze, during the past 4 weeks

Redness of the eyelid(s)

Diffuse redness of the conjunctiva, covering at least one quadrant

Swelling of the eyelid(s)

Chemosis

Swollen caruncle

Increase of proptosis of ≥ 2 mm during a period of 1–3 months

Decrease of eye movements in any direction $\geq 8^\circ$ during a period of 1–3 months

Decrease of visual acuity of ≥ 1 line(s) on the Snellen chart (using a pinhole) during a period of 1–3 months

Total

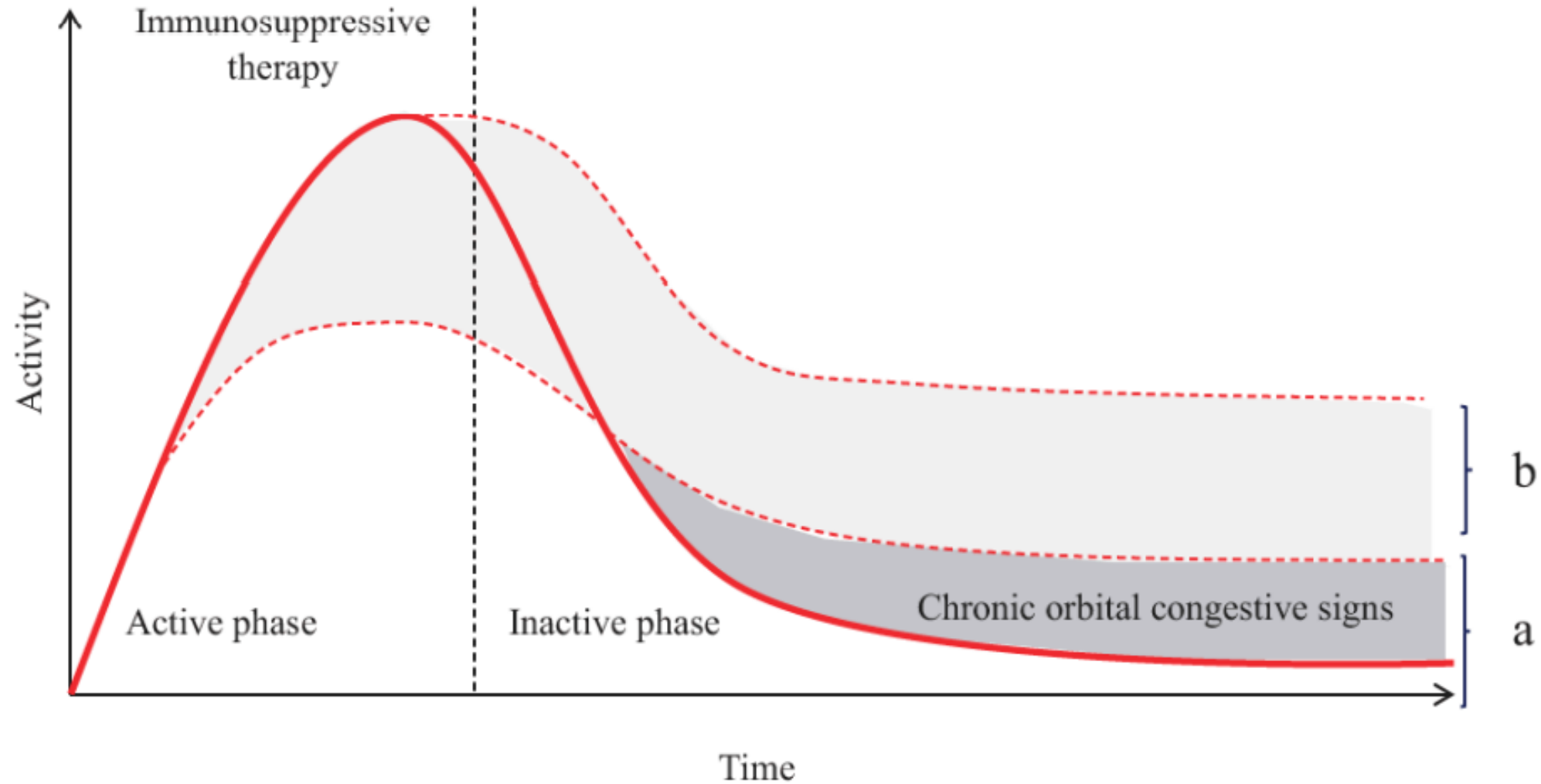
3/7 first visit
4/10 second visit

Active GO



Changes of GO activity in relation to the efficacy of immunosuppression

successful (a) or unsuccessful (b) response to therapy

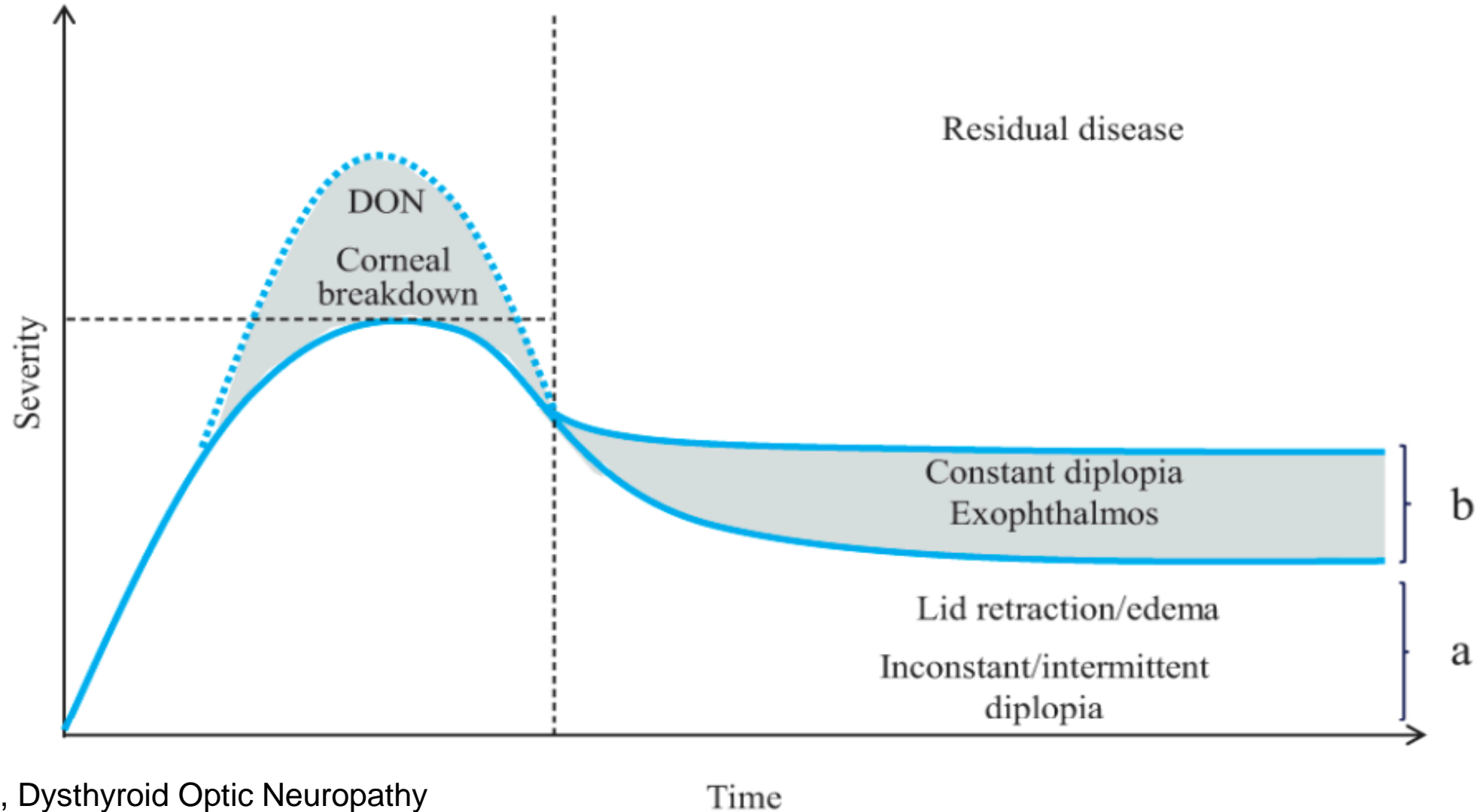


Classification of severity of Graves' orbitopathy

Classification	Features
<u>Mild GO</u>	<p>Patients whose features of GO have only a minor impact on daily life that have insufficient impact to justify immunomodulation or surgical treatment. They usually have one or more of the following:</p> <ul style="list-style-type: none">• minor lid retraction (<2 mm)• mild soft-tissue involvement• exophthalmos• <3 mm above normal for race and gender• no or intermittent diplopia and corneal exposure responsive to lubricants
<u>Moderate-to-severe GO</u>	<p>Patients without sight-threatening GO whose eye disease has sufficient impact on daily life to justify the risks of immunosuppression (if active) or surgical intervention (if inactive). They usually have two or more of the following:</p> <ul style="list-style-type: none">• lid retraction ≥ 2 mm• moderate or severe soft-tissue involvement• exophthalmos ≥ 3 mm above normal for race and gender• inconstant or constant diplopia
<u>Sight-threatening (very severe) GO</u>	<p>Patients with dysthyroid optic neuropathy and/or corneal breakdown</p>

Severity of GO according to the Rundle model

The degree of residual disease is related to successful (a) or unsuccessful (b) immunosuppression.



DON, Dysthyroid Optic Neuropathy

Time

Predictive score for the occurrence of GO (PREDIGO) based on features at presentation

Feature	Cut-Off Value	Score
Clinical activity score	0	0
	≥1	5
TSH-receptor antibodies (U/l)	<2	0
	2–10	2
	>10	5
Duration of hyperthyroidism (months)	<1	0
	1–4	1
	>4	3
Active smoking	No	0
	Yes	2

Conclusion

- Graves' orbitopathy (GO) is a rare autoimmune disease appearing in most cases as a mild disease but in a distinct minority of cases, a sight-threatening, life-altering and socially isolating disease.
- With regards to its known modifiable risk factors, related actions to control them would be helpful to prevent the occurrence or progression of GO.
- Treatment decisions are based on clinical activity, severity, and duration of GO.
- Validated scoring systems are available to classify GO activity and severity for an individualized management.

Thank you for listening.

