International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Scholarly Publisher
RS Global Sp. z O.O.
ISNI: 0000 0004 8495 2390

Dolna 17, Warsaw,
Poland 00-773
+48 226 0 227 03
editorial_office@rsglobal.pl

ARTICLE TITLE	GRAVES' ORBITOPATHY: AN UPDATED REVIEW OF PATHOGENESIS, CLINICAL FEATURES, AND TREATMENT STRATEGIES
DOI	https://doi.org/10.31435/ijitss.3(47).2025.3718
RECEIVED	03 August 2025
ACCEPTED	16 September 2025
PUBLISHED	19 September 2025
LICENSE	The article is licensed under a **Creative Commons Attribution 4.0 International License.**

GRAVES' ORBITOPATHY: AN UPDATED REVIEW OF PATHOGENESIS, CLINICAL FEATURES, AND TREATMENT STRATEGIES

Julia Lipiec *(Corresponding Author, Email: julialipiex@gmail.com)*
Independent Public Health Care Facility of the Ministry of Internal Affairs and Administration in Kielce, Poland
ORCID ID: 0009-0004-3351-4056

Alicja Bury
Orlowski Hospital in Warsaw, Poland
ORCID ID: 0009-0009-2950-8741

Konrad Kotte
St. Alexander Hospital in Kielce, Poland
ORCID ID: 0009-0008-9745-985X

Olaf Jadanowski
University of Health Sciences in Bydgoszcz, Poland
ORCID ID: 0009-0000-6279-3067

Kamil Łebek
Jan Kochanowski University, Kielce, Poland
ORCID ID: 0009-0005-4612-5022

Weronika Sobota
National Medical Institute of the MSWiA, Warsaw, Poland
ORCID ID: 0009-0000-7778-7030

Przemysław Piskorz
National Medical Institute of the MSWiA, Warsaw, Poland
ORCID ID: 0009-0000-9812-2230

Daria Litworska-Sójka
Wojewódzki Szpital Zespolony, Kielce, Poland
ORCID ID: 0009-0005-4590-3777

Bartosz Komsta
Military Institute of Medicine – National Research Institute, Warsaw, Poland
ORCID ID: 0009-0003-1159-5855

Wojciech Pabis
5th Military Research Hospital and Polyclinic, Cracow, Poland
ORCID ID: 0009-0006-3455-4724

ABSTRACT

Graves' orbitopathy (GO) otherwise known as thyroid ophthalmopathy or thyroid eye disease (TED) is an ocular disorder that involves autoimmune inflammation of the soft tissues of the orbit. This leads to exophthalmos of the eyeballs and a range of other associated ocular symptoms. It is a complication of the ongoing inflammatory process in the course of Graves-Basedow disease, which leads to temporary or permanent damage to the eye. Orbitopathy most often accompanies hyperthyroidism and is rarely the only symptom of Graves' disease.

KEYWORDS

Orbitopathy, Graves-Basedow Disease, Hyperthyroidism, Autoimmune Disease

CITATION

Lipiec Julia, Bury Alicja, Kotte Konrad, Jadanowski Olaf, Łebek Kamil, Sobota Weronika, Piskorz Przemysław, Litworska-Sójka Daria, Komsta Bartosz, Pabis Wojciech. (2025) Graves' Orbitopathy: An Updated Review of Pathogenesis, Clinical Features, and Treatment Strategies. *International Journal of Innovative Technologies in Social Science*. 3(47). doi: 10.31435/ijitss.3(47).2025.3718

Introduction

Graves' orbitopathy, also known as thyroid eye disease, is the most common extrathyroidal manifestation of Graves'disease (GD) and represents a complex autoimmune disorder with potentially sight-threatening consequences. The condition is characterized by inflammation and remodeling of the orbital tissues, leading to a spectrum of clinical manifestations ranging from mild ocular discomfort and periorbital swelling to proptosis, diplopia, and, in severe cases, compressive optic neuropathy. Although its association with autoimmune thyroid dysfunction has long been established, the underlying pathogenic mechanisms remain only partially understood and continue to be the subject of intensive research.

Over the past decades, significant progress has been made in elucidating the molecular and immunological basis of GO, highlighting the central role of autoantibodies directed against the thyrotropin receptor (TSHR) and insulin-like growth factor-1 receptor (IGF-1R). This deeper understanding has translated into the development of targeted therapies, which are gradually reshaping the clinical management of the disease. Nevertheless, challenges persist, particularly in identifying reliable predictors of disease activity and severity, and in optimizing treatment strategies to improve both functional outcomes and quality of life.

Given the ongoing evolution of knowledge in this field, a comprehensive review of the current understanding of GO is warranted. This article aims to provide an updated overview of the pathogenesis, clinical features, and treatment strategies of Graves' orbitopathy, emphasizing recent advances that may influence future diagnostic and therapeutic approaches.

Methodology

This review was conducted as a narrative synthesis of the current literature on Graves' orbitopathy. A comprehensive search of electronic databases was performed to identify relevant publications up to *August 2025*. The following keywords and combinations were used: *"Graves' orbitopathy," "thyroid eye disease," "pathogenesis," "clinical features," "diagnosis," "treatment,"* and *"therapy."* Reference lists of retrieved articles were also screened to identify additional pertinent studies. The selection process emphasized studies addressing three main domains: the pathogenesis and molecular mechanisms underlying Graves' orbitopathy, the spectrum of clinical manifestations and diagnostic evaluation and currently available as well as emerging treatment strategies. The evidence was synthesized qualitatively, with the aim of highlighting both consensus views and areas of ongoing debate or uncertainty.

Epidemiology

Thyroid orbitopathy is the most common extra-thyroid manifestation of Graves-Basedow disease. It occurs in approximately 30% of patients affected by the disease, and 5-10% of patients are affected by a severe form of the disease called infiltrative exophthalmos and require anti-inflammatory treatment. Orbitopathy may manifest simultaneously with the onset of hyperthyroidism or later within 18 months (70% of cases are affected), or it may appear before hyperthyroidism is manifested (25% of cases). It can also occur in patients without hyperthyroidism (<5%) or with hypothyroidism (<5%). Bilateral exophthalmos is the most common form, however, in some cases the autoimmune process is more severe in one orbit resulting in unilateral exophthalmos. Genetic, endogenous and environmental factors are involved in the development of the disease. A documented risk factor for this disease is smoking. Cigarette smokers have been shown to be at higher risk of developing ophthalmopathy and smoking has also been shown to correlate with disease severity. Graves' disease is 10 times more common in women than in men, although this ratio is only 2.5:1 for GO. The peak incidence is in women aged 40-44 and 60-64 years, and in men aged 45-49 and 65-69 years. The severity of GO increases with age, especially in men.

Predisposing factors for the development of ocular lesions in Graves' disease

The development of Graves' disease is multifactorial. To date, it has not been possible to identify a single factor that is fully responsible for the incidence and course of the disease. Based on studies that have been carried out on twins, it has been concluded that genetic factors are responsible for 80% of the development of the disease and environmental factors for 20%. Current research suggests that this is not a monogenic disease, but the result of interactions between multiple genes that result in a different predisposition to GD. The best proven genetic factor so far that predisposes to the development of Graves-Basedow disease are genes belonging to the major tissue compatibility system (HLA)-chromosome 6p21 and the CTLA-4 gene (a gene that encodes a T4 lymphocyte-associated antigen). These are not specific genes that predispose to the disease alone. They also influence the development of other autoimmune diseases. Although a significant influence of genetic factors on the development of disease has been demonstrated, the impact of these factors on the disease itself and the development of ophthalmopathy is not fully elucidated. There are studies that indicate a link between the occurrence of clinically overt thyroid orbitopathy and the role of the cytokine TNF. Environmental factors that have an impact are past infections, stress and iodine supply.

Pathogenesis

Three key processes can be identified in the pathogenesis of ocular lesions in Graves-Basedow disease: infiltration, oedema and extraocular tissue fibrosis. Extraocular infiltration has been shown to be present in 70-90% of patients affected by Graves-Basedow disease, although clinically manifested in a smaller group of individuals. The development of symptoms associated with orbitopathy is correlated with the presence of specific autoantibodies that are directed against extraocular muscle antigens within the eyeball or autoantibodies that cross-react with the aforementioned muscles and thyroid gland. A possible antigen common to both the thyroid gland and extraocular tissues is the receptor for TSH. A second possible potential antigen is thyroglobulin.

It has been observed that the severity of clinical signs associated with Graves' orbitopathy does not correlate with the degree of hyperthyroidism. They can often be present in euthyroid patients. In contrast, the severity of symptoms has been shown to be strongly correlated with TSH receptor antibody titres.

The infiltration of mononuclear cells (lymphocytes, fibroblasts, microcytes and plasma cells) plays a major role in the development of infiltrative and oedematous lesions. Along with these, cytokines (interferon gamma, tumour necrosis factor or interleukin 1 alpha) are released. Secondary to this process are the accumulation of glycosaminoglycans and the influx of more water, resulting in oedema of the extraocular tissues. These processes lead to ocular exophthalmos and compression of the optic nerve. This results in impaired venous blood outflow and impaired lymphatic outflow from the orbital space. Further consequences of the aforementioned processes are impaired oculomotor function and increased intraocular pressure. Glycosaminoglycan concentration is significantly related to the severity of the disease process. An increase in extraocular space volume from a value of 26ml to a value of 32ml increases exophthalmos by as much as 8mm. As the disease progresses, eyelid stroma regurgitation and deficits related to ocular lubrication may occur. The consequences of these disorders can be corneal inflammation and corneal ulceration and, with further progression of the disease, loss of vision.

At the present time, the pathogenesis of the development of ophthalmopathy is not completely clear. It has been concluded that the progression and development of ocular lesions in the course of Graves-Basedow disease is probably the result of an interplay of genetic, environmental and endogenous factors.

Clinical presentation

Patients with hyperthyroidism may present with swelling of the eyelids along with eyelid retraction and excessive lacrimation. These symptoms can occur regardless of the causative factor of hyperthyroidism and are the result of excessive activation of the sympathetic nervous system. These changes usually resolve themselves with treatment of the disease. This group of ocular manifestations in the course of Graves-Basedow disease is referred to as non-ocular ophthalmopathy. During the pathogenesis of these lesions, there is slight swelling of the soft tissues, widening of the eyelid crevices and excessive lacrimation. These lesions usually have a benign course, tend to be self-limiting and do not require treatment.

The second group of symptoms are oedematous and infiltrative lesions. Patients affected by this condition involving the soft tissues of the orbit complain of high sensitivity to sunlight, a "foreign body" feeling under the eyelids, excessive tearing and burning of the eyes. In addition, patients report eyeball pain and visual confusion, which is experienced as discomfort and difficulty when reading or looking at a distance. In the early stages of the disease, the eye discomfort is sporadic, usually during extreme eye position. As the disease progresses, the phenomenon is consistently present when looking in all directions.

The oedematous and infiltrative form of thyroid ophthalmopathy is caused by ocular changes, these are:

- Swelling and retraction of the eyelids
- Disturbances during synchronisation of eyelid and eye movements
- Lesions affecting the anterior compartment of the eye such as congestion and chemotic swelling of the conjunctiva including the lacrimal muscle and stasis affecting the venous vessels
- Damage to the cornea (this may be in the form of small epithelial defects up to and including ulceration with perforation)
- Orbital lesions that result in anterior displacement of the eyeballs
- Oedematous and infiltrative changes in the extraocular muscles, which lead to oculomotor disorders and are the cause of visual ambiguity and discoordination of eye movements, asymmetrical positioning of the eyeballs and the resulting compensatory tilted positioning of the head
- Lesions on the ocular fundus. The severity of their clinical presentation depends on the severity of the oedematous and infiltrative changes in the orbit. When they are of low severity, there are no abnormalities on ophthalmic examination. As extraocular tissues enlarge, compression within the posterior pole of the eyeball occurs, venous stasis develops and the borders of the optic disc become blurred. As the disease progresses, swelling of the central part of the retina and retinal-vascular undulations occur. In the later stages of the disease, there may also be partial or complete fading of the optic disc, indicating optic nerve atrophy
- Inflammatory infiltrated orbital soft tissues lead to compression of the suprachoroidal venous vessels leading to dysfunction in blood outflow and consequently an increase in intraocular pressure

Table 1. Summary of ocular symptoms most commonly reported by the patient with those found on ophthalmic examination

Symptoms reported by the patient	Symptoms found on eye examination
Photophobia	Exophthalmos (often asymmetrical)
Tearing	Eyelid crevice incompetence
Sensation of pushing the eyeballs forward	Eyelid retraction
Blurring of images	Moebius sign - convergence defects
Duplication (temporary or permanent)	Swelling and redness of the eyelids
Eye pain on movement	Conjunctival injection - a sensitive symptom
Swelling of the eyelids (morning)	Swelling and redness of the tear muscle
Redness of the eyes	Disruption of eye movements
	Blurring of vision
	Intraocular hypertension

Classification of ocular lesions in Graves-Basedow ophthalmopathy

The severity of ocular lesions is assessed individually for each eye. In 1969, the American Society of Thyreology developed a classification system for ocular lesions called NOSPESC (Table 2). This system was modified eight years later by Werner (Table 3). This classification assesses the occurrence of individual symptoms and determines their severity. The Donaldson ophthalmopathy index is also used to describe the ocular lesions. (Table 4). It includes indicators such as the magnitude of exophthalmos, damage to the oculomotor muscles as manifested by visual ambiguity, corneal condition, orbital soft tissue assessment and visual acuity. In each of the aforementioned categories in the assessment of ocular changes, the Donaldson Ophthalmopathy Index is assigned points from 1-3. The index is calculated by summing the points from all categories separately for each eye. It is mainly useful for assessing the dynamics of the changes and predicting the expected effects of treatment.

To assess the severity of the disease process, we also use the Mourits' disease activity score (CAS). (Table 5) It is based on clinical symptoms indicating the severity of the inflammatory process such as pain, redness, swelling and functional impairment. The severity of these symptoms is expressed on a point scale from 0 to 10. The index value is the sum of the assigned points and indicates the severity of the inflammatory process in the orbit.

Table 2. The NO SPECS classification according to American Thyroid Association, in every from 6 classes the intensification of changes evaluates in 3-grade scale: a - slight, b - moderate, c - severe

Class	Description	Symptoms
0	No signs or symptoms	
1	Only signs	Graefe's sign Wide eyelid crevice Eyelid retraction
2	Soft tissue involvement	Eyelid edema Conjunctival swelling Blurred vision
3	Proptosis	Exophthalmos 1) 20-23mm 2) 23-27mm 3) >27mm
4	Ocular muscle involvement (extraocular muscle involvement)	Restriction of ocular motility, twitching
5	Corneal involvement	Sensation of sand under the eyes Photophobia Corneal inflammation
6	Vision loss	Decrease in visual acuity Loss of visual field Colour vision disturbances

Table 3. The classification according to Werner involves 6 classes of ophthalmic changes

Class	Grade and severity of clinical complaints and symptoms	
0	No complaints or clinical symptoms	
1	Upper eyelid retraction Wide eyelid crevice Graefe's sign	
2	Orbital soft tissue involvement	0- absent A- slight B- moderately severe
3	Ocular pitting	0- absent A- by 3-4 mm > normal (23-24mm) B- by 5-7 mm > normal (25-27mm) C- by 8 mm or more > normal (>27mm)
4	Oculomotor dysfunction (Usually with douching and other complaints and symptoms)	0- absent A- restriction of mobility in extreme alignment of the eyeballs B- marked restriciton of the ocular motility C-complete immobility of the eyeball
5	Corneal damage	0-absent A- spotting of the cornea B- corneal ulceration C- necrosis and puncture of the cornea
6	Prummel modified visual acuity	0- visual acuity >0.67 A- visual acuity 0.67-0.33 or signs of stasis on the papilla of the optic nerve or restricted visual field B- changes as above and/or visual acuity 0.32-0.1 C- visual acuity <0.1

Table 4. Categories of ophthalmic changes in the Graves-Basedow disease according to Donaldson et al.

Orbital soft tissues Class II	Expression Class III	Oculomotor muscles Class IV	Cornea Class V	Visual acuity Class VI	Result
Slight conjunctival redness, congestion and swelling of the eyelids, minimal discomfort	20-21 mm	Occasional twitching in extreme eye position	Slight dryness	0,67-0,33	1
Moderate reddening of the conjunctiva, swelling of the eyelids, complaints moderately severe	21.5-24mm	Frequent douching, moderate restriction of eye movements	Pronounced dryness	0,32-0,1	2
Large swelling of conjunctiva, large swelling of eyelids, severe discomfort very severe	> 24mm	Constant twitching, severe disturbance of eye movements	Ulceration	<0,1	3

Table 5. The clinical activity score according to Mourits and Weetman

Points	Symptoms
Pain	1. Pain above or behind the eyeball for 4 weeks 2. Pain on eye movement for 4 weeks
Redness	3. redness of the eyelid 4. diffuse reddening of the conjunctiva over min. 1 quadrant
Swelling	5. swelling of the eyelids 6. conjunctival chemosis 7. lacrimal muscle oedema 8. progression of exophthalmos >1mm within 3 months
Functional impairment	9. decreased visual acuity by≥ 1 line on the Snellen chart for 1-3 months 10. reduction in eye movement by≥ 5 degrees in any direction for 1-3 months.

Diagnosis

There is no documented unequivocal criterion for a clear diagnosis of thyroid orbitopathy. The exponent of the diagnosis is the analysis of clinical findings and additional investigations. The diagnosis usually poses little difficulty in patients who have an earlier diagnosis of Graves-Basedow disease or present with hyperthyroidism. In patients in a clinically euthyroid state, the decisive test for the diagnosis of Graves-Basedow orbitopathy may be an increase in anti-TSHR antibodies in the blood or a decrease in TSH levels. During the diagnostic process, in addition to identifying the ongoing immune inflammation, it is also important to assess the severity of this process and whether the severity of symptoms requires initiation of treatment.

Table 6. Classification of severity of Graves' orbitopathy (GO).

Classification	Features
Mild GO	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: a) minor lid retraction (<2 mm) b) mild soft-tissue involvement c) exophthalmos d) <3 mm above normal for race and gender e) no or intermittent diplopia and corneal exposure responsive to lubricants
Moderate-to-severe GO	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: a) lid retraction≥ 2 mm b) moderate or severe soft-tissue involvement c) exophthalmos≥ 3 mm above normal for race and gender d) inconstant or constant diplopia
Sight-threatening (very severe) GO	Patients with dysthyroid optic neuropathy and/or corneal breakdown

Additional diagnostic tests

A full ophthalmological examination is required to determine the severity of the ongoing disease process. Imaging studies such as CT or MR imaging can visualise features of ocular muscle involvement. CT scanning offers the chance to simultaneously assess the soft tissues of the orbit together with its bony structures. This is particularly important when planning further treatment steps in particular surgical decompression. In addition, compared to MR, CT provides a better indication of the volume of the ocular muscles, is a less expensive examination and does not require the administration of contrast. Due to the aforementioned aspects, CT is the most commonly chosen imaging modality during the diagnostic process of Graves-Basedow orbitopathy. The advantage of MRI is that it gives a better assessment of the activity of the ongoing orbital soft tissue inflammation.

Differential diagnosis of Graves' orbitopathy

- Sarcoidosis
- Crohn's disease
- Scleroderma
- Lymphomas
- Metastases- melanoma, breast, gastrointestinal
- Bening tumors- hamartomas, rhabdomyomas
- Infections
- Vascular malformations
- Myasthenia gravis

Treatment

The treatment of Graves-Basedow orbitopathy represents a major therapeutic challenge for specialists. It has been proven that modification of risk factors, in particular smoking cessation and achieving a state of euthyroidism or topical agents are considered most effective for the mild form of thyroid orbitopathy. The beneficial effect of selenium in the treatment of GO has also been demonstrated.

The indications for initiating treatment depend on the activity of the disease, the severity of the symptoms (assessing whether it threatens vision or quality of life) and the impact on the patient's daily functioning.

The indication for initiating treatment of the oedematous infiltrative form of thyroid ophthalmopathy is a Werner score of at least grade 3c and a Donaldson ophthalmopathy index score of 4.

Further indications considered are:

- CAS≥ 4 points
- Length of symptom duration <18 months (dilation <6 months)
- Rapid dynamics of symptoms within 1-3 months
- Reduction in visual acuity by≥ 1 line on the Snellen chart
- Exacerbation of exophthalmos by >2mm or restriction of eye movement by 5 degrees in any direction

Indications for treatment of thyroid orbitopathy according to EUGOGO 2016:

1. Mild GO (mild)- Symptoms of the disease only slightly affecting the patient's daily functioning. Eyelid retraction <2mm, minor soft tissue inflammation, exophthalmos <3mm, with intermittent douching only, corneal symptoms resolving with moisturisers. This form does not require immunosuppressive or surgical treatment. If symptoms of the active form of GO develop rapidly, it may be necessary to implement GCS therapy. In selenium-deficient populations, selenium supplementation for six months is recommended, as it has been shown to reduce the risk of disease progression.
2. Moderate to severe GO- severity of symptoms significantly affects patients' daily functioning. No vision-threatening symptoms. Eyelid retraction >2mm, moderate to severe orbital soft tissue symptoms, exophthalmos >3mm, intermittent or persistent visual confusion. There is a rationale for starting immunosuppressive treatment if the disease is active (CAS≥ 3/7) or surgical treatment if the disease is not active.
3. GO threatening visual loss- there is optic nerve neuropathy and/or corneal abnormalities up to corneal disruption in the form of perforation or ulceration. Immediate immunosuppressive treatment and/or surgical treatment in the form of orbital decompression is required.

Achieving a state of euthyroidism

In each of the listed degrees of thyroid orbitopathy, equalisation and maintenance of a euthyroid state play a key role in the treatment process. Both hyperthyroidism and hypothyroidism negatively affect the course and efficacy of GO treatment. Antithyroid medication and thyroidectomy surgery have not been shown to negatively affect the severity of thyroid orbitopathy, however, radioiodine therapy has been shown to be associated with a slight exacerbation of orbitopathy particularly in smokers. EUGOGO guidelines recommend that the priority in patients with Graves' orbitopathy should be to restore and maintain thyroid balance, but in patients with moderate to severe and active forms of GO, treatment of thyroid orbitopathy should be the priority and a state of euthyroidism should be achieved with antithyroid drugs. There are currently 2 preparations available: thiamazole, which is the first-line drug used orally for 12-18 months, and propylthiouracil, used less frequently and recommended for women in the first trimester of pregnancy. In patients with Graves' disease who have undergone a first course of treatment with antithyroid drugs and have developed recurrent hyperthyroidism, treatment with radioactive iodine or thyroidectomy is recommended. The isotopic method is contraindicated in patients with active moderate to severe thyroid orbitopathy. It is only allowed in mild and active forms of the disease.

Smoking cessation

Regardless of the presence of thyroid orbitopathy and the severity and activity of Graves-Basedow disease, all patients should stop smoking. Smoking has been shown to increase the risk of de novo GO and to have a negative impact on the course of the disease in patients with previously diagnosed thyroid orbitopathy. Immunosuppressive treatment outcomes are poorer in active and passive smokers compared to non-smokers. It has been proven that smoking cessation can positively affect the course of orbitopathy.

In most cases of patients affected by thyroid orbitopathy, a three-stage treatment is used:

I- steroid therapy
II- orbital irradiation
III- surgical decompression of the orbits

Stages I and II are mainly used in the healing process in the infiltrative and oedematous phase, stage III finds its application in very advanced exophthalmos, also in the fibrotic phase.

Steroid therapy

Glucocorticoids (GCS) are first-line drugs in moderate to severe forms of thyroid orbitopathy. They are only used in the active form when CAS≥ 3/7. Oral administration of GCS is effective but is associated with the risk of many side effects. Prednisone is administered at a dose of 1-2mg/kg/day for a period of 10-12 weeks followed by a gradual reduction in dose until it is possible to discontinue GCS around week 20 of therapy. It is now increasingly common to use pulse therapy by administering intravenous methylprednisolone 1000mg on 2 consecutive days per week for one month. This modality has advantages over oral administration of GCS in terms of higher efficacy during treatment and fewer gastrointestinal complications. A limitation of intravenous administration is the need to administer the drug in medical centres. The main aim of glucocorticoids therapy is to reduce inflammation of the orbital soft tissues, improve oculomotor motility and have a positive therapeutic effect on neuropathy.

The possible complications resulting from intensive intravenous GCS therapy such as acute cardiac syndromes or fulminant liver failure should not be forgotten.

Radiotherapy

The safety of this method of treating orbitopathy is not fully established. Currently, radiotherapy of extraocular soft tissues with 6 MV photon radiation is most commonly used. It has been shown that lymphocytes are sensitive to radiation and that the production of glycosaminoglycans by orbital fibroblasts is inhibited by radiotherapy.

The use of this treatment modality can be considered in patients with moderate Graves-Basedow orbitopathy as monotherapy or in combination with corticosteroids. It is also a therapeutic option for patients with severe forms of the disease, where it is applicable as a combination treatment with GCS.

The EUGOGO position statement accepted that orbital radiotherapy should be used mainly when the patient has double vision and ocular motility disorders. In other sources, we can find information about the impossibility of using GCS in the treatment of orbitopathy (due to side effects or the presence of contraindications) as an indication to start orbital irradiation.

Radiotherapy is usually used until a total dose of 20 Gy is reached. This is administered in 10 fractions, over 2 weeks once daily.

Patient preparation for this treatment modality includes the fabrication of a thermoplastic mask to immobilise the head for the planning period and the treatment process, and an initial simulation to determine the range for CT scanning. The next step is for the physician to mark critical organs such as the pituitary gland, eyeballs, lens and outline the PTV (treatment planning area), which includes extraocular infiltrates.

Surgical treatment

In a small percentage of patients with Graves-Basedow orbitopathy, surgical treatment is required. Several possible treatment options are available and the process is usually multistage. Orbital decompression or tarsorrhaphy are the available treatment options for orbitopathy that is severe or threatens vision loss during the active phase of the disease. In the inactive phase of the disease, surgical treatment is the last step in the treatment of orbitopathy and is designed to improve the eye function and visual aspects of the patient. This treatment may include the following therapeutic approaches:

a) Orbital decompression
b) Surgery of the oculomotor muscles
c) Eyelid repositioning correction
d) Blepharoplasty

Orbital decompression

This is a procedure that aims to partially remove some of the bony walls of the orbit. This allows for the displacement of extraocular tissues into the periorbital space area. This process leads to a reduction in pressure within the orbit, which improves venous blood and lymph outflow. With this method, exophthalmos is reduced and there is less pressure of the orbital tissues on the optic nerve and less swelling.

Indications for surgical orbital decompression:

4. Optic nerve neuropathy-mainly in situations where intravenous GCS treatment has not had the intended therapeutic effect
5. Advanced exophthalmos and associated eyelid regurgitation, ocular subluxation or corneal lesions
6. Disease progression in patients with contraindications to immunosuppressive therapy and with resistance or dependency on GCS treatment
7. For cosmetic reasons in patients in the inactive phase of the disease to reduce exophthalmos

Orbital decompression is performed through two main methods - fat removal and removal of individual orbital walls. In studies involving patients who underwent orbital decompression with fat removal, improved vision was achieved by decreasing extraocular muscle tension and thus improving extraocular muscle mobility, which reduced the occurrence of double vision in patients. Other studies that included patients in whom individual bone components were removed during orbital decompression have shown that this method has a higher risk of complications. Based on observations, fat removal is only recommended for patients with mild to moderate visual impairment and those with little or no ocular muscle hypertrophy. Lipectomy is a highly effective procedure for reducing exophthalmos and has a long-lasting effect. The decompression method using resection of individual bone fragments is preferred in advanced disease processes or when the use of fat removal has not been successful. This method is used more often in men, and fat removal surgery is used about three times more often in women.

Decompression of the lower orbital wall is associated with a particularly high risk of developing postoperative double vision. The sudden loss of bony support for the fibrotic tissues causes them to collapse into the sinus area. Some scientists suggest abandoning decompression within the inferior orbital wall due to the significant rate of development of postoperative diplopia. They suggest that this method should be used as a last resort or only an option for patients whose vision has deteriorated significantly in a short period of time.

Ocular muscle surgery

The prerequisites for surgery concerning the extraocular muscles in patients with Graves-Basedow orbitopathy are the achievement of a state of euthyroidism for >6 months and the stabilisation of the ocular mobility abnormalities and the clinical picture of these lesions for a period of 3 months. The presence of double vision and a large angle of strabismus are absolute categories to be met as indications for surgical treatment. Before surgery is performed, it is important to carry out a passive eye movement test. When, during the above test, the extent of passive movement is greater than the active movement, it is assumed that the extraocular muscles are currently in a swollen stage. If the active movement corresponds to the amount of passive movement of the muscle - this should be interpreted as the start of the fibrosis process. A positive passive mobility test result may suggest the presence of fibrotic changes in the muscle. Patients whose double vision could not be corrected by other treatments should be qualified for surgery.

Eyelid alignment correction

One of the methods available for patients in the active phase of the disease is temporary eyelid suturing - partial or total tarsorrhaphy. This procedure allows the affected cornea to heal. Other methods, such as myotomy, cutting the upper eyelid lever muscle attachments or suturing the Muller muscle attachments, should be performed in the inactive phase of the disease. One undesirable effect of treatment when this method is chosen is excessive lowering of the upper eyelids. An alternative, albeit less effective method for eyelid alignment correction is botulinum toxin injection.

Blepharoplasty

Eyelid plasty can play a corrective role in patients with thyroid orbitopathy. This method is often performed together with orbital decompression. It is mostly performed in the final stage of correction when the disease is no longer active. The use of this method does not treat the cause of the orbitopathy, but only corrects the secondary lesions with which the eyelids of the affected patient are affected.

Immunoglobulins

One of the major disadvantages of using the above method is the cost it involves. Its therapeutic success can probably be achieved by blocking receptors on the surface of B lymphocytes and thereby reducing cytokine release. It may be useful when the patient has a type of orbitopathy refractory to intravenous GCS treatment and orbital radiotherapy. Researchers have obtained satisfactory results regarding the use of monoclonal antibodies such as rituximab or tocilizumab, TNF-α inhibitors and selective immusuppressants such as mycophenolate mofetil in the treatment of Graves-Basedow orbitopathy. Many substances are still in the research phase such as belimumab, whose action is to reduce the proliferation and survival time of B lymphocytes and to limit antibody synthesis.

Discussion and conclusions

Thyroid-associated orbitopathy is a syndrome of symptoms manifested in the ocular region associated with chronic autoimmune inflammation of the orbital soft tissues. In its development, a key role is played by an autoimmune reaction activating orbital fibroblasts, which leads to the accumulation of glycosaminoglycans and, consequently, a series of consequences such as inflammation or changes in the orbital soft tissues. It is characterised by the development of swelling around the eyes, which can lead to symptoms such as exophthalmos, double vision, conjunctival congestion or strabismus. The development of Graves-Basedow disease is multifactorial. Smoking is a documented risk factor for this disease. The diagnosis of orbitopathy is a combination of several elements such as a thorough ophthalmological examination, laboratory tests and imaging. Measuring the activity and severity of the disease is an important aspect to help choose the appropriate treatment. In the majority of patients, the changes are mild and harmless to vision and resolve as the patient reaches a state of euthyreosis. In some patients, the symptoms associated with the disease can significantly impair the quality of life by causing increased exophthalmos and, in extreme cases, can lead to optic nerve damage. In these more advanced forms of the disease, treatment depends on the severity of the lesions and may include glucocorticosteroid administration, radiotherapy or surgery. Detection of orbitopathy at an early stage and the use of an appropriate therapeutic approach significantly improves the patient's prognosis. This makes it possible to reduce the risk of complications. During the diagnostic as well as the therapeutic process, cooperation of several specialists such as an ophthalmologist, endocrinologist or surgeon is necessary in many cases. Thyroid-associated orbitopathy is often a major clinical challenge and therefore requires an individual and holistic view of the patient.

REFERENCES

1. Ciarmatori, N., Quaranta Leoni, F., & Quaranta Leoni, F. M. (2025). Redefining treatment paradigms in thyroid eye disease: Current and future therapeutic strategies. *Journal of Clinical Medicine*, *14*(15), 5528. https://doi.org/10.3390/jcm14155528
2. Kulbay, M., Tanya, S. M., Tuli, N., Dahoud, J., Dahoud, A., Alsaleh, F., Arthurs, B., & El-Hadad, C. (2024). A comprehensive review of thyroid eye disease pathogenesis: From immune dysregulations to novel diagnostic and therapeutic approaches. *International Journal of Molecular Sciences*, *25*(21), 11628. https://doi.org/10.3390/ijms252111628
3. Tamhankar, P., Syed, R., Brutsaert, E., Urdániz, E., Vainilovich, Y., Heyes, A., Gildea, L., & Sales-Sanz, M. (2025). The burden of illness in thyroid eye disease: Current state and future needs. *Frontiers in Ophthalmology*, ...(…), Article 1565762. https://doi.org/10.3389/fopht.2025.1565762
4. Gaillard, F., Sharma, R., Bell, D., et al. (2024). Thyroid-associated orbitopathy. *Radiopaedia Reference Article*. https://doi.org/10.53347/rID-2180
5. Nivean, P. D., Madhivanan, N., Kumaramanikavel, G., Berendschot, T. T. J. M., Webers, C. A. B., & Paridaens, D. (2024). Understanding the clinical and molecular basis of thyroid orbitopathy: A review of recent evidence. *Hormones (Athens, Greece)*, *23*(1), 25–34. https://doi.org/10.1007/s42000-023-00498-8
6. Kulbay, M., Tanya, S. M., Tuli, N., Dahoud, J., Dahoud, A., Alsaleh, F., Arthurs, B., & El-Hadad, C. (2024). *A Comprehensive Review of Thyroid Eye Disease Pathogenesis: From Immune Dysregulations to Novel Diagnostic and Therapeutic Approaches*. *International Journal of Molecular Sciences, 25*(21), 11628. https://doi.org/10.3390/ijms252111628
7. Moledina, M., Damato, E. M., & Lee, V. (2024). *The changing landscape of thyroid eye disease: Current clinical advances and future outlook*. *Eye*. Advance online publication.
8. Ma, C., Li, H., Lu, S., & Li, X. (2024). *Thyroid-associated ophthalmopathy: The role of oxidative stress*. *Frontiers in Endocrinology, 15*, Article 1400869. https://doi.org/10.3389/fendo.2024.1400869
9. Alves Junior, J. M., Bernardo, W., & Villagelin, D. (2024). *Effectiveness of different treatment modalities in initial and chronic phases of thyroid eye disease: A systematic review with meta-analysis*. *Journal of Clinical Endocrinology & Metabolism, 109*(11), 2997–3009. https://doi.org/10.1210/clinem/dgae526

10. Mahoney, N. R., & Rajaii, F. (2021). *Current Management of Thyroid Eye Disease*. *Neurologic Ophthalmology and Otology*, *23*, Article 21. https://doi.org/10.1007/s11940-021-00675-3
11. Bartalena, L., Kahaly, G. J., Baldeschi, L., Dayan, C. M., Eckstein, A., Marcocci, C., Marinò, M., Vaidya, B., & Wiersinga, W. M.; EUGOGO. (2021). The 2021 European Group on Graves' orbitopathy (EUGOGO) clinical practice guidelines for the medical management of Graves' orbitopathy. *European Journal of Endocrinology, 185*(4), G43–G67. https://doi.org/10.1530/EJE-21-0479
12. Smith, T. J., Kahaly, G. J., Ezra, D. G., Fleming, J. C., Dailey, R. A., Tang, R. A., Harris, G. J., Antonelli, A., Salvi, M., Goldberg, R. A., Gigantelli, J. W., Couch, S. M., Shriver, E. M., Hayek, B. R., Hink, E. M., Woodward, R. M., Gabriel, K., Magni, G., & Douglas, R. S. (2017). Teprotumumab for thyroid-associated ophthalmopathy. *The New England Journal of Medicine, 376*(18), 1748–1761. https://doi.org/10.1056/NEJMoa1614949
13. Douglas, R. S., Kahaly, G. J., Patel, A., Sile, S., Thompson, E. H. Z., Perdok, R., Fleming, J. C., Fowler, B. T., Marcocci, C., Marinò, M., Antonelli, A., Dailey, R., Harris, G. J., Eckstein, A., Schiffman, J., Tang, R., Nelson, C., Salvi, M., Wester, S., … Smith, T. J. (2020). Teprotumumab for the treatment of active thyroid eye disease. *The New England Journal of Medicine, 382*(4), 341–352. https://doi.org/10.1056/NEJMoa1910434
14. Kahaly, G. J., Riedl, M., König, J., Pitz, S., Ponto, K. A., Diana, T., Kanitz, M., Ponto, L. L. A., Kahaly, N., Pitz, S., Hommel, G., & Bartalena, L. (2018). Mycophenolate plus methylprednisolone versus methylprednisolone alone in active, moderate-to-severe Graves' orbitopathy (MINGO): A randomised, observer-masked, multicentre trial. *The Lancet Diabetes & Endocrinology, 6*(4), 287–298. https://doi.org/10.1016/S2213-8587(18)30020-2
15. Marcocci, C., Kahaly, G. J., Krassas, G. E., Bartalena, L., Prummel, M., Stahl, M., Altea, M. A., Nardi, M., Pitz, S., Boboridis, K., Sivelli, P., Wiersinga, W. M., & the European Group on Graves' Orbitopathy. (2011). Selenium and the course of mild Graves' orbitopathy. *The New England Journal of Medicine, 364*(20), 1920–1931. https://doi.org/10.1056/NEJMoa1012985
16. Bartalena, L., & Tanda, M. L. (2022). Current concepts regarding Graves' orbitopathy. *Journal of Internal Medicine, 292*(5), 692–716. https://doi.org/10.1111/joim.13524
17. Perros, P., Hegedüs, L., Bartalena, L., Marcocci, C., Kahaly, G. J., Baldeschi, L., Salvi, M., Lazarus, J. H., Feldt-Rasmussen, U., Wiersinga, W. M., & European Group on Graves' Orbitopathy (EUGOGO). (2017). Graves' orbitopathy as a rare disease in Europe: A European Group on Graves' Orbitopathy (EUGOGO) position statement. *Orphanet Journal of Rare Diseases, 12*, 72. https://doi.org/10.1186/s13023-017-0625-1
18. Schuh, A., Ayvaz, G., Baldeschi, L., Baretić, M., Bechtold, D., Boschi, A., Brix, T. H., Burlacu, M.-C., Ćirić, J., Covelli, D., Currò, N., Donati, S., Eckstein, A. K., Fichter, N., Führer, D., Horn, M., Jabłońska-Pawlak, A., Juri Mandić, J., Kahaly, G. J., … Hintschich, C. R. (2024). Presentation of Graves' orbitopathy within EUGOGO centres from 2012 to 2019 (PREGO III). *British Journal of Ophthalmology, 108*(2), 294–300. https://doi.org/10.1136/bjo-2022-322442
19. Lanzolla, G., Marcocci, C., & Marinò, M. (2020). Oxidative stress in Graves' disease and Graves' orbitopathy. *European Thyroid Journal, 9*(Suppl. 1), 40–50. https://doi.org/10.1159/000509615
20. Moledina, M., Azzam, S., & Stokes, J. (2024). The changing landscape of thyroid eye disease: Current concepts in diagnosis and management. *Eye, 38*, 521–537. https://doi.org/10.1038/s41433-024-02967-9
21. Szczeklik, A. (2020). *Interna Szczeklika*. Medycyna Praktyczna.
22. Ziółkowska, E., Kubiak, M., Wiśniewski, T., & Zarzycka, M. (2007). Ophthalmopathy in the course of Graves-Basedow disease – diagnosis and treatment with regard to the role of radiotherapy. *Współczesna Onkologia*, 11(9), 463-466
23. Sewerynek, E. (2007). Rozpoznanie i leczenie objawów ocznych w przebiegu chorób tarczycy o podłożu autoimmunologicznym. *Forum Medycyny Rodzinnej*, 1(2), 144-146
24. Bednarczuk, T. (2004). Związek pomiędzy polimorfizmami wybranych genów i rozwojem oftalmopatii u pacjentów z chorobą Gravesa-Basedowa w populacji polskiej. *Endokrynologia Polska*, 55(3).
25. Kawalec-Herbut, B., & Mrukwa-Kominek, E. (2010). Objawy oczne w chorobie Gravesa-Basedowa. *Magazyn Lekarza Okulisty*, 4(6), 298. https://www.magazynokulisty.pl/public/pdf/MLO_06_2010str298.Gravesa-Basedowa....pdf
26. Kulig, G., Pilarska, K., Syrenicz, A., Sewerynek, E., & Lewiński, A. (2002). Obraz kliniczny oftalmopatii tarczycowej w przebiegu choroby Gravesa-Basedowa. *Endokrynologia Polska*, 53(2), 203-207
27. Bartalena, L., Kahaly, G. J., Baldeschi, L., Dayan, C. M., Eckstein, A., Marcocci, C., Marinò, M., Vaidya, B., & Wiersinga, W. M. (2021). The 2021 European Group on Graves' orbitopathy (EUGOGO) clinical practice guidelines for the medical management of Graves' orbitopathy. *European Journal of Endocrinology*. https://doi.org/10.1530/EJE-21-0479
28. Boddu, N., Jumani, M., Wadhwa, V., Bajaj, G., & Faas, F. (2017). Not all orbitopathy is Graves': Discussion of cases and review of literature. *Frontiers in Endocrinology*, 8, 184. https://doi.org/10.3389/fendo.2017.00184
29. Ruchała, M., Hernik, A., & Zybek, A. (2014). Orbital radiotherapy in the management of Graves' orbitopathy — current state of knowledge. *Endokrynologia Polska*. https://doi.org/10.5603/EP.2014.0054
30. Wierzbowska, J. (2020). Aktualne i nowe strategie leczenia aktywnej orbitopatii tarczycowej [Current and novel strategies for the treatment for active thyroid orbitopathy]. *Ophthatherapy*, 7(2[26]), 110.
31. Nowak, M., Marek, B., Kos-Kudła, B., Siemińska, L., Londzin-Olesik, M., Głogowska-Szeląg, J., Nowak, W., & Kajdaniuk, D. (2019). Optymalizacja leczenia umiarkowanej do ciężkiej i aktywnej orbitopatii tarczycowej z uwzględnieniem zaleceń European Group on Graves' Orbitopathy (EUGOGO) [Optimization of the treatment of moderate to severe and active thyroid orbitopathy considering the recommendations of EUGOGO]. *Endokrynologia Polska*, 70(9), 770-771