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+15878858911
editorial-office@sciformat.ca

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PATHOPHYSIOLOGY AND CLINICAL ASPECTS OF GRAVES' ORBITOPATHY: AN ANALYSIS OF THE CURRENT STATE OF KNOWLEDGE AND THERAPEUTIC TRENDS

Damian Świerczek (Corresponding Author, Email: swierczekd1@gmail.com)
Medical University of Silesia Poniatowskiego 15, 40-055 Katowice, Poland
ORCID ID: 0009-0000-8915-824X

Anna Piwko
Medical University of Silesia Poniatowskiego 15, 40-055 Katowice, Poland
ORCID ID: 0009-0003-9301-9471

Szymon Starowicz
Medical University of Silesia Poniatowskiego 15, 40-055 Katowice, Poland
ORCID ID: 0009-0008-7154-5370

Łukasz Stachowicz
Medical University of Silesia Poniatowskiego 15, 40-055 Katowice, Poland
ORCID ID: 0009-0001-0710-7367

Daniel Ściana
Medical University of Silesia Poniatowskiego 15, 40-055 Katowice, Poland
ORCID ID: 0009-0006-7008-5603

Adriana Grądzka
Kazimierz Pułaski University of Technology and Humanities Malczewskiego 29, 26-600 Radom, Poland
ORCID ID: 0009-0002-4412-8367

ABSTRACT

Graves' orbitopathy (GO), also referred to as thyroid eye disease (TED) or endocrine orbitopathy (EO), is the most common extrathyroidal manifestation of Graves' disease, affecting approximately 25–40% of patients. The pathogenesis of GO is complex and multifactorial, primarily involving autoimmune processes driven by antibodies against the thyrotropin receptor. These antibodies interact with both the TSH receptor and the insulin-like growth factor 1 receptor, leading to the activation of orbital fibroblasts, which results in chronic inflammation, soft tissue swelling, and fibrosis. The clinical presentation varies from mild symptoms to severe complications, such as dysthyroid optic neuropathy. Smoking remains the most critical modifiable risk factor, significantly worsening prognosis and reducing treatment efficacy. Diagnosis relies on a comprehensive assessment, including the Clinical Activity Score, laboratory evaluation of TRAb levels, and orbital imaging to determine disease activity and severity. Treatment strategies depend on the clinical phase: intravenous glucocorticosteroids are the first-line therapy for active moderate-to-severe disease, while modern biological therapies are increasingly used for refractory cases. In the inactive phase, surgical and rehabilitative interventions are primarily indicated. Due to the potential for relapse and the impact on quality of life, a multidisciplinary approach involving endocrinologists and ophthalmologists is essential for long-term management and improved patient outcomes.

KEYWORDS

TSH Receptor Antibodies, Biological Therapy, Thyroid Eye Disease, Hyperthyroidism, Orbital Inflammation

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1. Introduction and Purpose

Graves' orbitopathy (GO), also referred to as thyroid eye disease (TED) or endocrine orbitopathy (EO), is the most common extrathyroidal manifestation of Graves' disease and occurs in approximately 25–40% of patients. The condition more frequently affects women, although a severe course is observed more often in older men. Epidemiological data on GO are limited and vary depending on the studied population and methodology used. The estimated incidence ranges from 2.9 to 16 cases per 100,000 people per year, while prevalence is estimated at 90–300 cases per 100,000 people [1]. GO is a disease with a complex and not fully understood pathogenesis. Key mechanisms involve autoimmune processes associated with the presence of antibodies against the thyrotropin receptor (TRAb), which, through interaction with the TSH receptor (TSHR) and the insulin-like growth factor 1 receptor (IGF-1R), lead to activation of orbital fibroblasts. Numerous cytokines and signaling pathways are also involved in this process, highlighting the multifactorial nature of the disease [2]. An important role in the course of GO is played by the control and elimination of risk factors. The most important include smoking, which worsens prognosis and reduces the effectiveness of immunosuppressive therapy, as well as thyroid dysfunction, high serum TRAb levels, treatment with radioactive iodine, and hypercholesterolemia [3]. The clinical presentation of GO is variable and depends on disease activity and severity. The most common symptoms include exophthalmos, eyelid retraction, and swelling and redness of orbital tissues. In more advanced cases, impaired ocular motility and optic neuropathy may occur, resulting from fibrosis and tissue remodeling within the orbit [4]. Due to its potentially severe course, GO requires close cooperation between ophthalmologists and endocrinologists in both diagnosis and treatment [5]. Early referral to a specialized center is crucial. Diagnostic evaluation includes assessment of clinical activity using the CAS scale, full ophthalmological examination, imaging studies, thyroid function tests, and measurement of serum TRAb levels [6]. The choice of treatment depends on disease severity. In mild cases, in addition to risk factor modification, local treatment and selenium supplementation are used. In moderate-to-severe cases, first-line therapy consists of intravenous methylprednisolone, often in combination with sodium mycophenolate. Second-line therapies include glucocorticoids combined with other immunosuppressive agents, orbital radiotherapy (usually in combination with glucocorticoids), biological therapy, and surgical treatment [3]. The aim of this article is to present current data on GO, with particular emphasis on contemporary diagnostic methods and therapeutic strategies, as well as to discuss its pathogenesis, clinical presentation, risk factors, and prognosis.

2. Material and Methods

This review is based on an analysis of the current literature on GO. A total of 71 scientific publications were included, comprising clinical studies, systematic reviews, meta-analyses, and international clinical guidelines, particularly those developed by the European Group on Graves' Orbitopathy. The selected articles were chosen to provide a comprehensive and up-to-date overview of the disease, including its pathogenesis, clinical presentation, risk factors, diagnostic approaches, and therapeutic strategies.

3. Pathophysiology and Immunological Mechanisms

GO is a complex autoimmune disease characterized by chronic inflammation of orbital tissues. A key role in its pathogenesis is played by orbital fibroblasts, which are characterized by increased expression of TSHR. TRAb antibodies, whose serum concentration correlates with disease activity and severity, bind to this receptor, stimulating the production of glycosaminoglycans, especially hyaluronic acid. They also induce differentiation of fibroblasts into adipocytes and myofibroblasts, leading to swelling of extraocular muscles, expansion of orbital adipose tissue, and fibrosis of orbital connective tissue [2,7,8]. An important element in the pathogenesis of GO is also IGF-1R, which is expressed both on thyrocytes and orbital fibroblasts [9]. It

has been shown that immunoglobulins from patients with Graves' disease (GD-IgG) can interact with IGF-1R present on the surface of orbital fibroblasts, which show its overexpression. This interaction leads to activation of signaling pathways, including mTOR/AKT/p70S6K, and to increased expression of cytokines and chemokines such as interleukin-16 and RANTES, which are responsible for the recruitment of CD4⁺ T lymphocytes and the intensification of the inflammatory response [10]. Additionally, the cooperation of TSHR and IGF-1R enhances hyaluronan synthesis and promotes adipogenesis [11]. The immunological process in GO involves an inflammatory infiltrate composed of macrophages and T lymphocytes, mainly CD8⁺, as well as CD4⁺. CD4⁺ lymphocytes activate orbital fibroblasts through CD40–CD154 interaction, leading to their proliferation and release of pro-inflammatory cytokines. This results in increased hyaluronan synthesis, enhanced adipogenesis, and increased expression of adhesion molecules [12]. In the early phase of the disease, Th1 cells predominate, producing cytokines such as IL-1 β , IL-2, IL-6, TNF, and IFN- γ , whereas in later stages there is a predominance of a Th2 response, associated with the secretion of IL-4, IL-5, IL-10, and IL-13. Moreover, in patients with GO an increased number of Th17 lymphocytes and a reduced population of regulatory T cells (Tregs) is observed, which promotes persistence of chronic inflammation [4]. In summary, the pathogenesis of GO is multifactorial and involves complex immunological interactions, including an immune response directed against TSHR, cooperation between TSHR and IGF-1R, inflammatory infiltration, and the activity of numerous pro-inflammatory cytokines, leading to the development of characteristic morphological changes and clinical manifestations of the disease.

4. Risk Factors

Smoking is the most important modifiable risk factor for the development of GO. The effect of smoking on the course of the disease during treatment is dose-dependent, and treatment efficacy in smokers is significantly reduced and delayed [13,14]. Smoking is also associated with a higher incidence of Graves' disease and promotes the development of more severe ocular manifestations. It is believed that it may act as a triggering factor for the disease process in genetically predisposed individuals, as well as increase the risk of more severe forms of GO [15,16]. Radioiodine therapy in Graves' disease is also considered a factor that may induce or exacerbate GO. In patients treated with this method, a greater need for more intensive therapeutic strategies has been observed compared to patients treated pharmacologically or surgically. It has been shown that the introduction of levothyroxine after radioiodine treatment reduces the risk of GO occurrence or progression [17]. In a study involving 168 patients with Graves' disease, it was demonstrated that individuals treated with iodine-131 were at higher risk of developing de novo GO or its progression (33%) compared to patients treated pharmacologically or surgically (10–16%). Additionally, elevated serum triiodothyronine levels before treatment were associated with a greater risk of worsening ocular symptoms [18]. Female sex is also a risk factor GO occurs approximately 3–4 times more frequently in women than in men [19]. Furthermore, both hypothyroidism and hyperthyroidism in the course of Graves' disease may contribute to a more severe course of orbitopathy [20].

5. Clinical Presentation

GO affects approximately half of patients with hyperthyroidism in the course of Graves' disease. It most commonly presents with dry eye symptoms and a foreign body sensation, which are associated with the presence of proptosis [23]. These symptoms primarily result from orbital tissue remodelling, the consequence of which is proptosis. Proptosis in GO is caused by expansion of retrobulbar tissues, leading to anterior displacement of the globe and increased intraorbital pressure. This may result in optic nerve dysfunction secondary to impaired venous outflow from the orbit. In this context, proptosis may also act as a mechanism of partial orbital decompression. Optic nerve damage leads to reduced visual acuity, colour vision disturbances, and, in severe cases, permanent vision loss [21,28]. In parallel with neuro-ophthalmic changes, involvement of the orbital soft tissues develops. Retrobulbar pain may be present. Soft tissue expansion leads to lagophthalmos, resulting in exposure-related symptoms such as excessive tearing, lacrimal gland enlargement, and prolapse of orbital fat [27]. With persistence of the inflammatory process, chronic structural changes develop. Ongoing inflammation and oedema lead to fibrosis and contracture of the extraocular muscles, resulting in restricted ocular motility. Concurrent eyelid and conjunctival oedema contributes to the characteristic “staring” appearance [21,26]. Impaired ocular motility leads to diplopia. Restricted eye movements frequently result in double vision, typically due to asymmetric muscle involvement. Diplopia may be intermittent or persistent and can occur in horizontal, vertical, or oblique gaze positions [28]. Extraocular

muscle dysfunction may also involve the eyelids. Upper eyelid retraction may occur, with impaired physiological lid movement, particularly on downgaze [25]. The disease course is usually bilateral and slowly progressive; however, unilateral involvement is observed in approximately 15% of patients. Severe disease, characterised by persistent proptosis, pain, optic neuropathy, inflammatory activity, or sight-threatening corneal ulceration (alone or in combination), occurs in 3–5% of cases [22,24]. GO and hyperthyroidism most commonly occur simultaneously or within 18 months of each other. Subclinical skin changes in the pretibial region or other locations are observed in approximately 13% of patients with severe disease [22,23].

6. Diagnosis

GO is based on clinical assessment, laboratory tests, and imaging techniques, which together allow determination of disease activity and severity. The key tool for assessing inflammatory activity is the CAS (Clinical Activity Score), used both for evaluating the clinical condition and monitoring treatment efficacy. The most commonly used is the 7-point scale, in which each inflammatory sign corresponds to one point (CAS < 3 indicates inactive disease, whereas CAS ≥ 3 indicates active disease). There is also an extended 10-point version of the scale. It should be emphasized, however, that CAS is not fully objective, as some assessed parameters, such as pain, are subjective in nature. An important complement to disease activity assessment is the EUGOGO (European Group on Graves' Orbitopathy) classification, which allows determination of disease severity. It distinguishes three forms: mild, moderate-to-severe, and sight-threatening, which is crucial for selecting the appropriate therapeutic strategy [2,3]. Laboratory tests also play an important role in the diagnostic process, particularly the measurement of TRAb. High levels of these antibodies correlate with the risk of developing GO and with disease activity, making them a valuable prognostic marker. However, their measurement is not routinely used in clinical practice, mainly due to organizational limitations and the lack of clear recommendations for widespread use [3]. Imaging studies are also an important component of diagnostics, allowing detailed assessment of orbital structures and identification of disease complications. Magnetic resonance imaging is particularly useful in assessing inflammatory activity, enabling evaluation of orbital soft tissues, including extraocular muscles. The use of multiparametric magnetic resonance imaging increases the diagnostic value of the examination by simultaneously assessing the fat and water fractions within the muscles and orbital tissues, allowing more precise detection of inflammatory changes [29]. Computed tomography, on the other hand, is the primary tool for assessing orbital morphology. It enables precise visualization of anatomical structures such as the extraocular muscles, orbital fat, globe, optic nerve, and lacrimal gland, allowing evaluation of their enlargement and detection of possible optic nerve compression [30]. Due to its high spatial and contrast resolution, accurate tissue differentiation is possible, with orbital fat appearing as a lower-density area compared to surrounding structures. However, the risk associated with ionizing radiation exposure must be considered, particularly regarding lens exposure, which, when exceeding the threshold dose, may lead to cataract formation [31]. A comprehensive diagnostic approach, combining clinical, laboratory, and imaging assessment, allows precise determination of GO activity and severity, thereby enabling the implementation of optimal therapeutic management.

7. Conservative Management

Smoking cessation is a key component in the management of patients with GO. Patients should be actively advised to quit smoking and, if possible, referred to structured smoking cessation programs. Both active and passive smoking significantly increase the risk of developing GO, worsen its course, increase the risk of progression after radioiodine therapy, and reduce the effectiveness of glucocorticosteroid treatment [3,14,32,33]. Moreover, the disease tends to be more severe in smokers compared to non-smokers [3]. In patients with mild GO, selenium supplementation has been shown to provide beneficial effects, including improvement in quality of life, reduction in ocular symptoms, and slowing of disease progression [3,34]. Selenium is most commonly administered as sodium selenite; however, depending on availability, it may be replaced with selenomethionine [3]. In cases of concomitant ocular surface inflammation and dry eye syndrome, the use of lubricating eye drops during the day and gels or ointments at night is recommended. In more severe cases, mechanical protection of the eyelids may be necessary. This approach applies both to patients with clinically overt GO and to those with Graves' disease without evident orbitopathy but presenting symptoms of dry eye syndrome [3,49].

8. Pharmacological Treatment

Intravenous glucocorticosteroids are the first-line treatment for active, moderate-to-severe GO due to their strong anti-inflammatory and immunosuppressive effects [3]. Oral therapy is also possible; however, it is associated with poorer tolerance and lower efficacy [36]. Combined intravenous and oral regimens may increase treatment effectiveness and reduce relapse rates, although they are associated with a higher risk of adverse effects [37]. The efficacy of intravenous pulse therapy with methylprednisolone has been confirmed in active, moderate-to-severe GO [3,35]. The most commonly used regimen involves a cumulative dose of 4.5 g administered in 12 weekly infusions (six doses of 0.5 g followed by six doses of 0.25 g), while in more severe cases, cumulative doses up to 7.5 g may be used [3]. Mycophenolate exerts antiproliferative effects on B and T lymphocytes and reduces antibody production by inhibiting inosine monophosphate dehydrogenase [38]. According to EUGOGO recommendations, it is indicated for the treatment of active, moderate-to-severe GO [3]. Meta-analyses suggest that mycophenolate may be more effective than glucocorticosteroids both as monotherapy and in combination therapy. Its combination with low-dose steroids may provide additional benefits in chronic complications such as proptosis and diplopia. It also demonstrates a more favorable safety profile, making it a valuable second-line option [39]. Cyclosporine, a calcineurin inhibitor, suppresses T-cell proliferation and interleukin-2 synthesis. While less effective than glucocorticosteroids as monotherapy, combination therapy has shown superior efficacy, leading to better clinical outcomes and lower relapse rates [3]. It is particularly useful in cases resistant to other treatments [40]. Azathioprine is not effective as monotherapy in GO; however, when combined with glucocorticosteroids, it may improve ocular motility and reduce diplopia [41,42]. It can be used as a steroid-sparing agent, although its use is limited by a less favorable tolerability profile [3].

9. Modern Therapies

Modern biological therapies are playing an increasingly important role in the treatment of GO, particularly in cases resistant to standard treatment. Teprotumumab, a monoclonal antibody targeting the IGF-IR, has demonstrated high efficacy in active, moderate-to-severe GO, with a rapid and progressive therapeutic response [43,44]. The treatment is generally well tolerated, although it may be associated with adverse effects such as muscle cramps, hearing impairment, and hyperglycemia. Despite FDA approval, its widespread use is limited by high cost, availability, and lack of long-term data [3]. Rituximab, an anti-CD20 monoclonal antibody, leads to B-cell depletion and has shown effectiveness in reducing disease activity and TRAb levels, with limited impact on proptosis [46]. It may be particularly useful as a second-line therapy in patients with high disease activity and short disease duration [45]. However, its use carries the risk of serious adverse effects, including infusion reactions and cytokine release syndrome [3]. Tocilizumab, a monoclonal antibody against the IL-6 receptor, has demonstrated efficacy in glucocorticosteroid-resistant GO, reducing disease activity and improving clinical outcomes, including a reduction in proptosis [47,48].

10. Surgical Treatment

Local treatment of upper eyelid retraction includes subconjunctival injections of botulinum toxin, which may result in significant but temporary improvement in eyelid position. This method is generally well tolerated, and adverse effects such as transient ptosis or diplopia are usually temporary [51]. The role of surgical treatment depends on the disease phase. In the active phase, orbital decompression is indicated in severe exposure keratopathy and in dysthyroid optic neuropathy resistant to glucocorticosteroid therapy. In the inactive phase, surgical procedures are reconstructive and aim to correct proptosis, eyelid malposition, and strabismus [3]. Endoscopic orbital decompression via a transnasal approach is an effective and safe technique, particularly in patients with optic nerve compression at the orbital apex [49].

11. Orbital Radiotherapy

Orbital radiotherapy is an adjunctive treatment option in patients with moderate-to-severe GO. It demonstrates moderate efficacy, primarily improving extraocular muscle function and reducing diplopia, with limited effect on proptosis and eyelid edema [52]. This method is considered relatively safe; however, it should not be used in patients with diabetic or hypertensive retinopathy. Potential long-term risks, including malignancy, should also be taken into account [3]. The best outcomes are achieved when radiotherapy is combined with glucocorticosteroids, as this approach is more effective than steroid therapy alone, leading to a reduction in extraocular muscle volume and lower relapse rates [53].

12. Prognosis

The prognosis of GO is generally favorable in most cases, although the disease course can be highly variable. The majority of patients present with a mild form of the disease, accounting for approximately 77% of cases. About 20% of patients develop a moderate-to-severe form, while sight-threatening disease is rare, occurring in approximately 1% of cases. This indicates that vision loss is an uncommon complication and, with appropriate treatment, is usually preventable [8,54,55]. The natural course of the disease is typically biphasic. Initially, there is an active (inflammatory) phase characterized by orbital tissue edema, redness, and pain. These changes are potentially reversible, and immunosuppressive treatment is most effective during this stage, playing a crucial role in determining long-term prognosis. Over time—after months or years—the disease transitions into an inactive (fibrotic) phase, in which inflammation subsides but structural changes become permanent. These include eyelid retraction, proptosis, and restricted ocular motility. In this phase, spontaneous improvement is unlikely, and treatment is primarily surgical [8,56,57]. In patients treated at the stage of mild disease, the prognosis is particularly good. More than half achieve complete remission of ocular symptoms without disease progression, and only a small proportion develop moderate or severe forms. The disease course may be improving, stable, or progressive; therefore, regular assessment of disease activity is essential for predicting outcomes [55]. Several factors are associated with a worse prognosis. The most significant is smoking, which not only increases the risk of developing GO but also worsens its course, reduces treatment efficacy, and increases the likelihood of relapse. Smoking cessation is one of the most important modifiable factors that can significantly improve prognosis. Male sex is another unfavorable factor—although men are affected less frequently than women, they tend to experience a more severe disease course and a higher risk of sight-threatening complications [58,59]. Prognosis also worsens with increasing age. Older patients are more likely to develop moderate-to-severe disease and tend to respond less favorably to pharmacological treatment. Comorbidities play an important role as well, particularly diabetes mellitus, which is associated with a higher risk of diplopia and dysthyroid optic neuropathy, one of the most severe manifestations of GO. Additionally, elevated cholesterol levels correlate with increased disease activity and severity, negatively affecting the clinical course [8,60,61,62,63]. Assessment of clinical disease activity is a key component in determining prognosis. Even low levels of inflammatory activity increase the risk of disease progression, while higher activity is associated with a greater risk of severe disease if left untreated. Paradoxically, however, active disease is also associated with a better response to immunosuppressive therapy. An important prognostic marker is the level of TRAb. High TRAb levels are strongly associated with increased disease activity and severity, as well as a higher risk of progression, whereas a decline in TRAb levels during treatment is associated with improved outcomes [57,64,65]. The most severe form of GO is dysthyroid optic neuropathy, which requires urgent treatment. Despite the seriousness of this complication, the prognosis does not have to be poor if therapy is initiated promptly. Appropriate pharmacological and/or surgical treatment leads to improvement or recovery of vision in the majority of patients. Modern biological therapies have also shown high efficacy in this form of the disease, although relapses may occur in some cases [66,67]. The relapsing nature of the disease represents another important aspect of long-term prognosis. GO may reactivate, particularly in smokers, patients with high TRAb levels, and in some cases following biological therapies. Therefore, long-term follow-up is essential even after clinical improvement has been achieved [8,68,69]. GO significantly affects patients' quality of life, especially during the active phase. Visual disturbances, changes in appearance, and chronic discomfort contribute to impaired psychological and social functioning. However, effective treatment—and, in the inactive phase, appropriately planned surgical interventions—can lead to significant improvement in both visual function and appearance, resulting in better long-term functional outcomes [70,71].

13. Discussion and Conclusions

GO is a complex autoimmune disorder with a multifactorial pathogenesis, in which TRAb and the interactions between the TSHR and IGF-1R play a central role. These mechanisms lead to a chronic inflammatory process within the orbit, followed by progressive tissue remodelling, including extraocular muscle enlargement, expansion of orbital fat, and fibrosis. As a result of these processes, the clinical presentation of the disease is highly variable, ranging from mild forms with limited ocular symptoms to severe cases associated with a risk of permanent vision loss. The course of GO is strongly influenced by risk factors, with smoking being the most important, as it worsens disease severity and reduces treatment efficacy. Therefore, accurate diagnosis requires a comprehensive approach combining clinical assessment, laboratory testing including TRAb measurement, and imaging studies that allow evaluation of disease activity and extent

of orbital involvement. Based on this, an optimal treatment strategy can be selected. In mild cases, risk factor modification and symptomatic treatment are the main approaches. In moderate-to-severe active disease, immunosuppressive therapy—primarily intravenous glucocorticosteroids, often in combination with other agents—forms the cornerstone of management. In refractory cases, biological therapies targeting specific immune pathways are increasingly used. Surgical treatment and orbital radiotherapy remain important options in the inactive phase or in sight-threatening conditions. In summary, early diagnosis, a multidisciplinary approach, and prompt initiation of appropriate therapy are crucial for achieving favourable outcomes. Despite the potentially severe course of the disease, most patients respond well to treatment; however, long-term follow-up is essential due to the risk of relapse and persistent structural orbital changes.

Conceptualization: Damian Świerczek, Anna Piwko

Methodology: Daniel Ściana, Łukasz Stachowicz

Software: Szymon Starowicz, Adriana Grądalska

Check: Damian Świerczek, Anna Piwko

Formal analysis: Anna Piwko, Daniel Ściana

Investigation: Łukasz Stachowicz, Daniel Ściana

Resources: Damian Świerczek, Adriana Grądalska

Data curation: Damian Świerczek, Anna Piwko

Writing - rough preparation: Szymon Starowicz, Daniel Ściana

Writing - review and editing: Szymon Starowicz, Daniel Ściana

Visualization: Adriana Grądalska, Anna Piwko

Supervision: Łukasz Stachowicz, Szymon Starowicz

Project administration: Damian Świerczek

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