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Ocular surface disorders and Graves' disease

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Summary: Ocular surface disorders in thyroid-associated orbitopathy result from an autoimmune inflammatory response within the orbital fibroadipose tissue, and their severity correlates with the degree of orbital inflammatory activity. Disease-related anatomical changes lead to increased ocular surface exposure and impaired blinking biomechanics. Concurrently, tear film destabilization and local overexpression of pro-inflammatory mediators develop. This cascade disrupts ocular surface homeostasis, leading to reduced tear production and increased evaporation due to tear film instability. In the clinical management strategy, the implementation of standardized diagnostic criteria based on the latest guidelines of the Tear Film and Ocular Surface Society Dry Eye Workshop III (TFOS DEWS III) plays a key role. Optimal therapeutic management of patients with thyroid-associated orbitopathy requires an integrated approach that includes simultaneous assessment of orbital inflammatory activity and multimodal treatment of ocular surface damage.

Key words: ocular surface disease, dry eye disease (DED), Graves' disease, thyroid-associated orbitopathy, Clinical Activity Score (CAS).

1. Introduction

Thyroid-associated orbitopathy (Graves' orbitopathy, GO) is an autoimmune disorder characterized by inflammation within the fibroadipose tissue of the orbit. It develops following T-lymphocyte activation against the thyroid-stimulating hormone receptor (TSH-R) and insulin-like growth factor-1 receptor (IGF-1R), expressed both in orbital tissues (on the surface of preadipocytes – a subset of orbital fibroblasts) and in thyroid epithelial cells [1]. The role of other autoantibodies targeting other connective tissue and muscle antigens remains unclear [2, 3]. The co-occurrence of GO and thyroid disorders is determined by the expression of shared autoantigens targeted by immune system lymphocytes within both of these anatomical structures. Ocular manifestations most commonly accompany hyperthyroidism in the course of Graves' disease, accounting for approximately 90% of cases. However, they may also develop in hypothyroidism associated with Hashimoto's disease (5% of patients), as well as in euthyroid individuals who do not exhibit clinical signs of thyroid dysfunction (5% of cases) [2–5].

Histological studies indicate that, in GO, the inflammatory process involves the periorbital adipose connective tissue as well as the fibrous connective tissue of the extraocular muscles, including the perimysium and endomysium [3]. Activated T lymphocytes infiltrate orbital tissues and release pro-inflammatory cytokines. This leads to stimulation and proliferation of fibroblasts, as well as induction of excessive glycosaminoglycan production, edema of the extraocular muscles, expansion of adipose tissue, and, in the end stage of the disease, fibrosis of the extraocular muscles and periorbital connective tissue [4, 5]. The progressive increase in the volume of orbital tissues results in clinical manifestations such as proptosis, impaired ocular motility, diplopia, and, in severe cases, corneal ulceration and optic neuropathy caused by compression of the neurovascular bundle at the orbital apex (Fig. 1–3).

The clinical course of GO is highly heterogeneous. Data on the natural progression of GO indicate that spontaneous regression of symptoms occurs in nearly 65% of patients, although full recovery of visual function is rarely achieved. In one in five individuals, the disease process stabilizes over the course of a year, whereas progression of lesions is observed in 15% of patients. Additionally, immunosuppressive therapy may be associated with periods of disease remission and reactivation [3].

Fig. 1. Eyelid edema and conjunctival chemosis in a patient with Graves' disease.

Fig. 2. Severe chemosis and conjunctival injection in a patient with Graves' disease.

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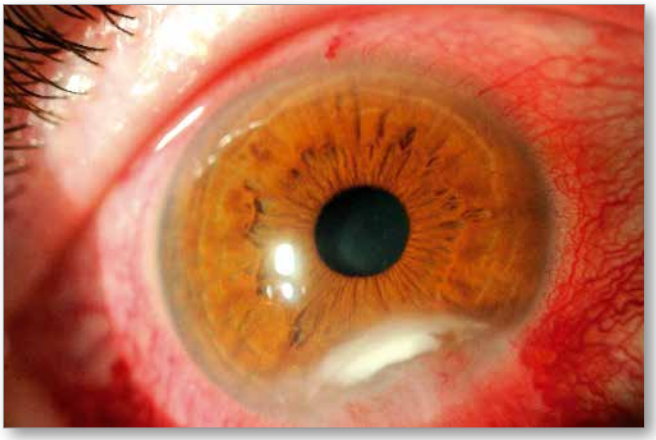

Fig. 3. Corneal ulceration in a patient with Graves' disease.

2. Thyroid-associated orbitopathy and ocular surface disease

Although the inflammatory process in GO typically involves the retrobulbar tissues, a relatively common complication is ocular surface damage, which usually precedes the classic clinical onset of the disease.

The pathogenesis of ocular surface disease resulting from GO is multifactorial. The degree of GO activity correlates positively with ocular surface involvement. It is believed that structural changes driven by orbital fibroblast expansion and differentiation lead to proptosis and eyelid abnormalities (retraction and lagophthalmos), increasing ocular surface exposure and impairing normal blinking dynamics [1, 6–8]. Concurrently, alterations in the tear film and increased expression of pro-inflammatory cytokines on the ocular surface also play a significant role. This disrupts ocular surface homeostasis by reducing tear production [1], and increasing evaporation secondary to tear film instability [9–14]. In addition, ocular surface tissues may themselves serve as direct targets of autoantibodies and inflammatory processes originating from the orbital space [15].

One of the primary causes of ocular surface damage in GO is dry eye disease (DED). The prevalence of DED in patients with GO is estimated by various authors to be between 65% and 95% [1, 7, 8, 11]. According to the definition proposed by the Tear Film and Ocular Surface Society Dry Eye Workshop III (TFOS DEWS III), DED is a multifactorial disease of the ocular surface characterized by a loss of tear film homeostasis and persistent parainflammation. The primary pathomechanisms of DED include tear film instability and hyperosmolarity, inflammation and damage to ocular surface structures, and neurosensory abnormalities [16]. Increased ocular surface osmolarity induces pathological changes in the corneal epithelium, including reduction of intercellular junctions, membrane damage, and cell shrinkage, ultimately leading to DNA damage and corneal epithelial cell apoptosis [17]. It has been demonstrated that increased tear film osmolarity also results in a loss of conjunctival goblet cells, which may be linked to tear film instability [18, 19]. This initiates a "vicious cycle" of tear film instability, excessive tear evaporation, and progressive ocular surface damage.

The biochemical profile of the tear film in GO is highly variable, with inflammatory mediator levels closely dependent on current disease stage and clinical activity. In the acute, inflammatory phase of GO, elevated concentrations of pro-inflammatory mediators are observed, including IL-1β, IL-6, IL-8, IL-16, IL-17, IL-23, and TNF-α [20–24]. It has been demonstrated that circulating IL-17A levels produced by T lymphocytes, as well as IL-1β, IL-6, and IL-8 concentrations in tears, correlate directly with the Clinical Activity Score (CAS), confirming their role as objective markers of disease activity. In contrast, healthy individuals and euthyroid patients exhibit a predominantly anti-inflammatory profile, mainly driven by IL-1α and IL-10, the latter of which dampens the inflammatory cascade by suppressing ICAM-1, IL-6, and TNF-α expression [24–26].

Clinically, ocular surface changes present as conjunctival hyperemia, dry eye or excessive tearing, foreign body sensation, photophobia, and blurred vision. This is associated with a deterioration in patients' quality of life.

Kashkouli et al. demonstrated that in the vast majority of patients with GO, the disease process is bilateral, which, in comparison with unilateral involvement, usually correlates with advanced patient age, greater disease severity, and a higher CAS. Nevertheless, asymmetry of lesions between both eyes remains a relatively common phenomenon [1, 27].

3. Diagnosis of thyroid-associated orbitopathy activity

The activity of GO is assessed using the Clinical Activity Score (CAS). Depending on whether the patient is undergoing an initial evaluation or a comparative assessment of disease progression, a 7-point or 10-point scale is used. The patient receives 1 point for each present symptom. A score of ≥ 3 points (on the 7-point scale) or ≥ 4 points (on the 10-point scale) indicates an active phase of the disease, which qualifies the patient for the initiation of immunosuppressive therapy. The CAS activity scale is presented in Table I.

	no.	Clinical sign
Primary criteria	1	spontaneous retrobulbar pain
	2	pain on upward or downward gaze
	3	redness of the eyelids
	4	conjunctival redness
	5	inflammation of the caruncle and/or plica semilunaris
	6	eyelid edema
	7	conjunctival edema (chemosis)
Additional criteria (assessment of disease progression)	8	increase in exophthalmos by ≥ 2 mm
	9	decrease in ocular motility by ≥8°
	10	decrease in visual acuity within the last 1–3 months

Tab. I. Clinical Activity Score (CAS) for thyroid-associated orbitopathy.

Laboratory diagnostics preceding the physical examination also play an important role in assessing disease activity. The key marker is the concentration of antibodies directed against thyroid-stimulating hormone receptors (anti-TSHR), which is tightly linked to the presence of GO. Lytton *et al.* demonstrated that all patients with Graves' hyperthyroidism and clinical manifestations of GO had positive anti-TSHR titers. The authors also confirmed a strong correlation between the concentration of these immunoglobulins and disease severity as assessed using the CAS scale [1, 28].

4. Diagnosis of DED in thyroid-associated orbitopathy

The wide discrepancy in the estimated prevalence of DED among patients with GO may stem from the method used for its evaluation. Routine assessment of GO patients for ocular surface pathology should primarily be based on the initial differentiation and classification of the disease into one of three categories defined as subjective, objective, or definite [1].

In one study involving 38 participants (74 eyes), it was demonstrated that symptoms reported by the patients themselves (subjective) occur more frequently (77%) than their confirmation in clinical diagnostic tests. This indicates that a subset of patients experiences discomfort even though routine objective examinations do not yet reveal full pathological changes. Among objective indicators, the reduction of tear break-up time (TBUT) is the most widespread, affecting up to 85% of subjects in extreme cases. This confirms that a crucial pathophysiological mechanism here is the impairment of tear stability. According to the authors, Meibomian gland disease affects nearly half of the patients (48–56.8%). These data suggest that in a large proportion of the subjects, DED has an etiology related to excessive tear evaporation rather than solely a lack of aqueous tear component production (which occurred less frequently: 19–39.2%). Definite DED, defined as the presence of both subjective and objective disease, occurred with a frequency of 67.7% [1, 9].

The most reliable indicator for the subjective assessment of DED appears to be the validated Ocular Surface Disease Index (OSDI) questionnaire. It is a 12-item questionnaire focused on DED symptoms, limitations in daily activities, and the relationship between symptoms and their triggers. Its values have been shown to be significantly higher in patients with active GO compared to individuals with the inactive form and the control group (healthy individuals). It has also been proven that the CAS serves as a prognostic indicator for a severe course of GO-induced DED. Each one-point increase in the CAS score was found to double the risk of achieving a high score on the OSDI scale [29]. Furthermore, recent reports indicate that in patients with elevated CAS and OSDI scores, Meibomian gland atrophy constitutes an additional pathological factor. Other researchers even suggest that this manifestation may be a direct consequence of DED associated with thyroid diseases [22, 30, 31].

Objective assessment of ocular surface disease focuses on slit-lamp examination with evaluation of anatomical structures (the ocular adnexa and the globe) and a thorough analysis of individual DED indicators.

The evaluation of the eyelids should include the presence of edema, erythema, retraction, and potential lagophthalmos, as well as an assessment of the palpebral fissure width. Exophthalmometry should be performed at each visit to assess the degree of proptosis. When examining the eyeball, the presence of conjunctival edema, lacrimal caruncle swelling, and conjunctival injection (mainly at the insertion sites of the extraocular muscles and in the superior bulbar conjunctiva), should be verified. Changes in this region may indicate superior limbic keratoconjunctivitis (SLK) [1].

An essential element of the diagnostic procedure is the evaluation of eyelid margin morphology, given that patients suffering from GO show a significantly higher predisposition to developing obstructive Meibomian Gland Dysfunction (MGD) compared to the healthy population. Authors of numerous reports confirm increased Meibomian gland atrophy in GO patients, with particular emphasis on the central part of the upper eyelid. Structural changes in the Meibomian glands (a higher meiboscore in non-contact meibography) show a close correlation with clinical signs of GO: exophthalmos and increased palpebral fissure height [1, 32–34].

Procedures for evaluating tear film integrity include the measurement of tear break-up time (TBUT). The test involves fluorescein instillation followed by observation of tear film breakup and dry spots on the cornea under cobalt blue light (Fig. 4). An intact tear film duration of less than 10 seconds is interpreted as an abnormal result [1].

Basal tear secretion is assessed using the Schirmer test type I. It involves placing specialized filter paper strips beneath the lower eyelid and measuring the length of tear wetting on the strips.

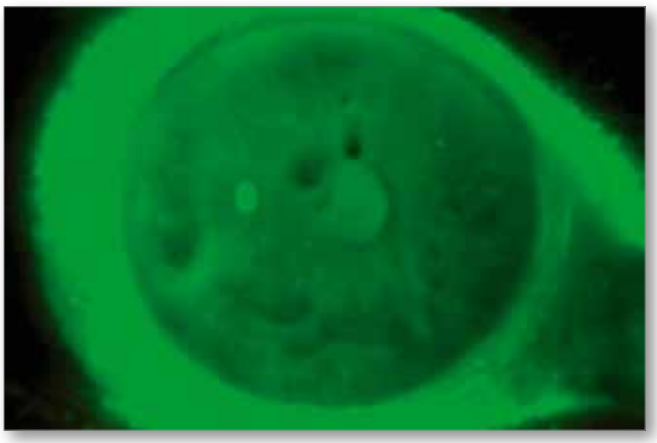

Fig. 4. Tear film breakup visible as areas of fluorescein loss on the cornea under cobalt-blue filter illumination.

A result greater than 15 mm is considered normal; values of 5 to 15 mm correspond to a tear deficit, and a result less than 5 mm indicates advanced DED. The diagnostic value of the Schirmer test has been repeatedly questioned due to significant variability in results across different stages of ocular surface disease. This method has been shown to lack sufficient reliability for diagnosing mild to moderate cases [1, 35].

Assessment of the cornea and conjunctiva should routinely include staining, usually with fluorescein or lissamine green, to detect potential superficial keratopathy characterized by epithelial defects (Fig. 5). The Oxford Scheme is the standard scale used to evaluate the integrity of the corneal and conjunctival epithelial barrier. This scale finds key application in the objective evaluation and monitoring of ocular surface pathology progression. Assessment of corneal sensitivity is also recommended. It has been shown that corneal sensitivity is reduced in patients with GO and demonstrates a positive correlation with the occurrence of ocular surface diseases [22, 36].

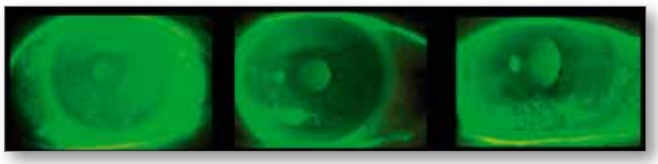

Fig. 5. Corneal epithelial defects visible after staining the conjunctival sac with fluorescein under cobalt-blue filter illumination.

Analyses based on corneal confocal microscopy images confirm that GO induces profound, chronic inflammatory changes in ocular surface structures. Consequences of this process include a reduction in corneal epithelial cell density, damage to corneal nerves, and increased keratocyte activity within the corneal stroma [37, 38]. The tissue remodeling described above is driven by immune mechanisms associated with elevated concentrations of the interleukins IL-1 and IL-6, which stimulate the nerve growth factor (NGF) [1].

The most reliable indicator for assessing the presence and severity of DED is a combined subjective-objective evaluation, which in this form is defined as definite. Traditional research protocols evaluating the condition of the ocular surface in patients with thyroid disorders were predominantly based on the separate consideration of patient-reported symptoms (subjective assessment) and clinical manifestations (objective assessment) [1]. Currently, the implementation of standardized diagnostic criteria based on the latest guidelines of the international Dry Eye Workshop (DEWS III) is recognized as critically important [16].

5. Treatment

The gold standard in the management of moderate to severe GO continues to be systemic corticosteroid therapy. Scientific reports indicate that intravenously administered glucocorticosteroids also reduce markers of ocular surface disease. Specifically, a statistically significant reduction in OSDI scores and a substantial decrease in the concentration of inflammatory mediators in the tear film have been demonstrated after 12 weeks of systemic treatment with methylprednisolone [20].

Symptomatic relief is achieved using preservative-free artificial tears, ointments, and lubricating gels. In lagophthalmos, nocturnal use of a moisture chamber is recommended to protect the cornea from exposure keratopathy. If standard lubrication is ineffective and investigations confirm pronounced inflammation, the integration of cyclosporine eye drops into the permanent therapeutic regimen is indicated [5]. During acute exacerbations, topical steroids are also employed, particularly in patients with contraindications to systemic steroid therapy. However, the necessity of frequent monitoring for steroid-induced intraocular pressure elevation, the risk of cataract development, and impaired corneal re-epithelialization must be taken into account [39, 40].

Stabilization of thyroid function and maintenance of euthyroidism are crucial for halting ophthalmic disease progression. Both hyperthyroidism and hypothyroidism exhibit pro-inflammatory activity, contributing to the development and progression of infiltrative and edematous changes within the anatomical structures of the orbit [5].

As part of non-pharmacological optimization of patient quality of life, the protection of the eyes from irritants plays an important role. Recommendations include the use of UV-blocking sunglasses to provide an effective barrier against ultraviolet radiation and environmental factors such as aerosols, dust, and wind.

In accordance with EUGOGO guidelines, the initiation of supplementary selenium therapy at a dose of 100–200 μg for 6 months is advised for patients with mild GO [5]. In the context of DED therapy, this element exhibits potent anti-inflammatory and antioxidant properties on the ocular surface. Selenium, as a component of glutathione peroxidase, plays a key role in protecting ocular structures against oxidative stress, and also reduces the synthesis of pro-inflammatory cytokines (e.g. IL-6), which induce chronic irritation of the ocular surface [41, 42]. The beneficial effect of this substance has been confirmed in a clinical study involving 218 patients with Graves' disease in a euthyroid state, in whom no signs of orbitopathy were observed. In the selenium-treated group, a statistically significant improvement in the condition of the ocular surface was observed. These patients achieved lower scores on the OSDI questionnaire and higher TBUT values relative to the control group [41]. These data indicate that selenium supplementation can be an effective supportive method for maintaining the functional and structural integrity of the ocular surface in individuals affected by Graves' disease [41, 42].

6. Conclusions

Ocular surface disorders associated with GO result from an autoimmune inflammatory response. Accurate diagnosis remains essential and should be based both on subjective patient-reported symptoms and objective indicators of ocular surface damage. To date, no pharmacological agents specifically targeting the treatment of GO-induced dry eye disease have been developed, nor have standardized treatment guidelines been established. Effective management of GO requires simultaneous monitoring of disease activity (CAS) and multidisciplinary treatment of ocular surface damage. Close collaboration between endocrinologists and ophthalmologists is therefore essential for disease stabilization and symptom regression.

Disclosure
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