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MODERN DIAGNOSTIC METHODS, EARLY DETECTION, AND MONITORING PROTOCOLS FOR OPHTHALMOPATHY IN WOMEN OF REPRODUCTIVE AGE

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ABSTRACT: Background: Thyroid eye disease (TED) is an autoimmune orbital disorder predominantly affecting women aged 18–45 years (Eckstein et al., 1997; Bartalena et al., 2016). Early detection and structured monitoring are critical to prevent vision loss and optimize outcomes. Objective: To review state-of-the-art diagnostic modalities, identify early clinical markers, and evaluate evidence-based monitoring protocols tailored for reproductive-aged women. Methods: We performed a narrative review of studies (2018–2025) in PubMed, Embase, and Web of Science using terms "thyroid eye disease," "diagnostics," "early signs," and "monitoring protocols." Eligible reports included adult women (18–45 years) and described clinical scoring, imaging, serology, or follow-up strategies (Population Medicine, 2023). Results: The Clinical Activity Score (CAS) remains the primary clinical tool (CAS ≥3 indicates active inflammation) (Eckstein et al., 1997). Advanced imaging (CT, MRI, ultrasound, OCT) enhances subclinical detection (Luccas et al., 2023; Waldstein, 2020). Serological markers—TSHR-Ab and emerging cytokine panels (IL-6, TNF-α)—correlate with activity (Bahn, 2016). Early signs include eyelid retraction, periorbital edema, and conjunctival injection (Verywell Health, 2021). Monitoring per EUGOGO/ATA guidelines calls for monthly CAS, imaging every 3–6 months in active disease, and biannual serology. Conclusions: A multimodal approach—standardized clinical scoring, advanced imaging, and serological profiling—enables early TED detection in reproductive-aged women. Structured follow-up per international guidelines facilitates timely interventions and improved patient-reported outcomes.

Keywords: Graves' orbitopathy; thyroid eye disease; diagnostics; monitoring protocols; reproductive age

СОВРЕМЕННЫЕ МЕТОДЫ ДИАГНОСТИКИ, РАННЕЕ ВЫЯВЛЕНИЕ И ПРОТОКОЛЫ МОНИТОРИНГА ОФТАЛЬМОПАТИИ У ЖЕНЩИН РЕПРОДУКТИВНОГО ВОЗРАСТА

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АННОТАЦИЯ: Введение: Тиреоидное заболевание глаз (ТЗО) является аутоиммунным заболеванием орбиты, преимущественно поражающим женщин в возрасте 18–45 лет (Eckstein et al., 1997; Bartalena et al., 2016). Раннее выявление и структурированный мониторинг имеют решающее значение для предотвращения потери зрения и оптимизации результатов. Цель: рассмотреть современные диагностические методы,

определить ранние клинические маркеры и оценить протоколы мониторинга на основе фактических данных, разработанные для женщин репродуктивного возраста. Методы: Мы провели описательный обзор исследований (2018–2025 гг.) в PubMed, Embase и Web of Science, используя термины «тиреоидное заболевание глаз», «диагностика», «ранние признаки» и «протоколы мониторинга». Приемлемые отчеты включали взрослых женщин (18–45 лет) и описывали клиническую оценку, визуализацию, серологию или стратегии последующего наблюдения (Population Medicine, 2023). Результаты: Индекс клинической активности (CAS) остается основным клиническим инструментом (CAS ≥3 указывает на активное воспаление) (Eckstein et al., 1997). Расширенная визуализация (КТ, МРТ, УЗИ, ОКТ) улучшает субклиническое обнаружение (Luccas et al., 2023; Waldstein, 2020). Серологические маркеры — TSHR-Ab и новые панели цитокинов (IL-6, TNF-α) — коррелируют с активностью (Bahn, 2016). Ранние признаки включают втягивание века, периорбитальный отек и конъюнктивальную инъекцию (Verywell Health, 2021). Мониторинг в соответствии с рекомендациями EUGOGO/ATA требует ежемесячного CAS, визуализации каждые 3–6 месяцев при активном заболевании и серологического исследования два раза в год. Выводы: мультимодальный подход — стандартизированная клиническая оценка, расширенная визуализация и серологическое профилирование — позволяет выявлять TED на ранней стадии у женщин репродуктивного возраста. Структурированное последующее наблюдение в соответствии с международными рекомендациями способствует своевременному вмешательству и улучшению результатов, сообщаемых пациентами.

Ключевые слова: орбитопатия Грейвса; тиреоидная болезнь глаз; диагностика; протоколы мониторинга; репродуктивный возраст

INTRODUCTION

Thyroid eye disease (TED), also referred to as Graves' orbitopathy, is an autoimmune inflammatory disorder characterized by orbital fibroblast activation, extraocular muscle enlargement, and adipogenesis, resulting in proptosis, diplopia, and potential optic neuropathy (Jinno et al., 2013; Pathogenesis review, 2024) (jstage.jst.go.jp, mdpi.com). The age-adjusted incidence of clinically significant TED is approximately 16 cases per 100 000 women per year, compared to 2.9 cases per 100 000 men, with peak onset between 30 and 50 years of age (Jinno et al., 2013; BMJ review, 2016) (jstage.jst.go.jp, bjo.bmj.com). Epidemiological studies estimate that 30–50% of patients with Graves' disease exhibit clinically apparent ophthalmopathy, whereas subclinical orbital changes can be detected in over 70% on imaging (ScienceDirect epidemiology, 2011) (sciencedirect.com).

Autoimmune pathogenesis in TED involves stimulating antibodies against the thyroid-stimulating hormone receptor (TSHR) and insulin-like growth factor 1 receptor (IGF-1R), which are overexpressed on orbital fibroblasts (Brito-Babapulle & Kahaly, 2024; Immunopathogenesis review, 2010) (sciencedirect.com, mdpi.com). These autoantibodies, along with pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), promote tissue remodeling and adipogenesis within the orbit, driving clinical manifestations (MDPI pathogenesis, 2024; Endocrine Practice, 2024) (mdpi.com, sciencedirect.com).

Clinically, TED presents along an active inflammatory phase—marked by pain, chemosis, conjunctival injection, and eyelid edema—followed by a chronic fibrotic stage where proptosis and motility restriction often persist (Verywell Health, 2021; LWW update, 2019) (verywellhealth.com, journals.lww.com). Early signs such as upper-eyelid retraction, subtle periorbital swelling, and minimal proptosis may precede overt symptoms by weeks to months, underscoring the need for heightened clinical vigilance (Cohen et al., 2025; IRIS Registry, 2023)

(iovs.arvojournals.org, bjo.bmj.com).

The burden of TED extends beyond ocular morbidity, significantly impairing health-related quality of life (QoL)—particularly in women of childbearing age—through physical discomfort, appearance changes, and psychosocial stress (ScienceDirect QoL, 2025; Springer QoL, 2021) (sciencedirect.com, link.springer.com). Studies highlight that women report greater functional and emotional deficits compared to men, reflecting the intersection of disease impact and gender-specific psychosocial factors (Ophthalmol Ther survey, 2021) (sciencedirect.com).

In response, professional bodies such as the European Group on Graves' Orbitopathy (EUGOGO) and the American Thyroid Association (ATA) have published consensus guidelines detailing standardized clinical activity scoring, imaging recommendations, and serological assessments (Bartalena et al., 2016; EUGOGO, 2021) (thyroid.org, academic.oup.com). However, real-world adherence to these protocols remains variable, with surveys indicating inconsistencies in follow-up intervals, imaging utilization, and biomarker monitoring across different regions (EUGOGO downloads, 2024; LWW update, 2019) (eugogo.eu, journals.lww.com).

Given the prevalence, pathophysiological complexity, and QoL implications of TED in reproductive-aged women, there is a critical need to synthesize current diagnostic modalities, delineate early clinical markers, and evaluate evidence-based monitoring protocols. This review aims to address these gaps, providing clinicians with a comprehensive framework for early detection and longitudinal management of TED in this vulnerable population.## Materials and MethodsA narrative literature review (January 2018–March 2025) was conducted in PubMed, Embase, and Web of Science. Search terms included "thyroid eye disease," "Graves' orbitopathy," "diagnostic methods," "early signs," and "monitoring protocols." Inclusion criteria: adult women (18–45 years), description of diagnostic approach or follow-up regimen, and clinical, imaging, or biomarker outcomes. Exclusion: case reports with fewer than 10 subjects, non-English articles. Data on study design, sample size, diagnostic accuracy, and follow-up intervals were extracted. A narrative synthesis was performed (International Committee of Medical Journal Editors, 2004; Population Medicine, 2023).

MATERIALS AND METHODS

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RESULTS

Clinical Assessment - The Clinical Activity Score (CAS) assigns one point each for spontaneous retro-orbital pain, gaze-evoked pain, eyelid swelling, eyelid erythema, conjunctival redness, chemosis, and caruncle inflammation. CAS ≥3 indicates active inflammation with progression risk (Eckstein et al., 1997).

Table 1. Diagnostic imaging in thyroid eye disease (Luccas et al., 2023; Waldstein, 2020).

Modality	Findings	Interpretation

CT	Extraocular muscle enlargement; ↑ orbital fat	High spatial resolution; quantifies proptosis
MRI	T2 hyperintensity in muscles	Differentiates active edema vs. fibrosis
Ultrasound	Muscle thickness; Doppler flow	Bedside, cost-effective inflammation marker
OCT	Lacrimal gland volume; optic nerve head	Early optic neuropathy detection

TSHR-Ab titers correlate with disease activity (sensitivity ~85%, specificity ~90%) (Bahn, 2016). Emerging markers (IGF-1R antibodies, IL-6, TNF-α) show promise but lack standardized assays (Endocrine Practice, 2024).

Subtle early features—eyelid retraction (>2 mm), mild periorbital edema, conjunctival injection—often precede proptosis and diplopia. Incorporating patient-reported eye discomfort increases detection sensitivity (Verywell Health, 2021).

Table 2. EUGOGO/ATA-based monitoring recommendations (European Group on Graves' Orbitopathy, 2021; Bahn, 2016).

Component	Active TED	Inactive/Mild TED
CAS assessment	Monthly	Every 6–12 months
Imaging (CT/MRI)	Every 3–6 months	As clinically indicated
GO-QoL questionnaire	Each visit	Annually
TSHR-Ab & cytokines	Every 6 months	Annually

Table 3. Diagnostic performance metrics (Eckstein et al., 1997; Bahn, 2016).

Modality/Marker	Sensitivity	Specificity	Comments
CAS ≥3	74%	88%	Rapid, bedside
MRI T2 hyperintense	81%	92%	Differentiates active vs. chronic
TSHR-Ab	85%	90%	May lag behind clinical flares

DISCUSSION

Combining CAS with imaging and serology yields superior early TED detection compared to any single modality (Luccas et al., 2023; Smith, 2021). CAS is practical but may overlook subclinical inflammation, whereas MRI and ultrasound detect anatomical and vascular changes

before overt signs (Waldstein, 2020). Serological assays complement imaging by providing systemic activity measures, though assay standardization remains a challenge (Endocrine Practice, 2024). Structured follow-up per EUGOGO and ATA guidelines ensures timely intervention windows for immunosuppression or radiotherapy, ultimately improving quality-of-life outcomes (European Group on Graves' Orbitopathy, 2021; Bahn, 2016). Future research should standardize novel biomarker assays and define imaging thresholds for subclinical disease.

CONCLUSION

This comprehensive review underscores the critical importance of a multimodal diagnostic framework for thyroid eye disease (TED) in women of reproductive age. By integrating the Clinical Activity Score (CAS) with advanced imaging techniques—computed tomography (CT), magnetic resonance imaging (MRI), ultrasound, and optical coherence tomography (OCT)—and complementing these with serological biomarkers (TSHR-Ab titers and emerging cytokine panels), clinicians can achieve sensitive, specific, and early detection of orbital inflammation. Early identification of active disease allows prompt immunosuppressive or surgical intervention, reducing the likelihood of irreversible fibrosis, compressive optic neuropathy, and other vision-threatening complications.

Structured monitoring protocols, as recommended by the European Group on Graves' Orbitopathy (EUGOGO) and the American Thyroid Association (ATA), provide a clear roadmap for follow-up: monthly CAS evaluations during active TED, imaging every 3–6 months to quantify anatomical changes, and semiannual serological assessments to track systemic immune activity. Incorporation of patient-reported outcome measures, such as the Graves' Orbitopathy Quality-of-Life (GO-QoL) questionnaire, ensures a patient-centered approach that addresses both clinical signs and the psychosocial impact of disease.

Clinicians are encouraged to adopt and adapt these evidence-based guidelines to individual patient profiles, considering factors such as disease severity, thyroid status, treatment response, and resource availability. Investment in clinician training, standardized imaging protocols, and validated biomarker assays will promote consistent care delivery and facilitate early therapeutic decision-making.

Looking forward, research priorities include large-scale validation of novel biomarkers (e.g., IGF-1R antibodies, IL-6, TNF-α), development of artificial intelligence-assisted imaging algorithms for detection of subclinical orbital changes, and prospective cost-effectiveness analyses of varied monitoring schedules. Longitudinal studies assessing the impact of early intervention on long-term visual and quality-of-life outcomes will further refine personalized management strategies for this vulnerable population.## AcknowledgementsWe thank the University Hospital Research Fund for support.

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