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Ophthalmic Findings in Pediatric Patients with Graves' Disease—Single-Center Study

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Abstract

Background: Hyperthyroidism caused by Graves' disease (GD) is a rare condition in the pediatric population. It is important to point out that GD is not just a thyroid disease, and Graves' orbitopathy, also known as thyroid eye disease (TED), can develop. The aim of this study was to evaluate ophthalmologic status in pediatric patients with GD at a tertiary care referral center. **Methods:** Eighteen pediatric patients previously diagnosed with Graves' disease received a complete ophthalmological exam, including exophthalmometry readings, clinical activity score (CAS) and ultrasound of extraocular muscles, and were graded according to the European Group on Graves' Orbitopathy (EUGOGO) classification. General endocrine status, thyroid hormones (TSH, fT3, fT4, anti-Tg, anti-TPO and TSHRAb) and duration of disease were also collected. **Results:** The prevalence of TED in our cohort of children and adolescents with GD was 55.6%. The most common presentation was mild hyperemia (7 subject, 38%). After stratifying subjects according to clinical activity score, subjects with CAS ≥ 1 had a statistically greater MLPS-MRS muscle length compared to subjects with CAS 0. (4.64 ± 0.79 vs. 3.25 ± 0.95 vs., $p = 0.001$). **Conclusions:** This study provides the first study on the characteristics and prevalence of TED in Croatia; demonstrating TED prevalence and predominantly mild severity and clinical activity in children. Additionally, we would like to highlight the use of orbital ultrasonography as a safe, cost-effective, and reproducible method for assessing and monitoring pediatric TED.

Keywords: Graves' disease; thyroid eye disease; pediatric thyroid disease; Graves' orbitopathy

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1. Introduction

Hyperthyroidism caused by Graves' disease (GD) is uncommon in the pediatric population, with a reported incidence of approximately 3–5 per 100,000 children per year [1,2]. GD is an autoimmune disorder characterized by TSH-receptor antibodies (TSHRAb), which stimulate thyroid hormone production, suppress pituitary thyrotropin (TSH) secretion, and result in hyperthyroidism. Its etiology is multifactorial, with genetic susceptibility interacting with environmental and immunological factors [3–5]. Importantly, GD is a systemic autoimmune disorder rather than solely a thyroid disease. Extrathyroidal manifestations include Graves' orbitopathy, also termed thyroid eye disease (TED), and, rarely, localized dermopathy [1].

Although TED has been extensively characterized in adults, its frequency, phenotype, and natural history in children remain less well defined [6,7]. Robust global prevalence estimates for pediatric TED are lacking. In adults with GD, a meta-analysis reported an overall TED prevalence of approximately 40%, with substantial geographic variation [8]. A recent systematic review and meta-analysis of pediatric TED identified proptosis, eyelid retraction, and ocular surface symptoms among the most frequently reported manifestations [9]. Published pediatric cohorts from different regions also demonstrate variation in presentation and prevalence, emphasizing the need for region-specific clinical data [10–13].

Recognition of pediatric TED is clinically relevant because even mild ocular manifestations may affect comfort, appearance, school activities, and quality of life, while the rarity of severe sight-threatening disease may contribute to under-recognition. In addition, pediatric assessment requires particular attention to methods that are objective, repeatable, and minimize radiation exposure. These considerations support a multidisciplinary approach involving pediatric endocrinology and ophthalmology and provide the rationale for systematic ocular assessment in children and adolescents with GD [1,6,7].

Smoking is a well-known factor associated with greatly increased the risk for thyroid eye disease [14]. A survey conducted among physicians treating Graves' disease in Croatia, assessing the importance of smoking as a risk factor for thyroid eye disease, showed that 30% of them did not recognize smoking as a risk factor [15].

Pediatric and adult TED are generally considered manifestations of the same disease process, but their clinical phenotypes differ. Adult TED more often shows marked inflammation, restrictive myopathy, and severe complications, whereas pediatric TED is usually characterized by lower disease activity and milder severity; dysthyroid optic neuropathy and corneal breakdown are uncommon in children [6,7]. A population-based comparison from Hong Kong also reported lower CAS values and less extraocular muscle restriction in pediatric than in adult-onset TED [16].

Objective assessment of orbital involvement may be supported by computed tomography (CT), magnetic resonance imaging (MRI), or orbital ultrasonography [17]. CT is useful for orbital anatomy but should be used judiciously in children because it involves ionizing radiation. MRI avoids radiation but may be less accessible and can be more demanding in younger patients. Orbital ultrasonography is non-invasive, widely available, comparatively inexpensive, and free of ionizing radiation. Recent pediatric data have provided reference measurements for extraocular muscle dimensions and support further evaluation of ultrasonography as an objective adjunct in pediatric thyroid dysfunction [18].

The primary aim of this study was to characterize the prevalence, activity, and clinical spectrum of TED in children and adolescents with GD followed at a tertiary referral center in the Dalmatian region of Croatia. A secondary aim was to examine the relationship between CAS and ultrasonographic extraocular muscle measurements and to explore whether personal and/or family exposure to smoking-related products was associated with greater clinical activity.

2. Materials and Methods

This cross-sectional, single-center study included 18 children and adolescents with a previous diagnosis of Graves' disease established according to the 2022 European Thyroid Association (ETA) guideline [1]. Patients were eligible if they were being treated for GD at the Thyroid Clinic, Division of Pediatric Endocrinology, Department of Pediatrics, University Hospital of Split, during the study period. Exclusion criteria were hyperthyroidism due to causes other than GD, including toxic nodules and drug-induced hyperthyroidism, syndromic conditions affecting thyroid status, and concomitant ophthalmological disease that could interfere with the assessment of TED. All participants were routinely monitored

and treated by a pediatric endocrinologist according to ETA recommendations. Between March and July 2026, participants attending their scheduled endocrine follow-up were referred for a standardized ophthalmological assessment by an ophthalmologist trained in orbital disease at the Department of Ophthalmology, University Hospital of Split. The study protocol was reviewed and approved by the Ethics Committee of University Hospital of Split (2181-147/01-06/LJ.Z.-26-02) on 27 February 2026 and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from a parent or legal guardian, and verbal assent was obtained from the participating children and adolescents.

2.1. Pediatric Examination and Thyroid Hormone Status

At diagnosis and during routine follow-up, a detailed medical history and clinical assessment were obtained for signs and symptoms of hyperthyroidism. Standard laboratory evaluation included thyrotropin (TSH), free thyroxine (fT4), free triiodothyronine (fT3), anti-TSH receptor antibodies (TSHRAb), anti-thyroperoxidase antibodies (anti-TPO), and anti-thyroglobulin antibodies (anti-Tg), measured using routine laboratory methods. Thyroid function was monitored during follow-up, and antithyroid drug doses were adjusted according to a dose-titration approach. Thyroid ultrasonography with Doppler blood-flow assessment was routinely performed at diagnosis and annually using a LOGIQ S8 system (GE HealthCare, Chicago, IL, USA).

At the study visit, a structured personal and family history was obtained regarding conventional cigarette smoking, vaping, e-cigarette use, and similar inhaled nicotine/tobacco products. Exposure was classified as positive when the participant and/or either parent reported current use of at least one of these products.

2.2. Standardized Eye Examination

All participants underwent a standardized comprehensive ophthalmic examination at the Department of Ophthalmology. Best-corrected visual acuity (BCVA) was assessed using a Snellen chart. Intraocular pressure (IOP) was measured in the primary position and in upgaze. Eyelid position, conjunctival injection and swelling, ocular motility, diplopia, proptosis, and other clinically relevant orbital findings were systematically assessed. Corneal involvement was evaluated with fluorescein staining during slit-lamp biomicroscopy. The diagnostics of pediatric TED was based on a clinical finding proposed by Bartely and Gordman in 1995 including eyelid retraction in association with thyroid dysfunction, proptosis and extraocular muscle (EOM) enlargement [19]. Disease activity was assessed using the seven-item Clinical Activity Score (CAS) recommended in the 2021 EUGOGO guideline [20]. One point was assigned for each of the following: spontaneous retrobulbar pain, pain on attempted upward or downward gaze, eyelid redness, conjunctival redness, swelling of the caruncle or plica, eyelid swelling, and conjunctival swelling (chemosis). In the EUGOGO framework, CAS $\geq$ 3/7 indicates active disease [20]. For the exploratory analyses in this study, participants were additionally stratified as CAS 0 versus CAS $\geq$ 1 to evaluate whether any detectable inflammatory activity was associated with ultrasonographic muscle dimensions.

2.3. Extraocular Muscle Evaluation by Ultrasound

Orbital ultrasonography was performed in both eyes using a Quantel Medical Aviso S system (version 5.0.1). A B-scan examination of the globe and orbit was first performed with a 10 MHz probe. Standardized A-scan measurements were then obtained by positioning the probe at the opposite equator, perpendicular to the muscle being assessed. After identification of the tendon insertion, the probe was moved posteriorly to the widest measurable portion of the muscle, and the distance between the two surface spikes was measured with

electronic calipers. The medial rectus (MRM), lateral rectus (MRL), inferior rectus (MRI), and levator palpebrae superioris–superior rectus complex (MLPS-MRS) were evaluated. All orbital ultrasound examinations were performed by a single experienced examiner, and measurements were repeated during the examination to improve consistency.

2.4. Statistics

Statistical analyses were performed using Prism 11 for macOS (version 11.0.2; GraphPad Software, La Jolla, CA, USA). Distributional assumptions for continuous variables were assessed using the Kolmogorov–Smirnov test. Normally distributed continuous variables are presented as mean ± standard deviation (SD), whereas non-normally distributed variables are presented as median and interquartile range (IQR). Categorical variables are reported as counts and percentages. Between-group comparisons of continuous variables were performed using Welch's t-test or the Mann–Whitney U test, as appropriate, and categorical variables were compared using Fisher's exact test. Spearman's rank correlation coefficients were calculated to examine associations between CAS and ultrasonographic parameters. All tests were two-sided, and $p < 0.05$ was considered statistically significant.

3. Results

The study included 18 children and adolescents with GD, with a mean age of 15.75 ± 3.05 years. Ten participants (55.6%) were female and eight (44.4%) were male. The mean age at GD diagnosis was 12.72 ± 3.66 years, and the mean follow-up duration at the Thyroid Clinic was 3.03 ± 2.16 years. Baseline clinical and biochemical characteristics are summarized in Table 1.

Table 1. Clinical and biochemical characteristics of the subjects enrolled in the study.

Parameter	Subjects ($N = 18$)
Age (years)	15.75 ± 3.05
Age at diagnosis (years)	12.72 ± 3.66
Sex–*N* (%)	
Male	8 (44.4)
Female	10 (55.6)
TSH (mIU/L)	0.012 ± 0.02
fT4 (pmol/L)	36.25 (26.13–69.55)
fT3 (pmol/L)	19.67 ± 10.81
Anti-Tg (U/mL)	90.4 (31.75–357)
Anti-TPO (U/mL)	158.9 (61.9–482.3)
TSHRAb (IU/L)	7.05 (2.9–10.85)
Follow up time (years)	3.03 ± 2.16

TSH, thyrotropin; fT4, free thyroxine; fT3, free triiodothyronine (fT3); TSHRAb, anti-TSH receptor antibodies; anti-TPO, anti-thyroperoxidase antibodies; anti-Tg, anti-thyroglobulin antibodies.

TED was identified in 10 of 18 participants (55.6%). The most frequent ocular finding was mild hyperemia, observed in seven participants (38%), followed by upper-eyelid swelling in four (22%) and mild proptosis without functional impairment in three (16.6%). Other ocular findings are summarized in Table 2.

Table 2. Ocular presentation of the subjects enrolled in the study.

Ocular Presentation	Subjects ($N = 18$)
Proptosis *N* (%)	3 (16.6)
Retraction *N* (%)	3 (16.6)
Swelling *N* (%)	4 (22)
Hyperemia *N* (%)	7 (38)
Lagophthalmos *N* (%)	3 (16.6)
Punctal epithelial keratopathy *N* (%)	2 (11.1)
Diplopia *N* (%)	1 (5.6)
Optical neuropathy *N* (%)	0
Imaging available (MRI/ultrasound)	
Orbital fat expansion *N* (%)	1 (5.6)
EOM enlargement *N* (%)	9 (50)

EOM, extra ocular muscle.

When participants were stratified according to the exploratory CAS grouping, those with CAS ≥ 1 had a significantly greater MLPS-MRS measurement than participants with CAS 0 (4.64 ± 0.79 vs. 3.25 ± 0.95 mm; $p = 0.001$). No statistically significant between-group differences were observed for the medial rectus, lateral rectus, or inferior rectus measurements (Table 3).

Table 3. Ultrasound parameters after stratification according to clinical activity score.

Parameter	CAS 0 ($N = 8$)	CAS ≥ 1 ($N = 10$)	*p*
MLPS-MRS (mm)	3.25 ± 0.95	4.64 ± 0.79	0.001
MRM (mm)	3.24 (3–4.74)	3.74 (3.45–4.35)	0.309
MRL (mm)	3.62 ± 1.31	4.16 ± 0.95	0.267
MRI (mm)	2.8 (2.22–3.19)	2.7 (2.56–3.84)	0.618

CAS, clinical activity score; MLPS-MRS, levator palpebrae superioris–superior rectus; MRM, medial rectus; MRL, lateral rectus and MRI, inferior rectus.

A moderate positive correlation was observed between CAS and MLPS-MRS measurement (Spearman R = 0.550, $p = 0.005$). Correlations between CAS and the other measured extraocular muscles were not statistically significant (Table 4).

Table 4. Spearman's correlation coefficients between CAS score and ultrasound parameters of the eye and the orbit.

Parameter	All Eyes ($N = 18$)	
	R *	*p*
MLPS-MRS (mm)	0.550	0.005
MRM (mm)	0.191	0.371
MRL (mm)	0.173	0.428
MRI (mm)	0.014	0.947

MLPS-MRS-levator palpebrae superioris–superior rectus, MRM-medial rectus, MRL-lateral rectus, MRI-inferior rectus. * Spearman's a correlation coefficient.

In the exploratory analysis of smoking-related exposure, participants with a negative personal and family history had no CAS values above 1, whereas higher CAS categories occurred only among participants classified as having personal and/or family exposure. The overall difference did not reach statistical significance ($p = 0.176$; Figure 1).

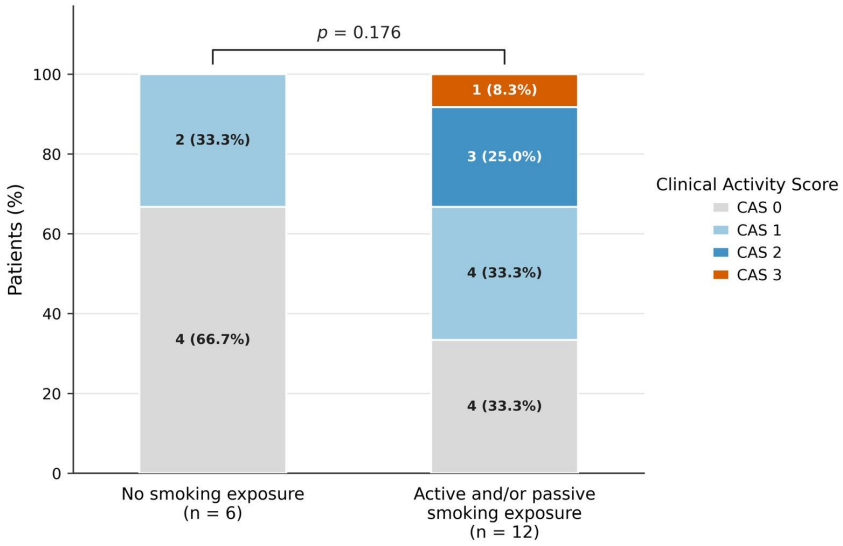


Figure 1. Clinical activity score after stratification according to negative versus positive personal and/or family history of smoking, vaping, e-cigarette use, or similar smoking-related products.

4. Discussion

In this study, we presented a prevalence of ocular involvement in pediatric patients with Graves' disease of 55.6%, most of whom had a mild clinical presentation. These results indicate the importance of early diagnosis and recognition of TED in children and adolescents, which in most cases is underdiagnosed. To the best of our knowledge, this is the first such study on the characteristics and prevalence of TED in Croatia.

In our study, we demonstrated a relatively higher prevalence of TED in the population of children and adolescents. Unfortunately, comparison with other studies is extremely challenging due to relatively small samples, age groups, and other differences between populations. In a large, predominantly European study in 25 countries, the cumulative prevalence of TED was 33% in the pediatric population in the period from 1995 to 2005, while in a similar period in the USA, 52% of children and adolescents had some ocular signs referable GD, and the majority with more severe symptoms were post-pubertal, which corresponds to the mean age of our cohort [21,22]. Additionally, a more recent study from the Gulf region reported a TED prevalence of 50% in the pediatric population; parental consanguinity was observed as a significant risk for development of TED, and no other statistically significant risks were observed that would affect the occurrence of TED [13].

Furthermore, smoking and passive smoking are a well-known risk factor for development and progression of TED in pediatric populations [7]. According to a World Health Organization (WHO) report from 2025, prevalence of tobacco and e-cigarette use by young people in the European Region is 11.6% (four million young people aged 13–15 years) [23]. In addition, according to the European School Survey Project on Alcohol and Other Drugs (ESPAD), a survey from 2024 reported that the prevalence of current cigarette smoking ranged from 4.2% in Iceland to 32.2% in Hungary. Upsetting and unfortunate data showed that Croatia takes high second place in the European region in tobacco consumption among the pediatric population, and also a very high third place in the European region in e-cigarette consumption among children and adolescents [24]. According to our results, children and adolescents with a positive history of smoking or passive smoking had higher CAS, which indicates once again the importance of smoking prevention in patients with GD and indicates the probable causes of the high prevalence of TED in our population. Furthermore, a study by Aranyoi et al. demonstrated that different types of smoking, including conventional smoking, heated tobacco products and e-cigarettes had a similar

influence on the cell index of fibroblasts in patients with Graves' orbitopathy [25]. Although personal smoking, vaping, parental smoking, and other smoking-related exposures are not equivalent, they may all be relevant to the activation of thyroid eye disease. Future studies should therefore distinguish between these different types of exposure to better elucidate their respective effects. Finally, long-term longitudinal studies are needed to demonstrate the impact of smoking and/or passive smoking on the further progression of TED, and we recommend preventive campaigns in European countries given the devastating results of the increase in smoking and e-cigarette consumption in the adolescent population.

Additionally, we displayed the use of ultrasound for detecting size enlargement of extraocular muscles in pediatric patients with Graves' disease. In contrast to typical clinical appearance in adults with TED with inferior rectus (MRI) enlargement, our results reveal an increase in levator palpebrae superioris–superior rectus (MLPS-MRS) size. Similar results were reported in a recent study by Yom et al. in 2024 which demonstrated significantly greater levator–superior rectus complex measurements in all pediatric age groups in contrast to adults with TED [18]. Furthermore, our results exhibit enlargement of all extraocular muscles in pediatric patients with greater clinical activity score (CAS ≥ 1) in accordance with a significant correlation with EOM size in the older age cohorts as previously published [18]. Given the small sample size and the number of comparisons performed, these findings should be interpreted with caution; however, they suggest a potential role for ultrasonography in the diagnosis of thyroid eye disease (TED), owing to its accessibility and non-invasive nature. Additional studies are needed with a larger sample and with longitudinal follow-up in order to clearly position ultrasound in the daily clinical practice of pediatric patients with TED.

Finally, CAS is the most commonly used tool for assessing TED activity. Given that the highly subjective method depends solely on the evaluator's expertise, there is a growing need for more technologically assisted options to standardize diagnostic testing [26,27]. Today, the use of artificial intelligence (AI) is increasing in daily clinical practice, and there is a possibility of further use in CAS scoring. A recent study presented high concordance between a qualified oculoplastic specialist and a machine learning (ML)-assisted system in detecting and scoring TED and demonstrated superiority compared to general ophthalmologists [26]. In addition, these findings can significantly help future research in standardizing the results and making adequate therapeutic decisions in regions where adequate ophthalmological care is not available.

This study has some limitations. Firstly, the cross-sectional design without long-term follow-up of TED development and progression could have prevented us from making any causal inferences. Secondarily, the relatively small sample size and data from a single center may have influenced the results. However, this was a considerable regional sample that represents a population of pediatric subjects with relatively low incidence of GD, which can possibly influence future research in this field.

5. Conclusions

This study provides the first regional data on pediatric thyroid eye disease (TED) in Croatia, demonstrating relatively high TED prevalence and predominantly mild severity and clinical activity in children and adolescents. Additionally, despite the limitations imposed by our small cross-sectional sample, our findings suggest that active and/or passive smoking may contribute to greater thyroid eye disease activity. Given that longitudinal monitoring and measurement reproducibility were not evaluated in the present study, we suggest that orbital ultrasonography be considered a potentially useful tool for assessing extraocular muscle size in pediatric patients with thyroid dysfunction, regardless of the presence or

absence of clinical ocular manifestations. However, further longitudinal studies are needed to establish its reproducibility and utility for monitoring changes over time.

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Informed Consent Statement: Informed consent was obtained from the legal guardians of all subjects involved in the study.

Data Availability Statement: The original contributions presented in this study are included in the article. Further inquiries can be directed to the corresponding author.

Conflicts of Interest: The authors declare no conflicts of interest.

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