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Ocular surface disease index in Graves' orbitopathy: a cross-sectional study

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Introduction: Graves' Orbitopathy (GO) is an autoimmune disorder characterized by inflammation of orbital tissues, leading to various ocular manifestations, including ocular surface disease. This cross-sectional study aimed to assess the presence of ocular surface disease using the Ocular Surface Disease Index (OSDI) in patients with Graves' disease (GD) and moderate-to-severe active GO compared to those with GD and mild non-active GO. Additionally, we aimed to investigate the correlation between ocular surface disease and the eye features of GO.

Methods: Consecutive GD patients with GO referred to the Ophthalmology and Endocrinology Units of the University Hospital of Pisa between June 2022 and February 2023 were enrolled. OSDI scores were obtained from 79 GD patients, categorized into moderate-to-severe active GO and mild non-active GO groups.

Results: OSDI scores were significantly higher in patients with moderate-to-severe active GO compared to those with mild non-active GO ($P=0.0006$). A cutoff value of 33 for positive tests revealed a higher frequency of pathological OSDI in moderate-to-severe active GO patients compared to mild non-active GO patients ($P=0.0221$; OR 3.673, CI 1.277-9.531). Within the moderate-to-severe active GO group, a significant positive correlation was found between OSDI and Clinical Activity Score (CAS) ($R=0.3867$, 95% CI from 0.1403 to 0.5880; $P=0.0030$). Using a cutoff value of 55 (the 75th percentile of the study population), patients with $CAS \geq 3$ had a significantly higher proportion of pathological OSDI compared to those with $CAS < 3$ ($P=0.0039$; OR 4.075, CI 1.619-10.39). Proptosis values ≥ 22 mm and the presence of lagophthalmos were identified as significant risk factors for ocular surface disease development ($P=0.0406$ and $P=0.0493$, respectively).

Discussion: Our study highlights a significantly higher prevalence of ocular surface disease, as measured by OSDI, in patients with moderate-to-severe active GO compared to those with mild non-active disease. The degree of GO activity positively correlates with ocular surface involvement, and proptosis and

lagophthalmos increase the risk of its occurrence. These findings emphasise the importance of assessing and managing ocular surface health in GO patients. Early identification and appropriate treatment of ocular surface disease need to be pursued to improve patient management.

KEYWORDS

Graves' orbitopathy, Graves' disease, dry eye disease, thyroid autoimmunity, ocular surface disease, ocular surface disease index

Introduction

Graves' orbitopathy (GO) is an autoimmune disease affecting orbital fibro-adipose tissue due to the interplay between cellular and humoral immunity against thyrotropic hormone (TSH) receptor (TSH-R) and possibly other autoantigens shared by thyroid epithelial cells and orbital fibroblasts (1, 2). Clinical manifestations of GO can be ascribed to three features: inflammation of soft tissues, glycosaminoglycans overproduction, and an increase in adipose tissue (3, 4). Along with inflammation, proptosis and diplopia, ocular surface damage may occur, frequently preceding the classic clinical onset of GO (5–12). One of the leading causes of ocular surface damage in GO is dry eye syndrome (DED) which is increasingly observed in patients with autoimmune diseases, including thyroid disorders (8–10). Previous studies have reported the prevalence of DED in GO patients to vary between 65 and 95% (5, 6, 11).

Dry eye disease (DED) is a multifactorial disease of the ocular surface characterized by loss of tear film homeostasis accompanied by ocular symptoms. Tear film instability, hyperosmolarity, ocular inflammation and neurosensory abnormalities are the main trigger factors (8, 13). Ocular surface changes can lead to blurred vision, burning, itchiness, redness, grittiness in the eye, and photophobia, eventually contributing to the clinical manifestations of GO (8–10).

While the association between GO and DED is well-acknowledged, the precise mechanism underlying this relationship remains incompletely understood. Proptosis and lid alterations are believed to disrupt ocular surface homeostasis, leading to corneal exposure and increased tear evaporation due to tear film instability (14). Moreover, ocular surface tissues themselves may serve as direct targets for autoantibodies and inflammation originating in the retrobulbar space (15). Interestingly, the potential correlation between DED and the severity and activity of GO has never been investigated.

Methods

Study design

The study was aimed at evaluating the presence of ocular surface disease in patients with Graves' disease (GD) and moderate-to-severe

active GO compared with patients with GD and mild non-active GO by using the Ocular Surface Disease Index (OSDI) in a cross-sectional design, which entailed the inclusion of consecutive patients over 9 consecutive months. In addition, we aimed to investigate the correlation between ocular surface disease and the eye features of GO. Given the absence of pre-existing data on the topic, a formal sample size calculation was not performed before starting the study. However, a *post hoc* analysis was conducted to determine the sample size needed for sufficient power. The study was performed according to the institutional guidelines and with the International Conference on Harmonization Good Clinical Practice guidelines and the principles of the Declaration of Helsinki (1975) and its revised version of 2013. The study was approved by the local Ethic Committee "Area Vasta Nord-Ovest", (approval no.24940). Data were anonymized for collection and analysis, avoiding a privacy data breach.

Setting

The investigation was carried out in a tertiary referral center from June 2022 to February 2023. MNM and GL collected the data and recorded them in a database. Database validation procedures included: allowed character checks, batch totals, missing records check, cardinality check, digits check, consistency check, control totals, cross-system consistency check, data type check, hash totals, limit check, logic check, presence check, range check, spelling and grammar check, and uniqueness check.

Participants

Inclusion criteria were: 1) diagnosis of GD, namely a history of hyperthyroidism along with previous or present detectable serum thyrotropin receptor binding antibodies (TRAbs); 2) diagnosis of GO, according to the European Group on Graves' Orbitopathy (EUGOGO) guidelines (4); 3) written, signed informed consent to data use and sample collection. Exclusion criteria were: 1) age < 18 years; 2) presence of corneal dystrophies; 3) local and/or systemic therapy with drugs known to have ocular toxicity; 4) presence of ocular or systemic pathologies that may interfere with assessments

(e.g. diabetes mellitus, Sjogren's syndrome); 5) previous decompressive orbitotomy or eye surgery related and/or unrelated to GO; 6) radioiodine treatment and/or external orbital radiotherapy in the last 12 months; 7) treatment with glucocorticoids or any other immune suppressive medication in the last three months. A total of 79 consecutive patients who satisfied the inclusion criteria and evaded the exclusion criteria were enrolled.

GO activity was assessed by Clinical Activity Score (CAS). GO severity was evaluated according to the EUGOGO criteria, which include the evaluation of eyelid retraction, proptosis, corneal involvement and the degree of diplopia (4).

Outcomes

The primary outcome was to assess the presence of ocular surface disease by using OSDI in patients with moderate-to-severe active GO compared to patients with mild non-active GO. The secondary endpoints were: 1) the correlation between OSDI and CAS; 2) the correlation between OSDI and the eye features of GO namely proptosis, diplopia, eyelid aperture and lagophthalmos.

Sources of data and measurements

An ophthalmological evaluation was performed in all patients, including 1) Hertel's exophthalmometry (Handaya, Tokyo, Japan); 2) eyelid aperture; 3) CAS; 4) assessment of diplopia evaluated using a Gorman score (16) (patients were divided into four categories accordingly, as shown in Table 1); 5) assessment of the corneal status; 6) presence of lagophthalmos; 7) examination of the fundi; and 8) assessment of visual acuity, measured as best corrected visual acuity (BCVA) in Logarithm of the Minimum Angle of Resolution (LogMar). Symptoms such as photophobia, lacrimation, irritation, blurred vision, burning, itchiness or grittiness and dryness were also investigated. Patients were asked to complete the OSDI questionnaire (Table 2). Developed by the Outcome Research Group at Allergan (Irvine, Calif) and copyrighted by AbbVie Inc. (North Chicago, Illinois, USA), this questionnaire is widely used to assess several aspects of ocular surface disease (17).

The OSDI is a validated tool for measuring the severity of DED, approved by the Food and Drugs Administration (FDA) for clinical trials (17). The questionnaire consists of 12 items, divided into three categories: symptoms of eye irritation, functional problems, and environmental triggers contributing to or causing ocular surface

TABLE 1 Demographic and clinical features of patients with Graves' orbitopathy (GO) based on the severity and the activity of the disease.

	Moderate-to-severe active GO (n=57)	Mild non active GO (n=22)	Statistics
Gender	Males: 15 (26.31) Females: 42 (73.68)	Males: 4 (18.18) Females: 18 (81.81)	OR: 1.60 95 % CI from 0.49 to 4.91 P=0.56*
Age (years)	55.34 (10.30)	46.89 (11.51)	Mean difference: -8.45 95 % CI from -13.79 to -3.11 P=0.0023**
Smoking	Never smokers: 75 (47.4) Ex-smokers: 23 (14.5) Current smokers: 56 (35.4)	Never smokers: 63 (58.8) Ex-smokers: 10 (9.3) Current smokers: 30 (28)	Chi-squared test: 1.95 P=0.37***
Time since diagnosis of hyperthyroidism (months)	26 (14-81)	33 (20-75)	Mann-Whitney U: 424.5 P=0.56 †
Time since diagnosis of Graves'orbitopathy (months)	21 (12-49)	24 (12-34)	Mann-Whitney U: 461.5 P=0.85†
TSH (mU/L) NV: 0.4-4	1.67 (0.41-3.96)	0.99 (0.40-2.75)	Mann-Withney U: 462 P=0.52†
FT3 (ng/L) NV: 2.7-5.7	3.73 (1.001)	3.58 (1.14)	Mean difference: -0.15 95 % CI from -0.73 to -0.42 P=0.59**
FT4 (ng/dL) NV:0.70-1.70	1.18 (0.34)	1.15 (0.30)	Mean difference: -0.02 95 % CI from -0.21 to -0.15 P=0.76**
TRAbs (UI/L) NV: <1.5	6.53 (3.40-19.97)	1.96 (0.64-9.22)	Mann-Withney U: 154 P=0.08†
Proptosis	22.5 (18-24.5)	16 (14-21)	Mann-Withney U: 7.9 P=0.69†
Clinical activity score	4 (3-5)	1(0-2)	Mann-Withney U: 0 P<0.0001†

(Continued)

TABLE 1 Continued

	Moderate-to-severe active GO (n=57)	Mild non active GO (n=22)	Statistics
Eyelid aperture (mm)	13.59 (2.86)	10.77 (2.89)	Mean difference: -2.81 95 % CI from -4.25 to -1.37 P=0.0002**
Diplopia	Absent: 20 (35.02) Intermittent: 11 (19.2) Inconstant: 13 (22.8) Constant 13 (22.8)	Absent: 20 (90.9) Intermittent: 2 (9.1) Inconstant: 0 (0) Constant 0 (0)	Chi-squared test: 20.81 P=0.0001***
Visual acuity (decimals)	0.98 (0.09)	0.98 (0.09)	Mean difference: -0.24 95 % CI from -0.24 to -0.62 P=0.69**

Data are n (%), mean (SD) or median (IQR).

NV, normal values; TSH, thyrotropic hormone; FT3, free triiodothyronine; FT4, free thyroxine; TRAbs: anti-TSH receptor autoantibodies.

Statistical tests: *Fisher exact test; **Student's t-test; ***Chi-squared test; †Mann-Whitney.

pathology. Each element is assigned a score from 0 to 4 and the total score ranges from 0 to 100. The score obtained can fall into four categories: 0-12: normal ocular surface; 13-22: mild dry eye condition; 23-32: moderate dry eye condition; 33-100: severe dry eye 16. In our study, results above 33 were considered pathological (8, 10, 11).

TABLE 2 Ocular Surface Disease Index (OSDI) Questionnaire.

Question	Response Options
Category I (eye irritation symptoms)	
1. Eyes sensitive to light	<input type="checkbox"/> Always <input type="checkbox"/> Almost always <input type="checkbox"/> Half of the time <input type="checkbox"/> Sometimes <input type="checkbox"/> Never
2. Gritty feeling in the eyes	<input type="checkbox"/> Always <input type="checkbox"/> Almost always <input type="checkbox"/> Half of the time <input type="checkbox"/> Sometimes <input type="checkbox"/> Never
3. Eye pain or irritation	<input type="checkbox"/> Always <input type="checkbox"/> Almost always <input type="checkbox"/> Half of the time <input type="checkbox"/> Sometimes <input type="checkbox"/> Never
4. Blurred vision	<input type="checkbox"/> Always <input type="checkbox"/> Almost always <input type="checkbox"/> Half of the time <input type="checkbox"/> Sometimes <input type="checkbox"/> Never
5. Poor vision	<input type="checkbox"/> Always <input type="checkbox"/> Almost always <input type="checkbox"/> Half of the time <input type="checkbox"/> Sometimes <input type="checkbox"/> Never
Category II (functional disease)	
6. Reading	<input type="checkbox"/> Always <input type="checkbox"/> Almost always <input type="checkbox"/> Half of the time <input type="checkbox"/> Sometimes <input type="checkbox"/> Never <input type="checkbox"/> No response
7. Night driving	<input type="checkbox"/> Always <input type="checkbox"/> Almost always <input type="checkbox"/> Half of the time <input type="checkbox"/> Sometimes <input type="checkbox"/> Never <input type="checkbox"/> No response
8. Working on a computer	<input type="checkbox"/> Always <input type="checkbox"/> Almost always <input type="checkbox"/> Half of the time <input type="checkbox"/> Sometimes <input type="checkbox"/> Never <input type="checkbox"/> No response
9. Watching TV	<input type="checkbox"/> Always <input type="checkbox"/> Almost always <input type="checkbox"/> Half of the time <input type="checkbox"/> Sometimes <input type="checkbox"/> Never <input type="checkbox"/> No response
Category III (environmental triggers)	
10. Windy conditions	<input type="checkbox"/> Always <input type="checkbox"/> Almost always <input type="checkbox"/> Half of the time <input type="checkbox"/> Sometimes <input type="checkbox"/> Never <input type="checkbox"/> No response
11. Very dry places	<input type="checkbox"/> Always <input type="checkbox"/> Almost always <input type="checkbox"/> Half of the time <input type="checkbox"/> Sometimes <input type="checkbox"/> Never <input type="checkbox"/> No response
12. Places with air conditioning	<input type="checkbox"/> Always <input type="checkbox"/> Almost always <input type="checkbox"/> Half of the time <input type="checkbox"/> Sometimes <input type="checkbox"/> Never <input type="checkbox"/> No response

Patients were asked to mark the box that best represents their condition.

Demographic data, including age, gender, smoking habit, GD and GO duration, previous treatment for both GD and GO, and general clinical data were collected. The following blood tests were performed in all subjects: free thyroxine (FT4) (Vitros Immunodiagnosics, Raritan, NJ); free triiodothyronine (FT3) (Vitros Immunodiagnosics, Raritan, NJ); TSH (Immulate 2000, Siemens Healthcare, Gwynedd, UK); TRAbs (Brahms, Berlin, Germany).

Statistical analysis

Continuous data are presented as mean and standard deviation (SD) or median (interquartile range IQR). The Shapiro-Wilk test for normality of distribution was performed on all variables. When appropriate, the following tests were performed: 1) Linear regression; 2) Mann-Whitney U; 3) Fisher exact test; 4) Chi-squared Test; 5) Student's t-test; 6) Multiple Linear regression. Statistical analysis was performed by using GraphPad Prism, version 9.4.1. P-values < 0.05 were considered statistically significant.

Results

The OSDI was assessed in 79 patients, whose demographical and clinical data are reported in Table 1. The study population included 57 patients with moderate-to-severe active GO and 22 patients with mild non-active GO. The patient's group did not differ in gender distribution, smoking habit, GD duration, and GO duration, while age was significantly different (P=0.0023). Notably, there was no correlation between age and OSDI (Figure 1). Sixty-five patients were on methimazole for hyperthyroidism treatment, but a minority of them (14 patients) had been previously treated with I¹³¹ (more than 12 months before enrolment) and were on levothyroxine (LT4) treatment for hypothyroidism. All patients were euthyroid. Among patients with moderate-to-severe active GO, 26 have been previously treated with ivGCs (more than 3 months before enrolling).

The OSDI was significantly higher in patients with moderate-to-severe active GO compared with patients with mild non-active

GO ($P=0.0006$ by Mann-Whitney; Mann-Whitney U: 318.5) (Figure 2A). Having established a cut-off value of 33 for positive tests, pathological OSDI was more frequent in patients with moderate to severe active GO than in those with mild non-active GO ($P=0.0001$; OR 7.200, 95% CI 2.578-18.81 by Fisher exact test) (Figure 2B).

Within patients with moderate-to-severe active GO, there was a significant direct correlation between OSDI and CAS ($R= 0.3867$, 95% CI 0.1403-0.5880; $P=0.0030$ by linear regression, using a Log10 for CAS) (Figure 3A). To increase specificity, we tested a cut-off value for the OSDI score of 55, which was equal to the 75th percentile of the study population. Using this cut-off, the

proportion of patients with pathological OSDI was significantly higher in the group of patients with $CAS \geq 3$ than in patients with $CAS < 3$ ($P=0.0039$; OR 4.075, 95% CI 1.619-10.39 by Fisher exact test) (Figure 3B). The choice for a cut-off value is arbitrary. Initially, we established a cut-off of 33, which is recognized to be diagnostic for a severe dry eye. Next, to increase the specificity, we tested a cut-off value of 55 which was equal to the 75th percentile of the study population.

The correlation between OSDI and the eye features of GO was also investigated. The OSDI was significantly greater in patients with proptosis ≥ 22 mm compared to those with mild proptosis ($P=0.0406$ by Mann-Whitney), and in patients with lagophthalmos

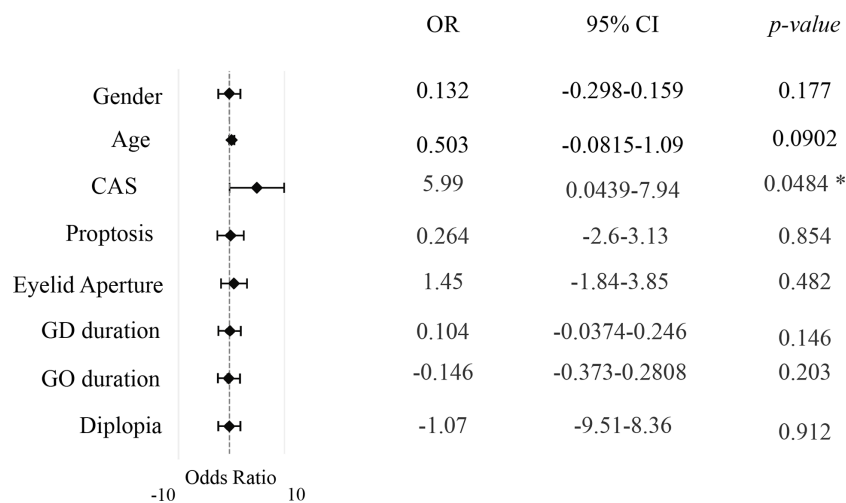


FIGURE 1 Multivariate effects of clinical and demographic key variables on Ocular Surface Disease Index (OSDI) in the cohort study population. The independent effects of age, CAS, proptosis, eyelid aperture, GD duration, GO duration and diplopia on the Ocular Surface Disease Index (OSDI) scores in the cohort. The analysis controls for potential confounders and reveals the unique contribution of each variable to the observed outcomes. P value significance: $P < 0.05$, *. CAS, clinical activity score; GD, Graves' Disease; GO, Graves' Orbitopathy.

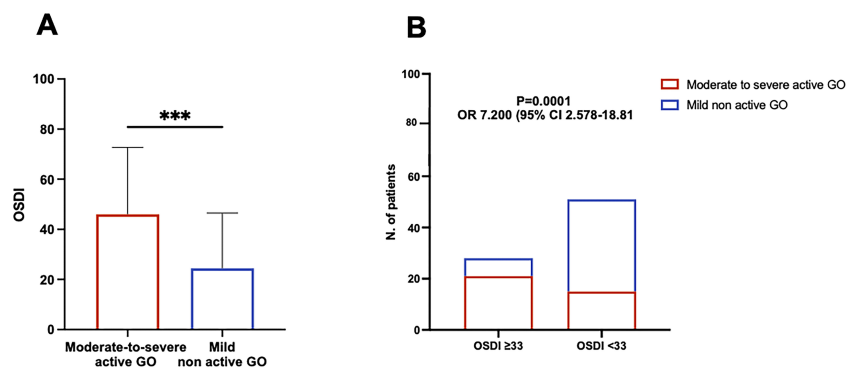


FIGURE 2 Patients with moderate-to-severe active Graves Orbitopathy (GO) experience worsened Ocular Surface Disease Index (OSDI) compared with mild non-active GO patients. **(A)** Comparison of the OSDI between patients with moderate-to-severe active GO and patients with mild non-active GO. The statistical significance was assessed by Mann-Whitney test. P value significance: $P < 0.001$, ***. **(B)** Comparison of the frequency of pathological OSDI (>33) between patients with moderate-to-severe active GO and patients with mild non active GO. Statistical analysis was performed using Fisher exact test yielding both P value and odds ratio (OR).

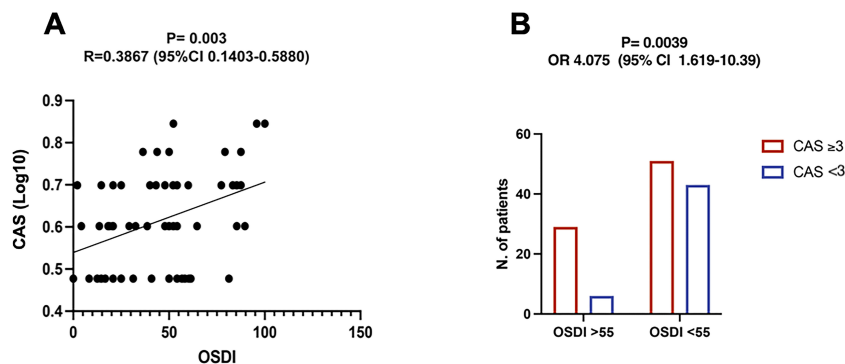


FIGURE 3

Ocular Surface Disease Index (OSDI) positively correlates with the Clinical Activity Score (CAS) in patients with moderate-to-severe active Graves Orbitopathy (GO). **(A)** Correlation between CAS (Log10 values) and OSDI within the group of moderate-to-severe active GO patients. The correlation coefficient (R) and its significance (P value) were obtained by linear regression analysis. **(B)** Comparison of the frequency of pathological OSDI between patients with CAS ≥ 3 and patients with CAS < 3 . A cutoff of 55, which was equal to the 75th percentile of the study population, was used to increase specificity. P value and odds ratio (OR) were obtained by Fisher exact test.

than in those without ($P=0.0493$ by Mann-Whitney), suggesting that proptosis and lagophthalmos are suitable risk factors for the occurrence of ocular surface disease (Figure 4). No correlation between OSDI and the other eye single features of GO, including eyelid aperture, and degree of diplopia was observed (Figure 1). Furthermore, OSDI did not correlate with GD and/or GO duration (Figure 1).

Discussion

The OSDI is a widely used questionnaire designed to assess the symptoms and impact of ocular surface diseases, particularly DED. It was developed to provide a standardized method for evaluating the severity of DED symptoms and their effect on patients' quality of life. Despite the well-recognized association of ocular surface disease with autoimmune thyroid diseases, particularly GO, the

potential interplay between DED and the activity and severity of GO remains unexplored. Furthermore, the suitability of OSDI for assessing DED in GO patients has not been investigated. To address this gap, the present study represents the first attempt to elucidate the relationship between DED occurrence and the clinical characteristics of GO. Specifically, the investigation aimed to evaluate ocular surface health in patients with GD and moderate to severe GO, in comparison to those with GD and mild non-active GO, utilizing the OSDI score as a measure.

Our results indicate a significantly higher prevalence of ocular surface disease in patients with moderate-to-severe active GO compared to those with mild non-active disease. Consistent with previous studies, this finding underlines the impact of active inflammation and tissue remodeling on ocular surface health (6, 18–20).

The majority of mild non-active GO patients presented with OSDI < 33 , while OSDI scores diagnostic for ocular surface disease

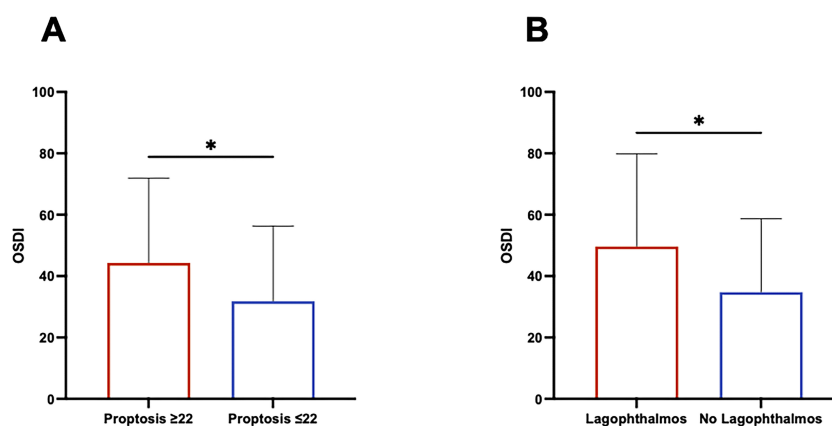


FIGURE 4

Proptosis and lagophthalmos are potential risk factors for the occurrence of ocular surface disease in patients with Graves' Orbitopathy. **(A)** Comparison of the Ocular Surface Disease Index (OSDI) between patients with proptosis ≥ 22 and patients with proptosis < 22 . The statistical significance was assessed by Mann-Whitney test. P value significance: $P < 0.05$, *. **(B)** Comparison of the OSDI between patients with and without lagophthalmos. The statistical significance was assessed by Mann-Whitney test. P value significance: $P < 0.05$, *.

were more commonly observed in patients with moderate-to-severe active GO. To increase the specificity of OSDI in our study population, we also tested a diagnostic cut-off of 55. Strikingly, GO patients with $CAS \geq 3$ exhibited pathological OSDI more frequently than those with $CAS < 3$. Along with the direct correlation between CAS and OSDI, this finding suggests that inflammation plays a key role in the development of ocular surface disease in GO patients.

DED is known as a possible consequence of GO, contributing to ocular discomfort and impaired vision (11). The occurrence of this condition affects the quality of life (QoL) and daily activities, particularly among patients with additional risk factors such as advancing age, gender disparities, hormonal dysfunctions, environmental influences, and lifestyle factors (8). Our results confirm the described association between GO and DED and elucidate it further, demonstrating that the degree of GO activity significantly contributes to DED occurrence. Since GO and DED may have a serious impact on QoL, it would be interesting to investigate the association between GO-QoL and OSDI, both assessed using the appropriate questionnaire. Although we evaluated GO-QoL in this study, the retrospective design led to an imbalance in the number of QoL questionnaires collected between groups, limiting the strength of our statistical analysis. Assessing the association between QoL and OSDI scores could offer valuable insights, and future studies with a prospective design and a more balanced data collection could better explore this relationship.

The exact pathogenetic mechanisms of DED in GO remain incompletely understood, but several potential contributing factors have been suggested. Primary among these is ocular surface exposure resulting from proptosis, eyelid retraction, widening of the palpebral fissure, and lagophthalmos. Any dysfunction in eyelid function can lead to increased tear evaporation and the development of ocular surface alterations. The OSDI questionnaire, as illustrated in the 12 items detailed in Table 2, specifically investigates dry eye symptoms and their impact on daily activities. During the administration of the questionnaire, the focus was kept strictly on dry eye symptoms to avoid any potential confounding effects related to diplopia or other visual impairments. Although age is known to be associated with a higher prevalence of dry eye due to age-related changes in tear production and ocular surface health, we did not find a significant correlation between age and OSDI scores. One possible explanation is that the OSDI questionnaire is designed to capture the patients' subjective experiences of dry eye symptoms in relation to their daily activities. Eyelid aperture, degree of diplopia, and visual acuity did not correlate with DED in our study.

Interestingly, we observed higher OSDI in patients with lagophthalmos and in those with proptosis ≥ 22 , indicating that proptosis and lagophthalmos may serve as risk factors for the development of ocular surface diseases in GO patients. Consistent with previous literature (19), this finding emphasizes the correlation between GO-related orbital anatomical changes and the onset of ocular surface disease. In addition to the OSDI questionnaire, which may introduce the possibility of subjective bias, objective measures

of ocular surface health, such as tear film stability or tear production tests, could provide complementary insights. Objective measurements could provide a more comprehensive understanding of how anatomical alterations can impact ocular surface health and patient QoL (21). Moreover, DED in GO seems to be predominantly of the evaporative type, with severe lower eyelid meibomian gland dysfunction (MGD) and worse lagophthalmos significantly associated with tear film instability in treatment-naive GO patients (21). This finding aligns with the importance of assessing tear film stability as part of the ocular surface evaluation in GO and supports the need for a multidimensional approach, to better address the complexity of ocular surface disease in GO patients. As the primary outcome of this study was to evaluate, as a proof-of-concept, the clinical utility of the OSDI questionnaire as a tool for exploring ocular surface health in GO patients, and given the retrospective design of our investigation, we did not include objective assessments of DED in our analysis.

The study's cross-sectional design also limits the ability to establish causal relationships between GO activity and ocular surface disease. In addition, the lack of a pre-study sample size calculation is a limitation that needs to be considered. However, a *post hoc* analysis was performed to evaluate the power of the study. Regarding the primary outcome, the effect size calculated (Cohen's $d = 4.63$) indicates a substantial difference between the groups. Specifically, the power analysis suggested that only eight patients per group would be required to achieve adequate power for this comparison. This confirms that our sample size (79 patients) was adequate. Next, we investigated the correlation between OSDI scores and CAS. The power analysis was performed by using the correlation coefficient as our effect size and setting a significance level (α) of 0.05. Although the *post-hoc* analysis suggested that a larger sample size (105 patients) would enhance the reliability of our results, the fact that we achieved statistical significance with our sample of 79 patients indicates that the correlation between CAS and OSDI is indeed detectable and meaningful in this context even in a smaller cohort.

Overall, our study demonstrates for the first time that OSDI can be used to efficiently assess the presence of ocular surface disease in GO patients and show an interesting correlation between the degree of GO activity and severity and the occurrence of DED. Our results highlight the clinical relevance of assessing ocular surface health in patients with GO, especially those with moderate-to-severe active GO. Integrating OSDI assessment with evaluation of GO severity and activity can aid in more accurate management and treatment decisions, potentially alleviating the burden of ocular surface disease and enhancing overall well-being in GO patients. Early identification and management of ocular surface disease are crucial for improving patient outcomes and minimizing ocular discomfort and visual impairment associated with GO.

Further studies, including both subjective measures like the OSDI questionnaire and objective assessments, such as tear film stability and tear production tests, are needed to confirm our results and investigate the suitability of using OSDI in clinical practice to improve the management of GO patients.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Comitato Etico Area Vasta Nord-Ovest (approval no.24940). The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

MNM: Conceptualization, Data curation, Investigation, Validation, Writing – original draft. GL: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software, Supervision, Validation, Writing – original draft, Writing – review & editing. MF: Writing – review & editing. GC: Writing – review & editing. SC: Writing – review & editing. MM: Writing – review & editing. FS:

Writing – review & editing. CP: Writing – review & editing, Resources, Validation.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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