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News in Graves' orbitopathy: Patients management and treatments

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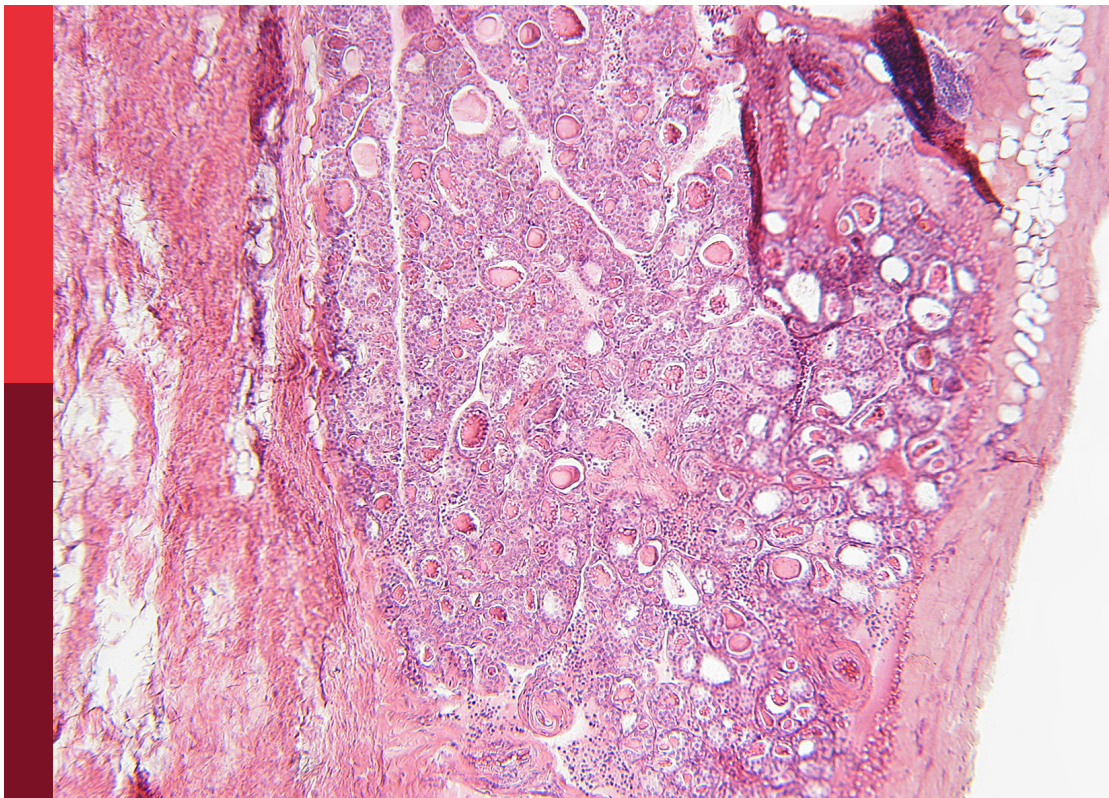

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News in Graves' orbitopathy: Patients management and treatments

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Editorial: News in Graves' orbitopathy: patients management and treatments

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KEYWORDS

Graves' disease (GD), thyroid autoimmunity, thyroid eye disease (TED), Graves' orbitopathy, thyroid, thyroid disease

Editorial on the Research Topic
News in Graves' orbitopathy: patients management and treatments

Graves' orbitopathy (GO) is an autoimmune disease observed in ~30% of patients with Graves' disease (GD) (1). Despite advancements in understanding, the current treatment of GO is not satisfactory. The ultimate pathogenetic mechanism is still being defined, and new risk factors, diagnostic methods, and treatment procedures have been proposed. This Research Topic consists of 11 insightful contributions that offer a timely overview of GO, from terminology to treatment novelties.

Currently, there is no widely accepted name for GO. Wagner et al. proposed thyroid eye disease (TED) as the preferred term since it is likely to give patients a better understanding of the disease. The authors discussed the appropriateness of "GO", which includes the eponymous "Graves" even though a small percentage of patients are not affected by GD. Despite TED gaining popularity among ophthalmologists, GO remains the term most used by endocrinologists. Interestingly, publications by multidisciplinary author teams showed an increase in using TED from 2000 to 2020, although GO remains the dominant term. While the change proposed by Wagner is intriguing, "TED" does not fully encompass the disease, since it is an "orbitopathy" that affects all structures within the orbit rather than exclusively the eye. Overall, a universally accepted terminology is necessary, thereby minimizing confusion and dichotomy among various specialists.

Given the knowledge that GO is due to a complex interplay between innate immunity, humoral immunity, and inflammatory response, several factors affecting immune tolerance and inflammation may have triggering or protective and therapeutic roles (1, 2). In a comprehensive retrospective study, Oeverhaus et al. confirmed that age, male sex, smoking, GD, and radioiodine are important risk factors for the development of severe stages of GO. Park et al. proposed the machine learning system eXtreme Gradient Boosting to predict the response to intravenous glucocorticoids (ivGCs) in GO patients. TSH, thyroid-stimulating immunoglobulins (TSI), and low-density lipoprotein cholesterol (LDL-C) were the features mostly influencing responsiveness. LDL-C had the greatest impact on the AI model, confirming it as a risk factor that can influence GO course and ivGCs response. Given the sample size and retrospective design, further, larger prospective studies are needed to validate this predictive system.

One of the most dreaded complications of GO is the impairment of visual function, caused by optic nerve compression at the orbital apex. Retinal and choroidal microvascular density have been proposed to evaluate the early stage of visual impairment in patients with GO (3, 4). Zeng et al. performed a cross-sectional study to assess macular vessel density (VD) in GO patients with chorioretinal folds (CRFs) with and without optic disc edema. They found a significant decrease in macular VD in GO patients with CRFs, which correlated with visual dysfunction, offering a new possible index to be considered in GO patients' management. Retinal perfusion is another parameter that can be investigated in patients with GO and visual field defects. Patients with sight-threatening GO may experience vascular insufficiency of retinal perfusion due to continuous mechanical compression and optic nerve stretching (5). Ye et al. showed that elevated pulse pressure correlate with reduced retinal peripapillary perfusion in GO patients, leading to visual field defects. These results suggest that vascular insufficiency may contribute to visual impairment in patients with GO by reducing retinal perfusion.

Immunosuppressive treatment is reserved for moderate-to-severe active GO, making assessment of GO activity a key element in determining the most appropriate treatment (2). Tissue inflammation is commonly evaluated using the clinical activity score (CAS) (2, 6). Even though it is a standardized and useful tool, CAS carries several limitations. Given the importance of GO activity in driving patient management, a more comprehensive score including several assessment factors, is needed. Since magnetic resonance imaging (MRI) provides information on orbital tissue expansion and distribution (2, 7, 8), Song et al. reviewed the potential application of MRI in quantifying GO activity. They confirmed that T2 relaxation time can be used to quantify GO activity and may aid in predicting the response to anti-inflammatory treatment. In the attempt to find new useful elements in identifying patients with active GO, Olejarz et al. proposed immunoglobulin G4 (IgG4) as a marker of GO activity. The role of IgG4 in thyroid disease has been investigated and high IgG4 levels have been reported in GD and GO, although their exact role and significance remain unclear (9–12). Olejarz et al. proposed a prospective observational study in which 60 patients with GO were divided into a high IgG4 group (>135 mg/dL) and a normal IgG4 group (<135 mg/dL). The high IgG4 group showed higher prevalence of active GO defined by MRI and higher TRAb titers compared to the normal IgG4 group. However, no significant difference in CAS was observed between the two groups. Further larger studies are needed to clarify the potential significance of high levels of IgG4 in GO before considering it a marker of activity.

Due to the lack of safe and well-tolerated treatments that guarantee a complete and satisfactory response, GO patients represent a challenge for endocrinologists and ophthalmologists. The targeted therapy with monoclonal antibodies is one of the most promising alternatives for patients with moderate-to-severe active GO (13–16). However, the safety profile and best-recommended dose are not yet fully defined. Wang et al. investigated the long-term (up to 224 weeks) efficacy and safety of using low doses (125 mg/m^2 weekly for 4 weeks) of rituximab, a monoclonal antibody that targets CD20 on the surface of pre-B and mature B-lymphocytes, to treat patients with moderate-to-severe active GO. A significant decrease in CAS, exophthalmos, and thickness of extraocular muscles was observed, with no major adverse events, suggesting that low doses of rituximab may be considered for GO patients. Hu et al. in a meta-analysis including 12 trials showed that the IL-6 receptor inhibitor tocilizumab was likely the best treatment for moderate-to-severe GO in terms of indirect contrast response, followed by teprotumumab (IGF-1 receptor blocking monoclonal antibody) and rituximab. Moreover, tocilizumab had the best result in reducing proptosis and a higher safety profile. These data are based on an indirect comparison and need to be confirmed by head-to-head trials. The optimal dose, safety, and long-term efficacy of monoclonal antibodies remain to be established, and this may change the treatment paradigm for GO in the future. Bottom line, monoclonal antibodies represent a new therapeutic area in GO and further randomized controlled studies with an appropriate sample size and study design are needed to confirm the promising results reported by Wang and Hu.

Despite medical progress and the discovery of new target therapies for patients with moderate-to-severe active GO, patients with inactive chronic disease benefit from orbital decompression, squint, and palpebral surgery (2). Savino et al. in a retrospective observational study including 29 patients with strabismus and diplopia compared the long-term effects of two types of eye surgery: bilateral medial recti recession or unilateral inferior rectus recession. Bilateral medial rectus recession leads to significant improvements in the deviation angle and diplopia, with stable under-correction over time, while inferior rectus recession leads to more unstable outcomes. Moreover, the latest advances in GO surgical procedures are reported by Baeg et al. to provide updated insights on the most appropriate choices.

This Research Topic offers encouraging updates on patient management, including advances in both the diagnosis and treatment of GO. The need for standardized terminology and improved disease activity assessment scores are interesting topics that can be investigated in future studies, as well as the possibility of using artificial intelligence systems to predict treatment response rates.

Author contributions

GL: Conceptualization, Writing – original draft, Writing – review & editing. ES: Writing – review & editing.

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.

Publisher's note

References

1. Bartalena L, Piantanida E, Gallo D, Lai A, Tanda ML. Epidemiology, natural history, risk factors, and prevention of Graves' orbitopathy. *Front Endocrinol (Lausanne)* (2020) 11:615993. doi: 10.3389/fendo.2020.615993

2. Bartalena L, Kahaly GJ, Baldeschi L, Dayan CM, Eckstein A, Marcocci C, et al. The 2021 European Group on Graves' orbitopathy (EUGOGO) clinical practice guidelines for the medical management of Graves' orbitopathy. *Eur J Endocrinol* (2021) 185(4): G43–67. doi: 10.1530/EJE-21-0479

3. Wu JH, Luo LY, Zhou H, Wu Y, Zhang J, Cheng JW. Reduced choroidal peripapillary capillaries in thyroid-associated ophthalmopathy with early stage of dysthyroid optic neuropathy. *Int J Ophthalmol* (2022) 15(7):1135–41. doi: 10.18240/ijo.2022.07.14

4. Zhang T, Xiao W, Ye H, Chen R, Mao Y, Yang H. Peripapillary and macular vessel density in dysthyroid optic neuropathy: An optical coherence tomography angiography study. *Invest Ophthalmol Vis Sci* (2019) 60(6):1863–9. doi: 10.1167/iovs.18-25941

5. Tu Y, Mao B, Li J, Liu W, Xu M, Chen Q, et al. Relationship between the 24-h variability of blood pressure, ocular perfusion pressure, intraocular pressure, and visual field defect in thyroid associated orbitopathy. *Graefes Arch Clin Exp Ophthalmol* (2020) 258(9):2007–12. doi: 10.1007/s00417-020-04733-5

6. Mourits MP, Prummel MF, Wiersinga WM, Koornneef L. Clinical activity score as a guide in the management of patients with Graves' ophthalmopathy. *Clin Endocrinol (Oxf).* (1997) 47(1):9–14. doi: 10.1046/j.1365-2265.1997.2331047.x

7. Kahaly GJ. Imaging in thyroid-associated orbitopathy. *Eur J Endocrinol* (2001) 145(2):107–18. doi: 10.1530/eje.0.1450107

8. Muller-Forell W, Kahaly GJ. Neuroimaging of Graves' orbitopathy. *Best Pract Research: Clin Endocrinol Metab* (2012) 26:259–71. doi: 10.1016/j.beem.2011.11.009

9. Li Y, Nishihara E, Hirokawa M, Taniguchi E, Miyauchi A, Kakudo K, et al. Distinct clinical, serological, and sonographic characteristics of Hashimoto's thyroiditis based with and without IgG4-positive plasma cells. *J Clin Endocrinol Metab* (2010) 95 (3):1309–17. doi: 10.1210/jc.2009-1794

10. Takeshima K, Inaba H, Furukawa Y, Nishi M, Yamaoka H, Miyamoto W, et al. Elevated serum immunoglobulin G4 levels in patients with Graves' disease and their clinical implications. *Thyroid* (2014) 24(4):736–43. doi: 10.1089/thy.2013.0448

11. Bozkirli E, Bakiner OS, Ersozlu Bozkirli ED, Haydardedeoglu FE, Sizmaz S, Izol Torun A, et al. Serum Immunoglobulin G4 levels are elevated in patients with Graves' ophthalmopathy. *Clin Endocrinol (Oxf).* (2015) 83(6):962–7. doi: 10.1111/cen.12671

12. Yu SH, Kang JG, Kim CS, Ihm S-H, Choi MG, Yoo HJ, et al. Clinical implications of immunoglobulin G4 to Graves' ophthalmopathy. *Thyroid* (2017) 27(9):1185–93. doi: 10.1089/thy.2017.0126

13. Smith TJ, Kahaly GJ, Ezra DG, Fleming JC, Dailey RA, Tang RA, et al. Teprotumumab for thyroid-associated ophthalmopathy. *N Engl J Med* (2017) 376 (18):1748–61. doi: 10.1056/NEJMoa1614949

14. Douglas RS, Kahaly GJ, Patel A, Sile S, Thompson EHZ, Perdok R, et al. Teprotumumab for the treatment of active thyroid eye disease. *N Engl J Med* (2020) 382 (4):341–52. doi: 10.1056/NEJMoa1910434

15. Perez-Moreiras JV, Gomez-Reino JJ, Maneiro JR, Perez-Pampin E, Lopez AR, Alvarez FMR, et al. Efficacy of tocilizumab in patients with moderate-to-severe corticosteroid-resistant Graves orbitopathy: A randomized clinical trial. *Am J Ophthalmol* (2018) 195:181–90. doi: 10.1016/j.ajo.2018.07.038

16. Stan MN, Salvi M. MANAGEMENT OF ENDOCRINE DISEASE: rituximab therapy for Graves' orbitopathy - lessons from randomized control trials. *Eur J Endocrinol* (2017) 176(2):R101–9. doi: 10.1530/EJE-16-0552

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Elevated pulse pressure correlated with reduced retinal peripapillary capillary in thyroid-associated ophthalmology with visual field defect

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Purpose: To quantify the retinal vessel density in thyroid-associated ophthalmology (TAO) patients with visual field (VF) defect and examine its associations with mechanical and system vascular risk factors for underlying pathogenesis of VF defect in TAO.

Methods: The cohort was composed of 62 TAO eyes (39 with VF defect and 23 without VF defect). The pulse pressure (PP), intraocular pressure (IOP), ophthalmic rectus muscular index (MI), superficial retinal capillary plexus (SRCP), radial peripapillary capillary (RPC) density, and other related parameters were measured. The associations among these factors and VF mean deviation (MD) were analyzed.

Results: In TAO patients with VF defect, reduced RPC density, higher PP, and larger horizontal and vertical MI were found (all $P < 0.03$) when compared to TAO patients without VF defect. The RPC density was correlated with VF MD value ($r = 0.242$, $P = 0.029$), while SRCP density was not ($P = 0.419$). In univariable general estimating equation (GEE) analysis with RPC density as the outcome, PP and its fluctuation showed a significant association (both $P < 0.04$). In the final RPC model with multivariable GEE analysis, only PP ($\beta = -0.082$, $P = 0.029$) showed significance while PP fluctuation ($P = 0.080$) did not.

Conclusions: The elevated PP was correlated with reduced retinal peripapillary perfusion in TAO resulting in VF defect. These data suggested that the system vascular factor may be important in the pathogenesis of reduced retinal perfusion resulting in visual impairment in TAO.

KEYWORDS

thyroid-associated ophthalmology (TAO), visual field (VF), optical coherence tomography angiography (OCTA), pulse pressure (PP), retinal capillary

Introduction

Visual field (VF) defect is one of the most frequent and almost the first clue of vision threats during the progression of thyroid-associated ophthalmology (TAO) (1). The pathogenesis of visual defect in TAO was still unclear. The mechanic compression due to the enlarged rectus muscles and increased orbital volume was widely accepted as the main cause (1). However, despite successful orbital decompression being done, some TAO patients still complained about progressively decreased visual function (2). In Dickinson's study, even rarely optic nerve stretch was found from the orbital coronal computed tomography scanning images in some TAO patients with extreme proptosis (3). There might be other mechanisms that play the important roles in visual field defect in TAO patients.

The health of the retinal perfusion might be of great importance in maintaining normal visual function. The impaired ophthalmic drainage and related retinal perfusion in TAO with visual impairment had been reported (4, 5). However, the mechanism of retinal perfusion alteration and its association with VF defect in TAO were still unclear. It was well known that abnormal blood pressure contributed to the perfusion damage of the end-organ (6, 7). Our previous study had already found abnormal blood pressure in TAO patients with severe VF defect, although the association between blood pressure and retinal perfusion in TAO with VF defect was unclarified (8). In addition, with continuous mechanic compression, there was a sustained stretching of the optic nerve that might also result in the vascular insufficiency of retinal perfusion (4, 9).

In the current study, we explore the retinal perfusion alteration, as an alternative important mechanism in TAO patients with visual defect, and examine the relative important risks in the pathogenesis of retinal perfusion alteration. It might help us understand the high risks of altered retinal perfusion and the underlying mechanism of VF defect in TAO.

Methods

Subjects and basic examination

All TAO patients were recruited from the Eye Hospital of Wenzhou Medical University, Wenzhou, China. The TAO diagnosis was decided by one professor, based on the criteria of Bartley (10). The patients with anti-glaucoma or antihypertension treatment, or other eye diseases (such as glaucoma, uveitis, and other retinal diseases) as well as systemic diseases (like diabetic retinopathy), were excluded. The patients who smoked were also excluded (11). All patients included were provided with informed consent. The current study was approved by the Ethics Committee Board, the Eye Hospital of Wenzhou Medical University, Wenzhou, China.

All TAO patients were given a comprehensive ophthalmic examination, including spherical equivalents with best-corrected visual acuity (BCVA) and slit-lamp examination. The VF test was done by a Humphrey field analyzer (SITA standard algorithms with a 30-2 program). All included VF results were with the reliable scans as false-positive error <15%, false-negative error <15%, and fixation loss <20%. The VF test with mean deviation (MD) ≤-2 dB was considered as a VF defect. We divided the TAO patients into two groups depending on their VF test result: (1) VF defect and (2) no VF defect. If one TAO patient has one eye with VF defect and the other without VF defect, it would be excluded. For both eyes with VF defect in the same TAO patients, only the severer eye would be included for analysis. For both eyes without VF defect in the same TAO patients, only the milder eye would be included for analysis. The orbital computed tomography (CT) scans were done to evaluate the ophthalmic rectus muscular index (MI) (12). Among all scanning images, only the image halfway between the posterior globe and the orbital apex was chosen to evaluate the ophthalmic rectus muscular index (MI) (12). The horizontal MI was defined as the percentage of orbital width occupied by the medial rectus and lateral rectus along the line through the optic nerve, while the vertical MI was defined as the percentage of orbital height occupied by the superior rectus and inferior rectus along the line through the optic nerve (12).

Diurnal measurements of blood pressure and intraocular pressure

Diurnal measurements of blood pressure (measured by a validated automatic sphygmomanometer, Omron, Tokyo, Japan) and intraocular pressure (IOP, measured by the Full Auto Tonometer TX-F; Topcon, Tokyo, Japan) were collected at 05:00, 07:00, 10:00, 14:00, 18:00, and 22:00 in a single day. The six time points chosen for measurement provided sufficient time to observe diurnal rhythms of blood pressure and IOP. All patients were forbidden to do any physical activities (like swimming) or have any alcohol (or caffeine), which could affect blood pressure and IOP. Both blood pressure and IOP were measured after patients had sat and rested for at least 5 min. The pulse pressure (PP) was defined as the difference value between systolic and diastolic blood pressure. The mean PP and IOP were calculated by the average value among six measurement points, and the fluctuation of PP and IOP was defined as its standard deviation (SD) value among six measurement points.

Optical coherence tomography angiography measurement

The optical coherence tomography angiography (OCTA) system (AngioVue; Optovue, Fremont, CA, USA), with a scanning speed of 70,000 A-scans per second, was used to image the retinal capillary distribution. The radial peripapillary capillary (RPC) imaging was centered on the optic nerve head with a scan size of 4.5 × 4.5 mm, and the superficial retinal capillary plexus (SRCP) imaging was centered on the fovea with the scan size of 3.0 × 3.0 mm (Figure 1). The RPC layer was extended from the internal limiting membrane (ILM) to the nerve fiber layer (NFL), and the SRCP layer was extended from ILM to 10 μm above the inner plexiform layer (IPL), which were segmented by a built-in program. From the report of the built-in program, we could get the vessel density of RPC and SRCP. The RPC density was defined as the percentage of small vascular area in the whole analyzed area. The whole RPC-analyzed area was a ring with a 2-mm inner diameter and a 4-mm outer diameter centered on the optic disc which was further separated into two sectors (superior and inferior sectors). The SRCP density was defined as the percentage of vascular area in the whole analyzed area. The whole SRCP-analyzed area was a ring with a 1-mm inner diameter and a 3-mm outer diameter centered on the fovea which was further separated into another four sectors (superior, nasal, inferior, and temporal sectors). The peripapillary retinal nerve fiber layer (pRNFL) thickness was from the same report of the built-in program as RPC density, which was separated into two areas (superior and inferior sectors) as well. The OCTA images with obvious eye movement, quality less than 4/10 (defined by the machine itself), wrong layer segmentation, etc., would be excluded. One masked reader checked all the OCTA images.

Statistical analysis

All continuous data were shown in the form of means ± SD and analyzed by SPSS 22.0 (SPSS, Inc., Chicago, IL, USA). The spherical equivalent (SE) was calculated as the spherical power plus one-half of the cylindrical power, and BCVA was converted into the form of the logarithm of minimal angle resolution (LogMAR). The independent t-test was used to compare the parameters between two groups, and χ^2 was used to test the gender difference. Pearson's correlation and general estimating equation (GEE) were used to calculate relationships among retinal capillary density, age, IOP, MI, and other related parameters. The GEE was also used to adjust the IOP

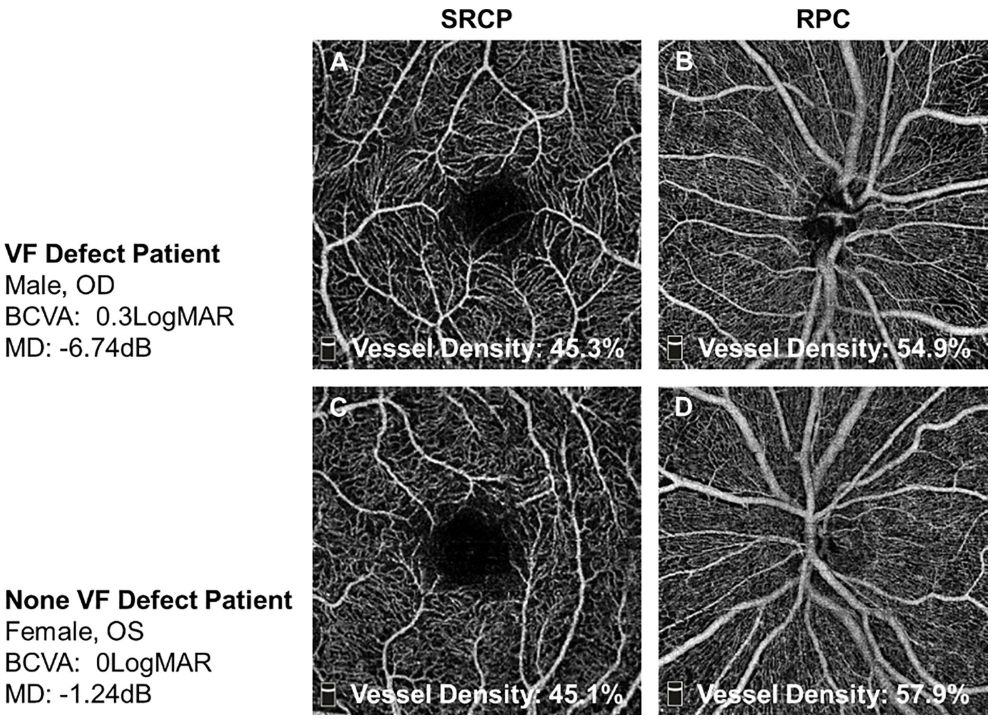

FIGURE 1
The representative OCTA images of TAO patients with or without VF defect. **(A, B)** In one VF defect TAO patient, his whole SRCP density was 45.3% and whole RPC density was 54.9%. **(C, D)** In one no-VF defect TAO patient, her whole SRCP density was 45.1% and whole RPC density was 57.9%. SRCP, superficial retinal capillary plexus; RPC, radial peripapillary capillary.

influence on the RPC density, SRCP density, and pRNFL thickness between the two groups. The P-value less than 0.05 was considered to be statistically significant.

Results

Basic information

Sixty-two TAO patients (39 with VF defect and 23 without VF defect) were included. The MD was -7.39 ± 6.36 dB in TAO with VF defect and -0.54 ± 0.79 dB in TAO without VF defect (P < 0.001). There was no significant difference in age, sex, and SE (P = 0.648, 0.149, and 0.109, Table 1) between the two groups. The TAO patients with VF defect were with worse BCVA and larger horizontal and vertical MI compared to the TAO patients without VF defect (P = 0.007, 0.006, and <0.001, Table 1).

Diurnal rhythm of pulse pressure and IOP

The mean PP was higher in TAO patients with VF defect when compared to the patients without VF defect (52.06 ± 12.27 vs. 46.87 ± 5.40 mmHg, P = 0.026, Table 2; Figure 2A), although the significant difference of PP between the two groups was found only at 14:00 and 18:00 (Figure 2A). Both TAO patients with and without VF defect had the lowest PP at 5:00, while TAO patients with VF defect had the highest PP at 18:00 and patients without VF defect had the highest PP at 22:00 (Figures 2B, C). For the PP fluctuation, there was no difference in TAO patients with and without VF defect (P = 0.733, Table 2, Figure 2A).

Although the mean IOP was higher in TAO patients with VF defect than in patients without VF defect, there was no significant statistical difference (18.44 ± 5.00 vs. 15.99 ± 4.85 mmHg, P = 0.065, Table 2; Figure 2D). Different from the diurnal rhythm of PP, both TAO patients with and without VF defect had the highest IOP at 5:00, while TAO patients with VF defect had the lowest IOP at 18:00 and patients without VF defect had the lowest IOP at 22:00 (Figures 2E, 2F). The IOP fluctuation did not differ between TAO patients with and without VF defect (P = 0.700, Table 2; Figure 2D).

TABLE 1 Basic information of all TAO patients.

	VF defect	None VF defect	P
N	39	23	–
Age, year	55 ± 8	54 ± 7	0.648
Gender, M: F	24:15	9:14	0.149
SE, diopter	-0.04 ± 1.63	-0.76 ± 1.70	0.109
BCVA, LogMAR	0.23 ± 0.24	0.09 ± 0.14	0.007
MD, dB	-7.39 ± 6.36	-0.54 ± 0.79	< 0.001
Horizontal MI	0.55 ± 0.11	0.46 ± 0.12	0.006
Vertical MI	0.64 ± 0.12	0.51 ± 0.11	< 0.001

M, male; F, female; SE, spherical equivalent; BCVA, best-corrected visual acuity; MD, mean deviation; MI, muscle index; VF, visual field.

Alteration of retinal capillary density, pRNFL thickness, and its associations with each other and with VF defect

The representative OCTA images from the two groups are shown in Figure 1. The whole RPC density was significantly decreased in TAO patients with VF defect when compared to the patients without VF defect (51.86 ± 3.43 vs. 53.51 ± 2.58, P = 0.025, Table 3). The same alteration tendency of RPC density was found in the superior peripapillary area (P = 0.015, Table 3) but not inferior peripapillary areas (P = 0.078, Table 3). Not only the whole SRCP density but also SRCP density in five separated areas were not significantly different between the TAO patients with and without VF defect (P = 0.143~0.436, Table 3). For the pRNFL thickness, neither the whole pRNFL thickness nor the pRNFL thickness in two respective areas did not show any significant difference between the TAO patients with VF defect and without VF defect (P = 0.056~0.113, Table 3).

When we further did Pearson's correlation of RPC/SRCP density with pRNFL thickness, we only included their corresponding data in the whole analyzed area. There was a significant correlation between RPC density and pRNFL thickness (r = 0.314, P = 0.013), while no correlation was found between SRCP density and pRNFL thickness (r = 0.106, P = 0.412).

When we further did Pearson's correlation of RPC and SRCP with VF MD value, we only included their density in the whole analyzed area. There was a significant correlation between RPC density and VF MD value (r = 0.242, P = 0.029), while no correlation was found between SRCP density and VF MD value (r = 0.026, P = 0.419).

Influence on RPC density

In the univariable GEE analysis with the RPC density as the outcome factor, the mean PP and its fluctuation (P = 0.013 and

TABLE 2 Blood pressure and IOP information in all TAO patients.

	VF defect	None VF defect	P
PP, mmHg			
Mean	52.06 ± 12.27	46.87 ± 5.40	0.026
Fluctuation	6.49 ± 2.91	6.71 ± 1.56	0.733
IOP, mmHg			
Mean	18.44 ± 5.00	15.99 ± 4.85	0.065
Fluctuation	2.72 ± 1.55	2.57 ± 1.53	0.700

PP, pulse pressure; IOP, intraocular pressure; VF, visual field.

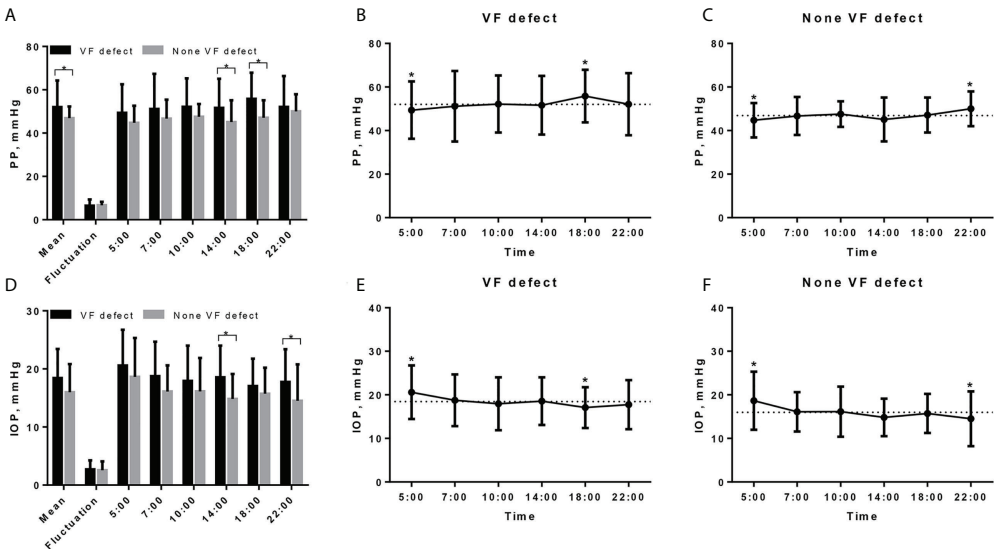

FIGURE 2
Diurnal rhythm of pulse pressure and IOP in TAO patients with and without VF defect. **(A)** Diurnal rhythm of PP in TAO patients with and without VF defect, * indicated significant difference between two groups. **(B)** Diurnal rhythm of PP in TAO patients with VF defect, dashed line indicates the mean PP value (52.06 mmHg) and * indicates the significant difference between PP value at that measurement point and mean value. **(C)** Diurnal rhythm of PP in TAO patients without VF defect, dashed line indicates the mean PP value (46.87 mmHg) and * indicates the significant difference between PP value at that measurement point and mean value. **(D)** Diurnal rhythm of IOP in TAO patients with and without VF defect, * indicates significant difference between two groups. **(E)** Diurnal rhythm of IOP in TAO patients with VF defect, dashed line indicates the mean IOP value (18.44 mmHg) and * indicates the significant difference between IOP value at that measurement point and mean value. **(F)** Diurnal rhythm of IOP in TAO patients without VF defect; dashed line indicates the mean PP value (15.99 mmHg) and * indicates the significant difference between PP value at that measurement point and mean value. PP, pulse pressure; IOP, intraocular pressure; VF, visual field.

0.035, respectively) were statistically significant, while age, gender, SE, vertical MI, horizontal MI, mean IOP, and its fluctuation were not significant (P = 0.067~0.860, Table 4). Only the parameters with P < 0.05 in univariable GEE analysis were included for further multivariable analysis. In the final multivariable GEE analysis (Table 4), the increased RPC density was only associated with less PP (β = -0.082, standard error = 0.038, P = 0.029), but not associated with PP fluctuation (P = 0.080).

TABLE 3 Alteration of retinal capillary density and peripapillary RNFL thickness.

	VF defect	None VF defect	P
RPC density, %			
Whole	51.86 ± 3.43	53.51 ± 2.58	0.025 (0.021)
Superior	51.53 ± 4.14	53.71 ± 2.86	0.015 (0.008)
Inferior	52.19 ± 3.12	53.31 ± 2.69	0.078 (0.052)
SRCP density, %			
Whole	41.09 ± 4.72	41.73 ± 5.63	0.314 (0.459)
Superior	45.59 ± 6.52	47.39 ± 6.16	0.143 (0.225)
Nasal	44.05 ± 4.67	44.30 ± 6.92	0.432 (0.436)
Inferior	45.56 ± 5.06	46.52 ± 6.24	0.256 (0.450)
Temporal	43.39 ± 5.90	43.09 ± 8.54	0.436 (0.318)
pRNFL thickness, μm			
Whole	113.79 ± 14.32	118.26± 7.50	0.056 (0.055)
Superior	114.36 ± 16.35	118.39 ± 9.70	0.113 (0.057)
Inferior	113.44 ± 15.02	118.00 ± 7.71	0.060 (0.051)

M, male; F, female; SE, spherical equivalent; BCVA, best-corrected visual acuity; MD, mean deviation; MI, muscle index; VF, visual field. P values in parentheses were the P values after the adjustment for the IOP by GEE analysis.

TABLE 4 The GEE analysis with RPC as the predictor factor.

Parameters	Univariable			Multivariable		
	β	Standard error	P	β	Standard error	P
Age, year	-0.075	0.055	0.172	–	–	–
Gender, Male	1.225	0.817	0.134	–	–	–
SE, diopter	-0.044	0.249	0.860	–	–	–
Horizontal MI	-6.096	3.333	0.067	–	–	–
Vertical MI	-3.377	3.050	0.268	–	–	–
PP mean	-0.094	0.038	0.013	-0.082	0.038	0.029
PP Fluctuation	-0.343	0.163	0.035	-0.279	0.159	0.080
IOP mean	-0.063	0.083	0.449	–	–	–
IOP Fluctuation	0.197	0.271	0.467	–	–	–

SE, spherical equivalent; MI, muscle index; PP, pulse pressure; IOP, intraocular pressure; GEE, general estimating equation.

Discussion

In the current study, we used OCTA to evaluate retinal vessel alteration in TAO patients. Our findings were consistent with most previous papers that TAO was with reduced retinal perfusion (Table 5). However, few of those papers focused on its risk factors and relation with VF defect in TAO patients. From our results, we demonstrated a strong association of elevated pulse pressure with reduced RPC perfusion in TAO patients with VF defect. It might support the importance of the "system vascular" factor (as reflected by PP) rather than the "mechanical" factor (as reflected by MI) in the pathogenesis of reduced retinal perfusion in TAO patients, which would further lead to visual field defect.

We found the decreased RPC perfusion in TAO patients with VF defect but not a significant alteration of SRCP perfusion when compared to the TAO patients without VF defect in the current study. The peripapillary vessels might be impaired more easily during the process of TAO. As an optic neuropathy, peripapillary vessels were more directly influenced as they were the branches of large blood vessels that went out from the optic disc. Moreover, different from macular vessels with frequent anastomoses as a long and straight form, the structure of peripapillary vessels might lead it to be impaired more easily than macular vessels. The peripapillary vessel had higher diagnostic accuracy to differentiate TAO patients with dysthyroid optic neuropathy (DON) and no-DON (5).

The reduced peripapillary vessel density was correlated with the degree of VF defect in TAO patients. The VF defect, as the result of several optic neuropathies, had been reported to be with peripapillary degeneration (5). The peripapillary vessels were essential to supplying oxygen and nutrition to the peripapillary tissue. The degeneration of the peripapillary tissue would further lead to reduced peripapillary perfusion, vice versa, resulting in VF defect.

How and why some TAO eyes had reduced retinal perfusion and resulted in VF defect, while others did not, were still unclear

TABLE 5 Summary of previous studies on retinal perfusion changes in TAO.

Study	Groups	Retinal perfusion changes
Current study	TAO (1) with and (2) without VF defect	The reduced RPC density in TAO patients with VF defect compared to patients without VF defect.
Zhang et al.5	TAO (1) with and (2) without DON	The reduced RPC density and unchanged SRCP density in TAO patients with DON compared to patients without DON.
Wu et al.13	(1) TAO with DON; (2) normal controls.	The reduced SRCP density in TAO patients with DON compared to normal controls.
Wu et al.14	(1) TAO; (2) normal controls.	The reduced SRCP density in TAO patients compared to normal controls.
Yang et al.15	(1) Severe inactive TAO; (2) normal controls.	The retinal venous diameter decreased significantly in severe TAO.
Tehrani et al.16	(1) Active TAO; (2) not active not compressive TAO; (3) normal controls.	The reduced RPC density and SRCP density in active TAO patients compared to not active not compressive TAO patients and normal controls.
Wu et al.17	TAO (1) with and (2) without DON	The reduced RPC density in TAO patients with DON compared to patients without DON.

TAO, thyroid-associated ophthalmology; RPC, radial peripapillary capillary; VF, visual field; SRCP, superficial retinal capillary plexus; DON, dysthyroid optic neuropathy.

and likely involved multiple factors. In the current study, we considered MI and PP as biomarkers for the "mechanical" and "system vascular" factors, respectively. The reduced retinal perfusion in TAO patients might be associated with both two factors. For the "mechanical" factor with orbital apex compression, the increased orbital volume resulted in the elevated retrobulbar space pressure with sustained stretching of the optic nerve and altered venous drainage (1, 4). However, the resistance index of the ophthalmic artery did not alter after orbital decompression in some TAO eyes (18). Less than half of TAO patients with compressive optic neuropathy had signs of optic swelling (19). Even rarely, optic nerve stretch was found from the CT in some TAO patients with extreme proptosis (3). Moreover, despite successful orbital decompression being done, some TAO patients still complained about progressively decreased visual function (2). Based on these phenomena, we hypothesized that besides the "mechanical" theory, there might be other important aspects of mechanisms associated with visual impairment in TAO patients.

From our multivariable GEE analysis results, the abnormal PP was more associated with the peripapillary perfusion compared to the "mechanical" factor of the enlarged muscle in TAO patients. The abnormal blood pressure would play a more important role in the retinal vessel changes even previous to the mechanical compression (20). In TAO patients with VF defect, they showed higher PP than patients without VF defect and it was correlated with the decreased retinal perfusion. The decreasing systemic vascular resistance in TAO may lead to increased systolic pressure and relatively reduced diastolic pressure, resulting in elevated PP (5, 21–23). The TAO patients were always with arterial stiffness, which led to the breakdown of blood pressure autoregulation and the expansion of pulse pressure (24). The continually abnormal blood pressure then contributed to end-organ damage, such as impairment of retinal vessels (6, 7). The abnormal deposition of the antibodies in the vasculature was related to the inflammatory process, which further led to the alteration of capillary density in TAO eyes (25–27). Due to the impact of arterial stenosis and venous stasis, retinal vessel perfusion was hindered (18, 28–30). The abnormal elevated PP during the progression of TAO with VF defect might be a sign of a vascular anomaly. At the same time, the elevated PP impaired the choroidal circulation and oxygen supplement, which further influenced the retinal perfusion (31). Moreover, the elevated PP also led to the decreased pressure of the cerebrospinal fluid and higher trans-lamina cribrosa pressure, resulting in the degeneration of the optic nerve (32–34). All the above might explain the association between the abnormal PP and RPC in TAO with VF defect. Altered PP would be a high risk for retinal perfusion damage with a VF defect in TAO.

There were still some limitations in our current study. The sample size we included was small, which still should be enlarged to further confirm our findings. We only measured the diurnal rhythms of the blood pressure and IOP but not the OCTA parameters in the current study. With the data of diurnal rhythms for OCTA parameters, the current conclusion of our study would be stronger, although it had been reported that these OCTA parameters would not be variable (34). We would also like to do a follow-up with all TAO patients to further confirm that abnormal PP might be a risk of the reduced peripapillary perfusion with a VF defect.

In conclusion, we demonstrated that PP but not MI was more associated with reduced RPC in TAO, which further led to visual field defect. The elevated PP was a high risk of reduced retinal peripapillary perfusion and visual field defect, although the interrelationships among the blood pressure, retinal perfusion, and visual function in TAO patients still warrant further study.

Data availability statement

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

Ethics statement

This study was reviewed and approved by the Ethics Committee Board, the Eye Hospital of Wenzhou Medical University, Wenzhou, China. The patients/participants provided their written informed consent to participate in this study.

Author contributions

JY, WW and YT contributed to the conception and design of the study. JY, WL and XH determined the experimental methods. JY, HXJ, MX and HCJ performed the experiments. JY, MW, ZL and QC analyzed and interpreted the data. JY and YT wrote and modified the manuscript. All authors contributed to the article and approved the submitted version.

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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.

Publisher's note

References

1. Alsuhaibani AH, Nerad JA. Thyroid-associated orbitopathy. *Semin Plast Surg* (2007) 21(1):65–73. doi: 10.1055/s-2007-967751

2. Kim WS, Chun YS, Cho BY, Lee JK. Biometric and refractive changes after orbital decompression in Korean patients with thyroid-associated orbitopathy. *Eye (Lond)* (2016) 30(3):400–5. doi: 10.1038/eye.2015.242

3. Dickinson AJ, Perros P. Controversies in the clinical evaluation of active thyroid-associated orbitopathy: Use of a detailed protocol with comparative photographs for objective assessment. *Clin Endocrinol (Oxf)* (2001) 55(3):283–303. doi: 10.1046/j.1365-2265.2001.01349.x

4. Saeed P, Tavakoli Rad S, Bisschop P. Dysthyroid optic neuropathy. *Ophthalmic Plast Reconstr Surg* (2018) 34(4S Suppl 1):S60–s67. doi: 10.1097/IOP.0000000000001146

5. Zhang T, Xiao W, Ye H, Chen R, Mao Y, Yang H. Peripapillary and macular vessel density in dysthyroid optic neuropathy: An optical coherence tomography angiography study. *Invest Ophthalmol Vis Sci* (2019) 60(6):1863–9. doi: 10.1167/iovs.18-25941

6. Rizzoni D, Palombo C, Porteri E, Muiesan ML, Kozàkovà M, La Canna G, et al. Relationships between coronary flow vasodilator capacity and small artery remodelling in hypertensive patients. *J Hypertens* (2003) 21(3):625–31. doi: 10.1097/00004872-200303000-00030

7. Ott C, Raff U, Harazny JM, Michelson G, Schmieder RE. Central pulse pressure is an independent determinant of vascular remodeling in the retinal circulation. *Hypertension* (2013) 61(6):1340–5. doi: 10.1161/HYPERTENSIONAHA.111.00617

8. Tu Y, Mao B, Li J, Liu W, Xu M, Chen Q, et al. Relationship between the 24-h variability of blood pressure, ocular perfusion pressure, intraocular pressure, and visual field defect in thyroid associated orbitopathy. *Graefes Arch Clin Exp Ophthalmol* (2020) 258(9):2007–12. doi: 10.1007/s00417-020-04733-5

9. Jou IM, Lai KA, Shen CL, Yamano Y. Changes in conduction, blood flow, histology, and neurological status following acute nerve-stretch injury induced by femoral lengthening. *J Orthop Res* (2000) 18(1):149–55. doi: 10.1002/jor.1100180121

10. Bartley GB, Gorman CA. Diagnostic criteria for graves' ophthalmopathy. *Am J Ophthalmol* (1995) 119(6):792–5. doi: 10.1016/S0002-9394(14)72787-4

11. Jamshidian-Tehrani M, Kasaei A, Mahdizad Z, Fard MA, Aminizade M. Effect of smoking on retinal thickness and vascular density in thyroid eye disease. *Korean J Ophthalmol* (2021) 35:376–82. doi: 10.3341/kjo.2021.0059

12. Barrett L, Glatt HJ, Burde RM, Gado MH. Optic nerve dysfunction in thyroid eye disease: CT. *Radiology* (1988) 167:503–7. doi: 10.1148/radiology.167.2.3357962

13. Wu Y, Tu Y, Wu C, Bao L, Wang J, Lu F, et al. Reduced macular inner retinal thickness and microvascular density in the early stage of patients with dysthyroid optic neuropathy. *Eye Vis (Lond)* (2020) 7:16. doi: 10.1186/s40662-020-00180-9

14. Wu Y, Tu Y, Bao L, Wu C, Zheng J, Wang J, et al. Reduced retinal microvascular density related to activity status and serum antibodies in patients with graves' ophthalmopathy. *Curr Eye Res* (2020) 45(5):576–84. doi: 10.1080/02713683.2019.1675177

15. Yang X, Huang D, Ai S, Liang X, Zhao J, Fang L. Retinal vessel oxygen saturation and vessel diameter in inactive graves ophthalmopathy. *Ophthalmic Plast Reconstr Surg* (2017) 33(6):459–65. doi: 10.1097/IOP.0000000000000826

16. Jamshidian Tehrani M, Mahdizad Z, Kasaei A, Fard MA. Early macular and peripapillary vasculature dropout in active thyroid eye disease. *Graefes Arch Clin Exp Ophthalmol* (2019) 257:2533–40. doi: 10.1007/s00417-019-04442-8

17. Wu Y, Yang Q, Ding L, Tu Y, Deng X, Yang Y, et al. Peripapillary structural and microvascular alterations in early dysthyroid optic neuropathy. *Eye Vis (Lond)* (2022) 9:30. doi: 10.1186/s40662-022-00301-6

18. Pérez-López M, Sales-Sanz M, Rebolleda G, Casas-Llera P, González-Gordaliza C, Jarrín E, et al. Retrobulbar ocular blood flow changes after orbital decompression in graves' ophthalmopathy measured by color Doppler imaging. *Invest Ophthalmol Vis Sci* (2011) 52(8):5612–7. doi: 10.1167/iovs.10-6907

19. Dickinson J, Perros P. Thyroid-associated orbitopathy: Who and how to treat. *Endocrinol Metab Clin North Am* (2009) 38(2):373–88. doi: 10.1016/j.ecl.2009.01.004

20. Sayın O, Yeter V, Arıtürk N. Optic disc, macula, and retinal nerve fiber layer measurements obtained by oct in thyroid-associated ophthalmopathy. *J Ophthalmol* (2016) 2016:9452687. doi: 10.1155/2016/9452687

21. Prisant LM, Gujral JS, Mulloy AL. Hyperthyroidism: A secondary cause of isolated systolic hypertension. *J Clin Hypertens (Greenwich)* (2006) 8(8):596–9. doi: 10.1111/j.1524-6175.2006.05180.x

22. Danzi S, Klein I. Thyroid hormone and blood pressure regulation. *Curr Hypertens Rep* (2003) 5(6):513–20. doi: 10.1007/s11906-003-0060-7

23. Perri P, Campa C, Costagliola C, Incorvaia C, D'Angelo S, Sebastiani A. Increased retinal blood flow in patients with active graves' ophthalmopathy. *Curr Eye Res* (2007) 32:985–90. doi: 10.1080/02713680701689773

24. Yildiz C, Altay M, Yildiz S, Çağir Y, Akkan T, Ünsal YA, et al. Arterial stiffness in hyperthyroid patients is deteriorated due to thyroid hormones. *Arch Endocrinol Metab* (2019) 63(3):258–64. doi: 10.20945/2359-3997000000135

25. Nielsen CH, Brix TH, Leslie RG, Hegedüs L. A role for autoantibodies in enhancement of pro-inflammatory cytokine responses to a self-antigen, thyroid peroxidase. *Clin Immunol* (2009) 133(2):218–27. doi: 10.1016/j.clim.2009.07.014

26. Morikawa Y, Morikawa A, Makino I. Relationship of thyroid states and serum thrombomodulin (TM) levels in patients with graves' disease: TM, a possible new marker of the peripheral activity of thyroid hormones. *J Clin Endocrinol Metab* (1993) 76(3):609–14. doi: 10.1210/jcem.76.3.7680353

27. Takano S, Kimura S, Ohdama S, Aoki N. Plasma thrombomodulin in health and diseases. *Blood* (1990) 76(10):2024–9.

28. Nakase Y, Osanai T, Yoshikawa K, Inoue Y. Color Doppler imaging of orbital venous flow in dysthyroid optic neuropathy. *Jpn J Ophthalmol* (1994) 38(1):80–6.

29. Dosso A, Safran AB, Sunaric G, Burger A. Anterior ischemic optic neuropathy in graves' disease. *J Neuroophthalmol* (1994) 14(3):170–4.

30. Kurioka Y, Inaba M, Kawagishi T, Emoto M, Kumeda Y, Inoue Y, et al. Increased retinal blood flow in patients with graves' disease: Influence of thyroid function and ophthalmopathy. *Eur J Endocrinol* (2001) 144(2):99–107. doi: 10.1530/eje.0.1440099

31. Dupas B, Feldman-Billard S, Bui Quoc E, Erginay A, Guillausseau PJ, Massin P. Influence of pulse pressure and spontaneous variations of macular thickness in patients with diabetic macular oedema. *Acta Ophthalmol* (2014) 92(5):e372–376. doi: 10.1111/aos.12369

32. Ren R, Wang N, Li B, Li L, Gao F, Xu X, et al. Lamina cribrosa and peripapillary sclera histomorphometry in normal and advanced glaucomatous Chinese eyes with various axial length. *Invest Ophthalmol Vis Sci* (2009) 50(5):2175–84. doi: 10.1167/iovs.07-1429

33. Fleischman D, Allingham RR. The role of cerebrospinal fluid pressure in glaucoma and other ophthalmic diseases: A review. *Saudi J Ophthalmol* (2013) 27(2):97–106. doi: 10.1016/j.sjopt.2013.03.002

34. Jonas JB, Wang NL, Wang YX, You QS, Xie XB, Yang DY, et al. Estimated trans-lamina cribrosa pressure difference versus intraocular pressure as biomarker for open-angle glaucoma. The Beijing eye study 2011. *Acta Ophthalmol* (2015) 93(1):e7–e13. doi: 10.1111/aos.12480

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Current insights of applying MRI in Graves' ophthalmopathy

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Graves' ophthalmopathy (GO) is an autoimmune disease related to Grave's disease (GD). The therapeutic strategies for GO patients are based on precise assessment of the activity and severity of the disease. However, the current assessment systems require development to accommodate updates in treatment protocols. As an important adjunct examination, magnetic resonance imaging (MRI) can help physicians evaluate GO more accurately. With the continuous updating of MRI technology and the deepening understanding of GO, the assessment of this disease by MRI has gone through a stage from qualitative to precise quantification, making it possible for clinicians to monitor the microstructural changes behind the eyeball and better integrate clinical manifestations with pathology. In this review, we use orbital structures as a classification to combine pathological changes with MRI features. We also review some MRI techniques applied to GO clinical practice, such as disease classification and regions of interest selection.

KEYWORDS

Graves ophthalmopathy, MRI, orbital fat, extraocular muscles, assessment

Abbreviations: GO, Graves ophthalmopathy; GD, Graves' disease; CAS, Clinical Activity Scores; EUGOGO, European Group on Graves' Orbitopathy; MRI, magnetic resonance imaging; TSHR, thyroid stimulating hormone receptor; insulin-like grow factor 1 receptor (IGF-1R); OFs, Orbital fibroblasts; TH, T helper; ECM, extracellular matrix; CT, computed tomography; T1WI T1 weight-images; T2WI T2 weight-images; T2RT, T2 relaxation time; SI, signal intensity; CHESS, Chemical Shift-selective Fat Suppression; STIR, short inversion time inversion recovery; SIR, signal intensity ratio; ADC, apparent diffusion coefficient; EPI, echo planar imaging; FF, fat fraction; Hu, Hounsfield units; ROIs, regions of interest; ECV, extracellular volume; TRAb, thyroid receptor antibody; DON, dysthyroid optic neuropathy.

Introduction

Graves' ophthalmopathy (GO) is an extrathyroidal manifestation of Graves' disease (1). Approximately 20%–30% of GD patients suffer from GO, and it is more common in women. The prevalence of GO is reported to be between 90 and 155 per 100,000 people in Europe and 100–300 per 100,000 in Asia (2, 3). Although the incidence rate of GO is relatively low, it has a significant impact on the quality of life of patients, whether in mental health or socio-economic status (4). Various clinical presentations can be observed in GO, including proptosis, eyelid retraction, periorbital tissue edema, and compressive optic neuropathy. Therefore, accurate treatment is important to improve the symptoms of patients. Despite the vast progress made in the understanding of GO pathogenesis, treating the condition can still be problematic. The management of GO depends on an accurate assessment of its severity and activity. Symptom-and-sign-based systems, such as Clinical Activity Scores (CAS), classifications by the European Group on Graves' Orbitopathy (EUGOGO), NOSPECS, and VISA (vision, inflammation, strabismus, and appearance), have been widely accepted to assess GO severity and activity (5). However, these classifications can be subject to clinical experience and patient status, and more objective assessments are needed.

Magnetic resonance imaging (MRI) is a non-invasive medical imaging method. It has long been applied in GO assessment and differential diagnosis, which is non-radiation and provides high resolution in soft tissue (6). Recently, major progress has been made in MRI for GO. This review summarizes the application of MRI sequences to different tissues involved in GO. We have compared the efficacy of these sequences in view of more objective prediction and diagnosis to assist physicians in selecting better protocols.

Pathogenesis of GO

It has been postulated that the thyroid-stimulating hormone receptor (TSHR) is the primary potential target for GO initiation. Recent studies have suggested that the insulin-like growth factor 1 receptor (IGF-1R) also plays a critical role in GO development (7). Orbital fibroblasts (OFs), which express TSHR and/or IGF-1R, are activated to secrete pro-inflammatory factors and extraocular matrix (ECM). Meanwhile, other immune cells such as T cells, B cells, and monocytes are mobilized *via* chemotaxis to reach retrobulbar tissue, forming an orbital inflammatory microenvironment (8, 9). In the early stage, T helper (Th) 1 cells play a major role, secreting IL-1β, IL-2, IFN-γ, etc. These pro-inflammatory cytokines promote the proliferation of OFs, accelerate the production of glycosaminoglycans, and induce the differentiation of OFs. Regarding the inactive or late phase, activation of Th2 cells leads to anti-inflammatory cytokines secretion, with representative as IL-4 and TGF-β, which promote tissue repairment (10). Th17 also serves as a critical cell, contributing to inflammation and fibrosis (11). As a result, the orbital fat expands, which results in overt exophthalmos. The extraocular muscles (EOMs) become swollen and suffer from limited motility, leading to diplopia or strabismus. This inflammatory microenvironment and ECM accumulation is associated with periorbital edema. In severe cases, the crowded orbit increases the mechanic pressure, exacerbating pain or even compressing the optic nerve and veins (8, 12, 13).

Why we choose MRI?

A small proportion of GO cases do not present with thyroid dysfunction, and, there are many alternative conditions that might mimic GO, such as idiopathic orbital inflammation, sarcoidosis, Sjogren syndrome, and vasculitis (14). Moreover, as aforementioned, soft tissues such as EOMs and orbital fat are involved in GO, and their pathology reflects the status of the disease. Thus, a comprehensive supplementary examination is necessary to help physicians identify GO from other diseases and classify GO more accurately.

Pathological biopsy provides the most accurate method for early diagnosis and staging of GO. However, this procedure presents a relatively high risk of side effects and suffers from low adherence, so it is problematic to promote. Another approach that could provide precise information is imaging, including computed tomography (CT), MRI, and ultrasound examinations. These have the advantages of being non-invasive and time-saving and provide the ability to detect subtle lesions in the retrobulbar structures, so imaging in GO diagnosis is now a research focus. The advantages and disadvantages of these methods are summarized in Table 1.

Despite some deficiencies, the advantages of MRI compared to CT or ultrasound are still remarkable, such as the lack of radiation, the high soft tissue resolution, the ability to perform multi-parametric imaging and post-processing, which has resulted in more attention from physicians for this procedure. The differential diagnosis according to symptoms and MRI findings is indicated in Table 2, and two cases mimicking GO are depicted in Figure 1. The basis for evaluating GO and selecting treatment is complicated pathology, and lots of pathological changes can be captured on MRI, including inflammation, steatosis, and fibrosis.

MRI for evaluation of GO

GO is a multi-stage disease in which multiple tissues are involved, causing variable morphological and histological changes in these tissues. As shown in Table 3, we briefly describe the anatomy and histology of these tissues in relation to the disease and summarize relevant MRI sequences based on the different target tissues.

TABLE 1 Comparison of three imaging modalities.

	Ultrasound	CT	MRI
Morphological changes in orbits	Medium, especially in blood flow	Strong, especially in bone	Strong, especially in soft tissue
Assessment for activity	Weak	Weak	Strong by multiple parameters
Treatment response monitoring	Weak	Medium	Strong
Examination time	Time-saving	Time-saving	Time-consuming
Cost	Price-friendly	Medium	Expensive
Radiation	No	Yes	No
Availability and convenience	Strong	Medium	Weak
Contraindications	–	Pregnancy	Claustrophobia, electronic or magnetic metal implanted

CT, computed tomography; MRI, magnetic resonance imaging.

Orbital fat

Anatomy, histology, and pathologic change in GO

About 50% of the orbital volume is formed by orbital fat, which serves to support other structures in the orbit and reduce friction (35) (Figure 2). Histologically, orbital adipose tissue can be divided into two types: large adipocytes with thin septa at the orbital apex and small adipocytes with more fibrous septa near the muscles and lacrimal glands (36, 37). To date, there are no studies about whether these two fats have different effects during GO progress. Orbital fibroblasts can differentiate into adipocytes and cause an expansion of fat volume, resulting in a more severe appearance. At the same time, lower orbital fat thickness seems to indicate the better responsive to glucocorticoid (18, 19), despite the relationship between the volume and CAS remains further elucidated (38, 39).

Exophthalmos

Proptosis is a common symptom that occurs in about 60% of GO patients (40). It probably results from the enlargement

TABLE 2 Differential diagnosis of GO.

	GO	Orbital lymphoma	IgG4 related ophthalmopathy	Idiopathic orbital inflammation	Carotid-Cavernous Fistulas
Sex distribution	Female	Male	No difference	No difference	Male
Thyroid Dysfunction	Always	Rarely	Rarely	Rarely	Rarely
Increased IgG4	Slightly	Rarely	Obviously	Rarely	Rarely
Clinical manifestations					
Bilateral	Frequently	Rarely	Frequently	Sometimes	Rarely
Pain	Frequently	Sometimes	Rarely	Frequently	Sometimes
Eyelid swelling	Frequently	Rarely	Frequently	Frequently	Rarely
Multiple organs involvement	Always, such as thyroid and pretibial myxedema	Frequently, such as periorbital bone	Always, such as salivary gland and pancreas	Rarely	Rarely
Proptosis	Frequently	Frequently	Frequently	Rarely	Frequently
Conjunctiva involvement	Frequently	Sometimes	Rarely	Frequently	Frequently
MRI features					
Extraocular muscle enlargement	Frequently, without tendon involved	Rarely	Sometimes, tendon can be involved	Sometimes, often in medial muscle, tendon can be involved	Frequently, multiple muscles
Lacrimal gland enlargement	Frequently	Frequently	Always	Sometimes	Rarely
Nerve involved	Sometimes, optic nerve compression	Sometimes, optic nerve compression	Rarely	Rarely	Rarely
Character of lesion on MRI	Active phase: T2WI ↑ Inactive phase: T1 T2 WI –/↓	T1WI – T2WI –/↓ with irregular margin	T1WI – T2WI –/↓ with homogenous and well-defined	Similar to GO	Enlargement and internal signal void of cavernous sinus on T1WI and T2WI

GO, Graves ophthalmopathy; IGG4, immunoglobulin G4; MRI, magnetic resonance imaging; T1WI, T1 weighted-image; T2WI, T2 weighted image. ↑, signal increased; ↓, signal decreased.

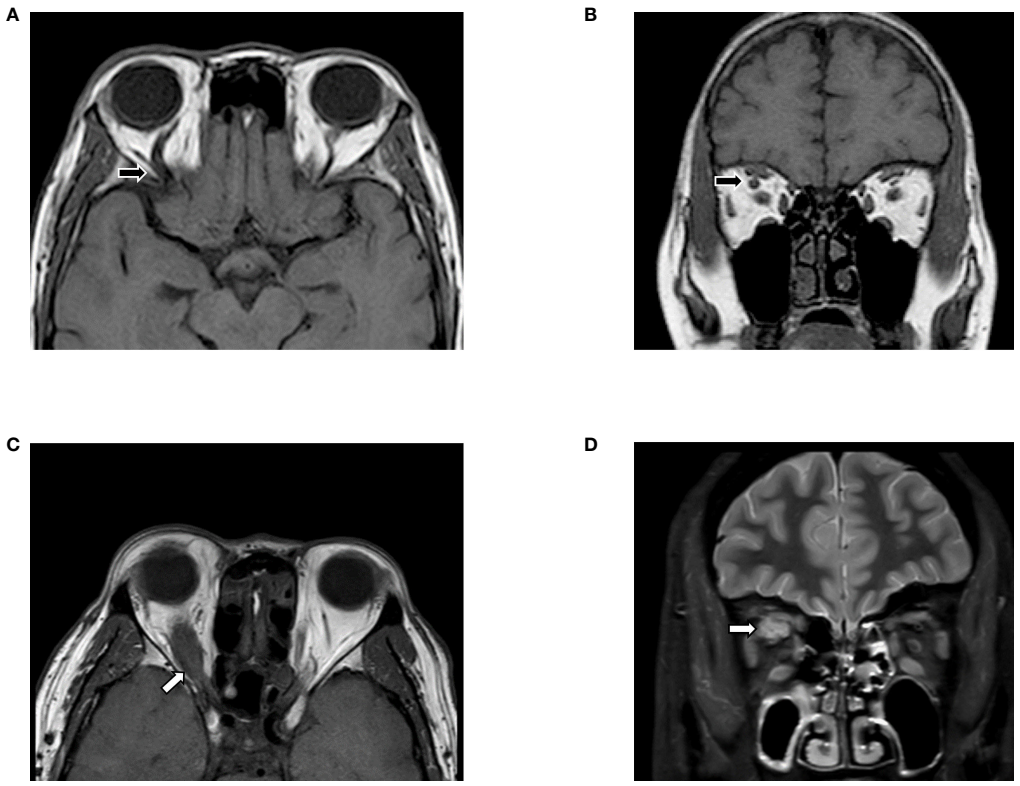

FIGURE 1
Differential diagnosis based on MRI. **(A, B)** Slightly enlarged EOMs were shown in T1WI, with the unilateral, augmented superior ophthalmic vein (black arrows). Features indicated carotid-cavernous fistulas instead of GO, which need to confirm *via* digital subtraction angiography (DSA). **(C, D)** MRI images suggested Imbalanced exophthalmos and the apparent swelling of superior rectus in the right eye. Meanwhile, in T2FS, increased signal of EOMs, combined with the tendon involved (white arrows) enlargement in superior rectus suggested orbital myositis. The figure is original.

of adipose tissue, which is the main component of the orbit (39). Exophthalmos, defined as a 3 mm greater than the upper limit of the normal range, contributes to assessing GO "severity" and treatment response (41, 42). However, the relationship between exophthalmos and activity is inexplicit (19, 43, 44). The degree of exophthalmos might be related to various factors, including sex, age, and race (45–49), which is recommended to establish a normal reference in their own area districts. Traditionally, the Hertel exophthalmometer is used to measure exophthalmos. Although it is portable and affordable, accuracy and comparability are limited due to some unavoidable factors, such as the experience of the observers and axial globe position (50, 51). Previous studies have shown that the interclinician reliability of exophthalmos obtained from Hertel ophthalmometry is not as perfect as that measured on imaging (52, 53). For this, the axial slice that most obviously depicts the EOMs and optic nerve is selected, and from which the perpendicular distance between the interzygomatic line and the surface of the cornea is measured (Figure 3A) (52). However, depending on the selection of either the anterior or the posterior corneal surface, there can be a difference of 1–2 mm for the exophthalmos determined by MRI and by Hertel ophthalmometry (15, 16). In summary, in the absence of guidance from an experienced ophthalmologist, measuring exophthalmos with MRI is a good diagnostic option.

Volume of orbital fat

Orbital fat has an irregular structure and fills the spaces among normal tissues such as nerves, eyeballs, and EOMs, making accurate measurement of the tissue by common MRI difficult (54). Early quantitative measurements were made by subtracting the volume of the six EOMs, the optic nerve, and the eyeball from the entire orbit. However, the fat volume thus derived still included other connective tissues such as the lacrimal gland and blood vessels (55). Another simple method is to measure the thickness of the orbital fat: the distance between the medial wall of the orbit and the medial wall of the eyeball (Figure 3B), but the accuracy of these methods is still challenging (19). With the development of three-dimensional

TABLE 3 MRI sequences applied in GO assessment.

Tissue or organs	Index	Method	MRI sequence	MRI findings	Reference
Orbital fat	Exophthalmos	the perpendicular distance between the interzygomatic line and the surface of the cornea	T1WI	1–2 mm difference between MRI and Hertel ophthalmometry	Cevik et al. (15) Maria et al. (16)
	Volume	ROI outlined and restructured by Mimics	T1WI with thin layers	Orbital fat volume in GO is higher than healthy control	Shen et al. (17)
	Thickness	The maximum distance between the eyeball and medial wall	T1WI	The thickness increased successively among the healthy control, responsive group and unresponsive group	Hu et al. (18) Xu et al. (19)
EOMs	Diameters	Short Diameter: medial and lateral rectus muscles were measured on axial images, others on coronal images	T1WI	Affected by many factors, a possible predictor of glucocorticoid response	Xu et al. (19)
	Volume	ROI outlined and restructured by Mimics	T1WI with thin section	EOMs volume in GO are higher than healthy control	Shen et al. (17)
EOMs	Inflammation	Draw ROI on the maximum EOMs cross-section	T2 mapping	T2RT got from T2 mapping is higher in therapeutic responsive group than unresponsive group	Zhai et al. (20)
		Draw ROI on the muscle with highest signal intensity	STIR-T2WI	SIR is correlate with CAS	Mayer et al. (21, 22)
			Dixon-T2WI	Dixon-T2WI has fewer artifacts and higher efficacy than traditional FS sequences	Ollitrault et al. (23) Chen et al. (24)
			Echo planar DWI, non-EPI DWI	Both sequences can discriminate GO from controls, but non-EPI DWI might have higher efficacy	Politi et al. (25) Feeney et al. (26)
	Fat infiltration	Intramuscular fat quantification by specific calculation	Dixon-T2WI	FF of EOMs in GO is higher than normal	Das et al. (27)
	Fibrosis	Draw ROI of inferior rectus and medial rectus muscles on the maximum cross-section	Non contrast T1 mapping	Although several EOMs show higher signal on FS sequence, decrease in T1 SI predict unresponsible to therapy	Matsuzawa et al. (28)
		Draw ROI of four rectus muscles at muscle belly precontrast and postcontrast	Pre/post contrast T1mapping	ECV is higher and relate to pathological findings in inactive groups	Ma et al. (29)
Lacrimal gland	Herniation	The perpendicular distance between the interzygomatic line and the most anterior tip	T2WI with FS	The herniation value is higher in active and glucocorticoid responsive patients	Gagliardo et al. (30)
	Inflammation	"Hotspot": ROI which only a little proportion of the whole cross-section placed on the highest SI region	T2WI with FS	SIR is higher in active GO than inactive	Hu et al. (31)
		Draw ROI on the maximum LG cross-section	T2 mapping	T2 value is higher in GO than GD and it's an independent predictor for the diagnosis of GO	Wu et al. (32)
Optic nerve	DON	Muscle index and T2 value got from four continuous slices and select the most efficacy slice	Dixon-T2WI, T2 mapping	Muscle index and T2 value are higher in DON	Zou et al. (33)
		The optic nerve sheath diameter, optic nerve diameter and optic nerve subarachnoid space got from two continuous slices and select the most efficacy slice	Modified Dixon-T2WI	The optic nerve subarachnoid space is larger in DON than GO and health control	Wu et al. (34)

MRI, magnetic resonance imaging; T1WI, T1 weighted image; ROI, regions of interest; GO, Graves ophthalmopathy; EOMs, extraocular muscles; T2RT, T2 relaxation time; SIR, signal intensity ratio; CAS, clinical activity score; T2WI, T2 weighted images; FS, fat suppressed; DWI, diffusion weighted image; EPI, echo planar imaging; FF, fat fraction; SI, signal intensity; ECV, extracellular volume; LG, lacrimal gland; GD, Graves' disease; DON, dysthyroid optic neuropathy.

technology, software such as MIMICS can measure the volume of orbital fat more accurately *via* reconstruction (Figure 2), and ratios of fat volume to orbital bony volume can neutralize gender differences (56). This method has been used for evaluating the therapeutic effect of teprotumumab, but it is widely based on CT rather than MR images (57, 58). However, benefiting from the high resolution of soft tissue, reconstruction with MRI may be more accurate than with CT (17).

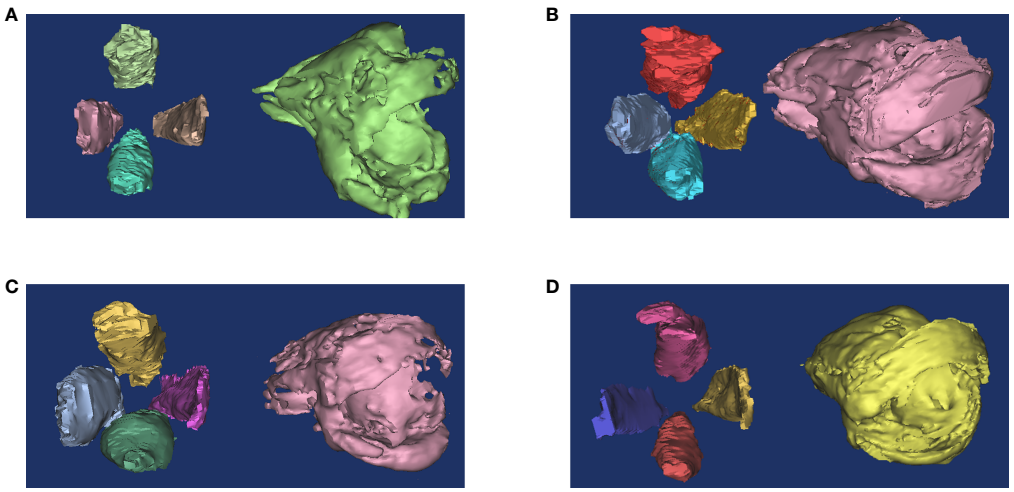

FIGURE 2
Reconstruction of orbital fat and EOMs. The ratio of orbital fat and EOMs usually change in GO patients. **(A)** Healthy people. **(B)** Both fat and muscle volume increased. **(C)** Muscle volume increased only. **(D)** Fat volume increased only. This figure is original and the classification is based on (39).

EOMs

Anatomy, histology, and pathologic change in GO

Six EOMs enable a wide movement range of the eye, including four recti muscles and two oblique muscles. However, the majority of studies have focused on the morphological and histological changes in the rectus muscles. Compared to limb skeletal muscles, EOMs have a more random arrangement of myogenic fibers and more variation in size. Pathologies such as fiber hypertrophy and myopathy can frequently be observed even in normal EOMs. Additionally, the EOMs contain more mitochondria and have a greater oxidative capacity than other skeletal muscles (59). These factors may have some impact on quantitative MRI. Future studies are needed to establish the baseline of EOMs in healthy subjects (60, 61).

Pathological changes in EOMs are common in GO, with approximately 70% of patients involved (39). These lesions involving the muscle belly are roughly consistent with the course of GO, and quantifying the extent of these lesions may be complementary indicators for assessment, including classification and prediction.

Morphological parameters of EOMs

The active phase of GO is usually accompanied by inflammatory edema, leading to changes in several measurable parameters of the EOMs (62). MRI can clearly show EOMs and further measure their diameter, cross-sectional area, and volume. Due to edema in EOMs during the active phase, the short diameter (thickness) measured from coronal MRI is often higher than that in the healthy group, suggesting great responsiveness to immunosuppressive therapy (Figure 3C) (19, 63). Another study demonstrated that the thickness of EOMs showed a strong correlation with cross-sectional area but a weak correlation with muscle volume, indicating that the measurement of EOM volume could not be replaced by thickness simply (64).

Classically, the volume of EOMs can be obtained by multiplying the sum of the cross-sectional areas by the layer thickness (65). Nowadays, similar to the fat volume, EOM volume can also be measured by 3D reconstruction (39) (Figure 2). Increased EOM volume is positively correlated with the GO severity and may contribute to optic neuropathy (56, 66). However, it remains inconclusive in GO activity (21, 38, 67, 68). One possible reason is that the enlargement of EOMs usually occurs earlier than obvious symptoms, which further highlights the role of imaging in early diagnosis.

Inflammation evaluating in EOMs

T2 relaxation time (T2RT)

EOMs usually appear edematous, and the inflamed portion may produce high signals on T2WI, which has been used to assess the activity of GO. Nowadays, quantitative MRI is available. This gives a higher accuracy compared to qualitative MRI. T2 mapping is a technique to construct a map based on the T2 value calculated for each voxel. The T2 value is defined as the time until T2 has decayed to 37% of the post-excitation transverse magnetization according to the curve acquired from several single-shot images. This provides a quantitative

parameter that describes the T2 signal (69). The T2RT reflects the water content of the tissue and is used as a way to assess the degree of inflammatory edema (70). This has been widely used in inflammation-related diseases such as myocardial edema, arthritis, and axial spondyloarthropathies (71–73). Likewise, T2RT of EOMs tends to increase in patients in the active phase and is positively correlated with CAS scores (27). Furthermore, T2RT showed a good prediction of the prognosis after immunosuppression therapy. Tachibana et al. found the coincidence rate of diagnosis by CAS and T2RT was relatively low (54.2%). Even in the CAS negative group, more than half had a prolonged T2RT and showed improvement after immunosuppressive therapy (43). Zhai and colleagues (20) divided patients into two groups according to the therapeutic effects of glucocorticoids. They found mean T2RT of EOMs is higher in responsive group as an independent predictor of prognosis, with area under the curve (AUC) = 0.764.

Fat suppression (FS) sequences

Although T2RT provides reliable information on parameters to indicate the degree of inflammation, measurement of T2RT must be accompanied by appropriate post-processing. In addition, the signal of adipose tissue is high on both T1 weight-images (T1WI) and T2 weight-images (T2WI), which can confound the water signal (74). FS sequences can suppress such fat signals to some degree, with negligible effects on water signals, allowing a better differentiation between adipose tissue and inflammatory edema (Figures 3D, E). Under these conditions, it was demonstrated that measurements of the signal intensity (SI) could be directly used to estimate the degree of inflammation. Commonly used fat suppression technologies include Chemical Shift-selective Fat Suppression (CHESS), short inversion time inversion recovery (STIR), spatial spectral pulse, and Dixon (75). Hoh and colleagues (76) measured signal intensities of the EOMs in 19 patients with Graves' ophthalmopathy by STIR sequences, showing that the temporalis muscle was structurally similar to the EOMs, with little inflammation occurring in GO. Therefore, they calculated the signal intensity ratio (SIR) of EOMs and temporalis muscles as being higher in GO patients than in healthy controls and positively correlated with Werner activity scores (76). Subsequently, other researchers also evaluated the SIR and activity scores in GO patients by STIR, confirming good agreement despite the different scoring criteria in these investigations (22, 77, 78).

Dixon is often used as a T2-weighted processing technique that can directly distinguish between fat and water signals, and Dixon-T2WI suffers from fewer artifacts than STIR sequences, making it quite suitable for head and orbital imaging. Except for a water map which is equal to the fat-suppressed sequences, Dixon-T2WI can also generate a fat map, allowing for quantitative analysis of the fat content. In some studies, investigators compared Dixon-T2WI with conventional T1WI, T2WI, and other FS sequences such as fat-sat. With higher signal values in the edematous fraction, Dixon-T2WI was shown to improve the sensitivity and specificity of the diagnosis (23, 24). Accordingly, the predictive performance of treatment response by FS sequence is better than T2RT (Figure 3F) (18, 20).

Diffusion-weighted imaging (DWI)

DWI is based on the different ability of water molecules to specifically move in different tissues. If their motility decreases, the signal intensity determined by DWI increases, and vice versa, thereby exploiting regional differences in tissue-specific diffusion capacity to produce contrast. This allows the use of the apparent diffusion coefficient (ADC) to describe the extent to which water molecules are confined in different tissues (79). The degree of diffusion sensitization is described by the b-value. Higher b-values correlate with diffusion effects positively and thus more pronounced signal attenuation, but this comes with increased noise, reducing the overall signal-to-noise ratio. It is important to optimize the SNR at each b-value for multiple b-values in DWI acquisition. DWI has been widely applied in distinguishing benign and malignant tumors of, for instance, the brain, liver, lung, kidney, and other parenchymal organs, and for the identification of acute cerebral infarction and showed great sensitivity and specificity (80). The ADC also shows superiority in the observation of orbital tissue lesions and inflammation (81–83).The value can also be used to quantify the degree of inflammation in EOMs. In one study, it was shown that ADC values of the four EOMs increased sequentially when comparing a healthy control group with, respectively, a GO-uninvolved group and a GO-involved group. Consequently, DWI might identify the inflamed EOMs earlier than other sequences as it can better distinguish less advanced GO cases from healthy controls (84).

There are two major techniques for DWI available, of which the most commonly used is echo planar imaging (EPI), but it suffers from low signal-to-noise ratio and is easy to form artifacts (85). The non-EPI alternative was initially used for the diagnosis of middle ear cholesteatoma, where it resulted in fewer artifacts and a higher resolution and could identify microscopic lesions as small as 2 mm, which is better than EPI for skull base imaging (86, 87). Recently, the effect of the non-EPI alternative technique for DWI was evaluated for GO, and such studies demonstrated good results for patients with active GO and optic neuropathy (26, 88).

Fat infiltration in EOMs

Fat infiltration in EOMs is often observed in MR images and is probably correlated with the severity of GO. The MRI signal of the EOMs was found to be slightly lower than normal signals in the FS sequence, indicating fat infiltration in EOMs (89, 90), but this method can only be used for qualitative diagnosis. The fat fraction

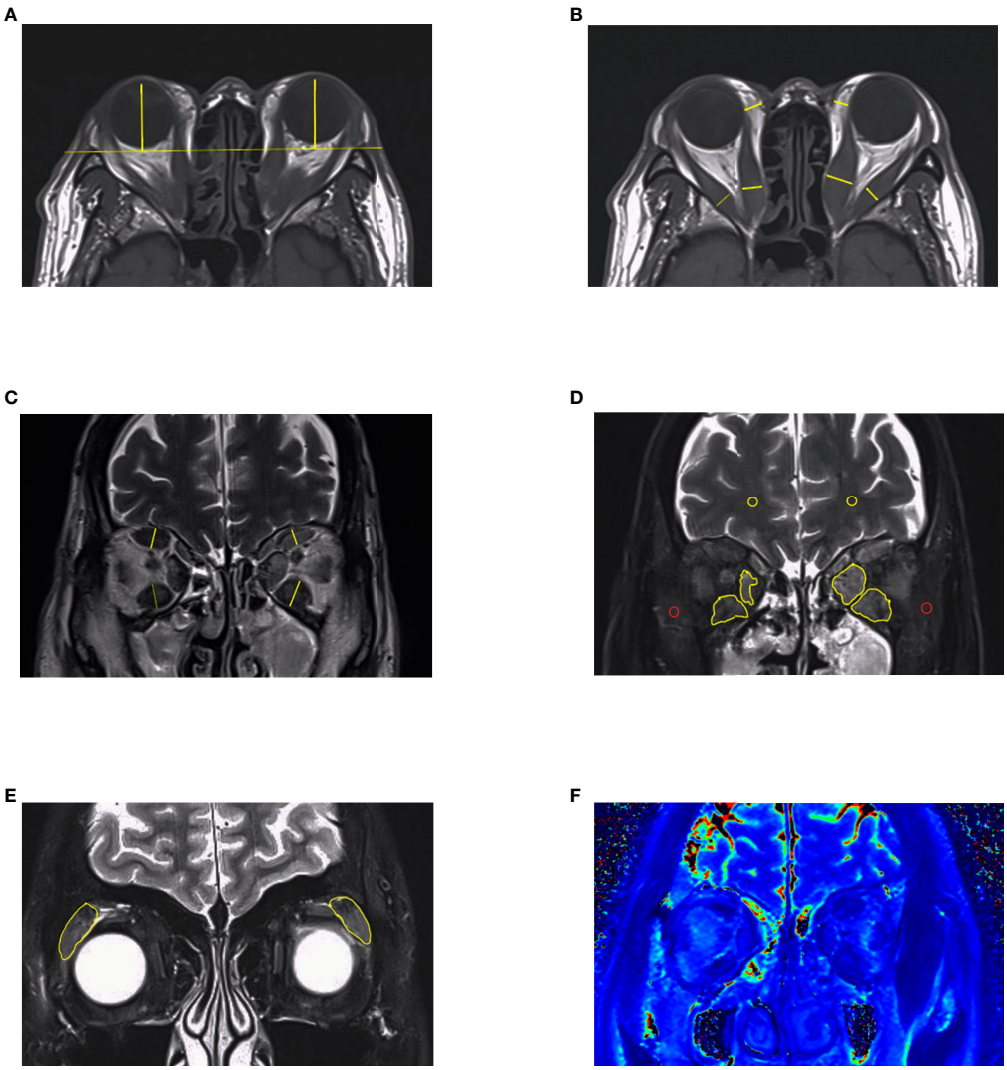

FIGURE 3
MRI measurements in GO. **(A–C)** Length parameters such as proptosis, thickness of extraocular muscles and thickness of orbital fat. It is noteworthy that thickness of medial rectus and lateral rectus muscles should be measured in axial images. **(D, E)** Signal intensity of extraocular muscles and lacrimal glands got from Dixon-T2WI sequence. The signal intensity of temporalis muscle (red circle) or white matter (yellow circle) on the same slice was used to calculated signal intensity ratio (SIR). **(F)** EOMs displayed on T2 mapping. This figure is original.

(FF) is a semiquantitative parameter of fat measurement, represented by the ratio of fat to the sum of water and fat in the EOMs obtained by post-processing of the data with defined calculation methods. It has been widely used to estimate fat infiltration, including vertebral tumor progression, and to evaluate surgical effects (91–93). The FF of EOM increases with the course of GO, which is consistent with its pathological process (27, 61), but the relationship between FF and the various stages of the disease is unclear. This may be related to the relatively small size of EOMs compared to other organs or tissues. The effect of edema remains large, despite an increase in fat content, causing the values of FF to fluctuate without consistent positive or negative correlation with CAS scores.

It cannot be neglected that CT is another modality to estimate fat infiltration of EOMs based on Hounsfield units (HU). The density ranges were set at −200 to −30 HU for fat, −30 to +100 HU for EOMs, and 0 HU for edema, which is sufficient to decrease the error from other infiltrations, including hyaluronic acid and lymphocytes (94, 95). However, two studies showed inconsistent results: Regensburg et al. found there was no statistical significance in the mean identity of EOMs between GO and controls, whereas Cohen et al. found

that fat infiltration is prevalent in GO patients (94, 96). The difference between regions of interest (ROIs) selection (entirety of EOMs or parts of fat infiltration) could be an explanation. Furthermore, investigation into the comparison of MRI and CT in EOM fat infiltration is still deficient.

Fibrosis in EOMs

There is a broad clinical overlap between the active and fibrotic phases, and EOMs with fibrosis can be refractory to glucocorticoid therapy (97). Although the occurrence of fibrosis is insidious and difficult to detect from the clinical presentation, MRI has significant advantages in detecting tissue fibrosis. Ollitrault et al. used the area with low signal in both the Dixon T2WI water map and in T2WI as a marker of EOM fibrosis (23). Alternatively, enlargement of EOMs with normal T2RT was used as the basis for determining chronic fibrosis (98). However, these methods do not provide a quantitative determination for the degree of fibrosis, and the diagnostics based on such imaging is highly subjective, so that a clinical significance of this method is unclear. Similar to T2 mapping, T1mapping has been used as it can color-code T1-based signal intensity, allowing for better highlighting of small lesions (99). This showed good prediction and assessment of fibrosis in the heart, liver, kidney, and other tissues (100–102). When T1 mapping and Dixon T2 were evaluated for EOMs in GO with diplopia, it was found that the value of T1 could more reliably estimate the fibrosis than Dixon T2. Patients with decreased T1 values may have entered a stage of fibrosis. At this time, glucocorticoid treatment is of little use, and surgery should be considered instead (28).

Nevertheless, the specificity and sensitivity of non-enhanced T1mapping are not satisfied, as T1 values can also reflect the inflammation in soft tissue (103). Based on increased extracellular matrix in tissues, extracellular volume (ECV) is a derived index from pre-contrast and postcontrast T1 values that has more efficacy in detecting fibrosis (Figure 4). Calculation of ECV:

$$ECV = (1 - \ hematocrit)\frac{1/T1(postcontrast \ \ rectus) - 1/T1(precontrast \ \ rectus)}{1/T1(postcontrast \ \ blood) - 1/T1(precontrast \ \ blood)}$$

A recent study indicated that one of the main pathological changes in inactive patients is muscle fibrosis. ECV rather than T1 significantly correlates with collagen volume fraction, which contributes to muscle fibrosis. This suggests that ECV may be more specific than T1 value as a parameter to assess EOM fibrosis (29).

Lacrimal glands

Anatomy, histology, and pathologic change in GO

The lacrimal glands are paired amygdaloid glands located in the zygomatic process of the frontal bone. They are divided into many lobules consisting of glandular tubules and acinar portions. The interstitium of secretory tubules is scattered by lymphoid cells, mast cells, and fibroblasts, and the acinar portions are surrounded by a basal layer of myoepithelial cells (104, 105).

The surface of the lacrimal glands in GO patients expresses TSHR. Similar to the involvement of EOMs in GO, immune-related lymphocyte and monocyte infiltration can also occur in lacrimal glands (106). Inflammatory markers such as C-reactive protein, IL-1β, and IL-6 increased in the tears of GO patients, representing that the lacrimal gland is also a target organ for thyroid receptor antibody (TRAb) (107, 108). More than 30% of GO patients suffer from dry eyes, while enlarged lacrimal glands can be observed on imaging in 11% of patients (109, 110). It can even occur in cases with no change in EOMs, which may contribute to early GO detection (111).

MRI appearance

Trokel et al. first found lacrimal gland enlargement in GO (112). Then, several studies demonstrated objectively quantitated parameters of the lacrimal glands, such as length, width, and area, are greater in GO than healthy control. However, these morphological parameters cannot discriminate between active and inactive patients (31, 113). The volume of the lacrimal gland cannot provide additional information about diagnosis neither (114). Similar to EOMs, quantifying the

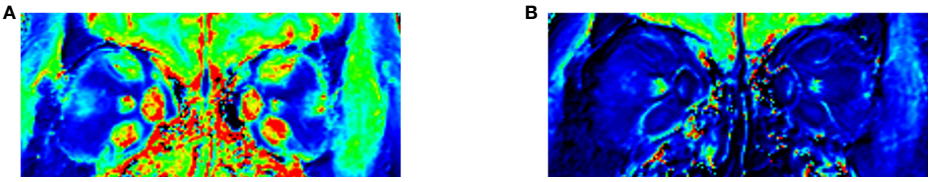

FIGURE 4
T1 mapping of EOMs. **(A)** Native T1 mapping. **(B)** Post-contrast T1 mapping for evaluating fibrosis in EOMs. Evaluating the T1 value or ECV of medial rectus and inferior rectus muscles may be sufficient for providing help for diagnosis. This figure is original.

degree of inflammation in the lacrimal gland may be more helpful in staging. The signal value of the lacrimal gland can also be measured on the T2 FS sequence, and the SIR can then be obtained by comparing it with the SI of the temporalis muscle. This approach can also be used as a criterion for differentiating between active and inactive GO (31). Meanwhile, the ADC and T2 values can also have a similar impact (32).

Lacrimal gland herniation is a special value characterized by Nugent et al. (115). The protrusion was determined to be at least half of the gland displaced anterior to the frontozygomatic process. This parameter was refined in subsequent studies, and reported greater bilateral lacrimal gland herniation in active GO patients than in inactive patients (30). Furthermore, compared to SIR, herniation can predict whether the patients have a response to glucocorticoids combined with orbital fat thickness (18).

Unfortunately, it seems difficult to find fibrosis in the lacrimal gland through biopsies after contrast injection (116), but the T1 value decreases more after contrast injection in active than inactive patients (32), providing a novel perspective for lacrimal gland fibrosis. It remains to be investigated whether fibrosis of the lacrimal gland has any influence on the evaluation of GO and on predicting the efficacy of glucocorticoids.

Optic nerve

Anatomy, histology, and pathologic change in GO

The optic nerve extends from the retina to the brain and can be divided into the intraocular, intraorbital, intracanal, and intracranial segments. The intraorbital segment starts from the posterior of the sclera to the optic canal, represents its longest part, and is closely related to GO. It is wrapped by the optic nerve sheath, which consists of the cerebral dura mater, arachnoid mater and cerebral pia mater. The subarachnoid space of the nerve connects to the intracranial subarachnoid space and is filled with cerebrospinal fluid (117).

Dysthyroid optic neuropathy (DON), with an incidence of about 5%, is one of the most severe complications of GO (118, 119). As a result, the early detection and treatment of DON plays a crucial role in preventing permanent blindness. Several situations promote DON, including compressed optic nerves, optic neuritis, or stretched optic nerves. Over 90% of patients with DON have an enlarged EOM compressing the optic nerve, so quantification of the degree of compression helps in diagnosis. In addition, a few biopsies of nerve make optic neuritis neglected (120), but MRI may detect inflammation of the nerve, which is recommended as a typical examination for diagnosis and follow-up (121). Meanwhile, 5% of DON cases may be caused by optic nerve traction, but this mechanism is still controversial (122, 123). In conclusion, the quantitative assessment of DON by MRI focused on the size of the EOMs and optic neuritis.

DON prediction by MRI

Currently, there are no consistent criteria for the diagnosis of DON, which is diagnosed based on clinical symptoms such as visual impairment, visual field defects, optic disc edema, and color vision disorder (124). However, these features are non-specific and can also occur in other diseases such as idiopathic orbital inflammation or cranial nerve palsy (125). A number of ophthalmic indicators can identify subclinical DON before the onset of obvious symptoms, such as blue-yellow deficiency and thinned macular inner retina. These tests require specialized equipment and experienced ophthalmologists (126, 127). MRI, however, can clearly show the posterior state of the eye and improve the diagnosis of DON, depending on the underlying mechanism. Early studies concentrate on morphologic parameters by CT to quantify the compression. Barrett et al. defined a muscle index as a classic method by calculating the diameters of four EOMs occupied orbit (128). Weis and colleagues found that the diameter of medial muscles is suitable for predicting DON. The ROC for diagnosis was 0.83, but they did not define a specific cut-off value (66).

Rutkowska-Hinc et al. found cerebrospinal fluid in the optic nerve sheath was different between DON and non-DON patients (129). As previously mentioned, because T2 mapping and FS sequences exactly reflect the moisture content of tissues, they can be used as a new indicator for identification. Zou and colleagues modified the Barrett index by using Dixon-T2WI with higher resolution, and they calculated the index at four slices behind the eyeball. Muscle index at 21 mm combined with T2 mapping, which could indicate the rupture of the optic nerve myelin sheath and edema, improved the accuracy of diagnosis (33). On the other hand, the optic nerve subarachnoid space will increase with the edema of the optic nerve in DON. It is convenient to qualify the subarachnoid fluid volume by determining the diameters between the optic nerve sheath and the optic nerve on FS sequences and using this as a predictor (34).

Discussion and future perspectives

In this review, we discussed comprehensive tissue-based approaches to estimating GO and provided several MRI features in different situations. We also summarized several methods for parameter measurement, but we did not provide clarity regarding how these features influence the activity phase and guide management. For example, to what extent does MRI change suggest the need for surgery or second-line therapies? Which MRI feature suggests local treatments are sufficient?

Although achievements in MRI and GO are growing rapidly, most previous studies were based on cross-sectional and retrospective analysis. Prospective studies that combine the results of treatment with multi-parameter MRI are still important. Future studies should focus on developing new

sequences to improve temporal resolution, such as T1 rho, a relatively new sequence that has better characterization in injury than T1 (130). The improvement of image analysis methods for imaging, including histogram analysis, also provides more accurate ways for GO evaluation (131, 132). Furthermore, radiomics and deep learning have been widely used in image segmentation, ROI extraction, and automatic analysis to assist in diagnosis. Song and Lin et al. established two systems to discriminate GO from healthy people and detect active and inactive phases (133, 134), but investigations including larger samples and prognosis are still needed.

Conclusion

To sum up, MRI is promising for GO assessment by providing high-resolution images and multiple functional sequences that allow physicians to intervene at the subclinical stage of GO. However, there are still some issues to be addressed, including machine diversity, time-consuming, and higher economic burden. It is crucial to establish a generally accepted test mode consisting of the necessary sequences, which is time-saving and price-friendly. This requires the coordinated efforts of endocrinologists, radiologists, and ophthalmologists.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

Author contributions

CS and GY wrote the manuscript. YL, HC, and JS revised the manuscript. The final manuscript was read and approved by all authors.

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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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References

1. Perros P, Hegedus L, Bartalena L, Marcocci C, Kahaly GJ, Baldeschi L, et al. Graves' orbitopathy as a rare disease in Europe: A European group on graves' orbitopathy (EUGOGO) position statement. *Orphanet J Rare Dis* (2017) 12(1):72. doi: 10.1186/s13023-017-0625-1

2. Bartalena L, Piantanida E, Gallo D, Lai A, Tanda ML. Epidemiology, natural history, risk factors, and prevention of graves' orbitopathy. *Front Endocrinol (Lausanne)* (2020) 11:615993. doi: 10.3389/fendo.2020.615993

3. Tanda ML, Piantanida E, Liparulo L, Veronesi G, Lai A, Sassi L, et al. Prevalence and natural history of graves' orbitopathy in a large series of patients with newly diagnosed graves' hyperthyroidism seen at a single center. *J Clin Endocrinol Metab* (2013) 98(4):1443–9. doi: 10.1210/jc.2012-3873

4. Wang Y, Zhu M, Li J, Xiong Y, Wang J, Jing H, et al. Overexpression of PSMC2 promotes the tumorigenesis and development of human breast cancer *via* regulating plasminogen activator urokinase (PLAU). *Cell Death Dis* (2021) 12 (7):690. doi: 10.1038/s41419-021-03960-w

5. Bartalena L, Kahaly GJ, Baldeschi L, Dayan CM, Eckstein A, Marcocci C, et al. The 2021 European group on graves' orbitopathy (EUGOGO) clinical practice guidelines for the medical management of graves' orbitopathy. *Eur J Endocrinol* (2021) 185(4):G43–67. doi: 10.1530/EJE-21-0479

6. Gontarz-Nowak K, Szychlinska M, Matuszewski W, Stefanowicz-Rutkowska M, Bandurska-Stankiewicz E. Current knowledge on graves' orbitopathy. *J Clin Med* (2020) 10(1):16. doi: 10.3390/jcm10010016

7. Wiersinga WM. Advances in treatment of active, moderate-to-severe graves' ophthalmopathy. *Lancet Diabetes Endocrinol* (2017) 5(2):134–42. doi: 10.1016/S2213-8587(16)30046-8

8. Taylor PN, Zhang L, Lee RWJ, Muller I, Ezra DG, Dayan CM, et al. New insights into the pathogenesis and nonsurgical management of graves orbitopathy. *Nat Rev Endocrinol* (2020) 16(2):104–16. doi: 10.1038/s41574-019-0305-4

9. Fang S, Lu Y, Huang Y, Zhou H, Fan X. Mechanisms that underly T cell immunity in graves' orbitopathy. *Front Endocrinol (Lausanne)* (2021) 12:648732. doi: 10.3389/fendo.2021.648732

10. Lacheta D, Miskiewicz P, Gluszko A, Nowicka G, Struga M, Kantor I, et al. Immunological aspects of graves' ophthalmopathy. *BioMed Res Int* (2019) 2019:7453260. doi: 10.1155/2019/7453260

11. Fang S, Huang Y, Zhong S, Li Y, Zhang Y, Li Y, et al. Regulation of orbital fibrosis and adipogenesis by pathogenic Th17 cells in graves orbitopathy. *J Clin Endocrinol Metab* (2017) 102(11):4273–83. doi: 10.1210/jc.2017-01349

12. Potgieser PW, de Win M, Wiersinga WM, Mourits MP. Natural course of mild graves orbitopathy: Increase of orbital fat but decrease of muscle volume with increased muscle fatty degeneration during a 4-year follow-up. *Ophthalmic Plast Reconstr Surg* (2019) 35(5):456–60. doi: 10.1097/IOP.0000000000001319

13. Boschi A, Daumerie C, Spiritus M, Beguin C, Senou M, Yuksel D, et al. Quantification of cells expressing the thyrotropin receptor in extraocular muscles in thyroid associated orbitopathy. *Br J Ophthalmol* (2005) 89(6):724–9. doi: 10.1136/bjo.2004.050807

14. Marino M, Ionni I, Lanzolla G, Sframeli A, Latrofa F, Rocchi R, et al. Orbital diseases mimicking graves' orbitopathy: A long-standing challenge in differential diagnosis. *J Endocrinol Invest* (2020) 43(4):401–11. doi: 10.1007/s40618-019-01141-3

15. Cevik Y, Taylan Sekeroglu H, Ozgen B, Erkan Turan K, Sanac AS. Clinical and radiological findings in patients with newly diagnosed graves' ophthalmopathy. *Int J Endocrinol* (2021) 2021:5513008. doi: 10.1155/2021/5513008

16. Segni M, Bartley GB, Garrity JA, Bergstralh EJ, Gorman CA. Comparability of proptosis measurements by different techniques. *Am J Ophthalmol* (2002) 133 (6):813–8. doi: 10.1016/S0002-9394(02)01429-0

17. Shen J, Jiang W, Luo Y, Cai Q, Li Z, Chen Z, et al. Establishment of magnetic resonance imaging 3D reconstruction technology of orbital soft tissue and its preliminary application in patients with thyroid-associated ophthalmopathy. *Clin Endocrinol (Oxf)* (2018) 88(5):637–44. doi: 10.1111/cen.13564

18. Hu H, Xu XQ, Chen L, Chen W, Wu Q, Chen HH, et al. Predicting the response to glucocorticoid therapy in thyroid-associated ophthalmopathy: Mobilizing structural MRI-based quantitative measurements of orbital tissues. *Endocrine* (2020) 70(2):372–9. doi: 10.1007/s12020-020-02367-5

19. Xu L, Li L, Xie C, Guan M, Xue Y. Thickness of extraocular muscle and orbital fat in MRI predicts response to glucocorticoid therapy in graves' ophthalmopathy. *Int J Endocrinol* (2017) 2017:3196059. doi: 10.1155/2017/3196059

20. Zhai L, Luo B, Wu H, Wang Q, Yuan G, Liu P, et al. Prediction of treatment response to intravenous glucocorticoid in patients with thyroid-associated ophthalmopathy using T2 mapping and T2 IDEAL. *Eur J Radiol* (2021) 142:109839. doi: 10.1016/j.ejrad.2021.109839

21. Mayer EJ, Fox DL, Herdman G, Hsuan J, Kabala J, Goddard P, et al. Signal intensity, clinical activity and cross-sectional areas on MRI scans in thyroid eye disease. *Eur J Radiol* (2005) 56(1):20–4. doi: 10.1016/j.ejrad.2005.03.027

22. Mayer E, Herdman G, Burnett C, Kabala J, Goddard P, Potts MJ. Serial STIR magnetic resonance imaging correlates with clinical score of activity in thyroid disease. *Eye (Lond)* (2001) 15(Pt 3):313–8. doi: 10.1038/eye.2001.102

23. Ollitrault A, Charbonneau F, Herdan ML, Berges O, Zuber K, Giovansili L, et al. Dixon-T2WI magnetic resonance imaging at 3 tesla outperforms conventional imaging for thyroid eye disease. *Eur Radiol* (2021) 31(7):5198–205. doi: 10.1007/s00330-020-07540-y

24. Chen L, Hu H, Chen HH, Chen W, Wu Q, Wu FY, et al. Usefulness of two-point Dixon T2-weighted imaging in thyroid-associated ophthalmopathy: comparison with conventional fat saturation imaging in fat suppression quality and staging performance. *Br J Radiol* (2021) 94(1118):20200884. doi: 10.1259/bjr.20200884

25. Politi LS, Godi C, Cammarata G, Ambrosi A, Iadanza A, Lanzi R, et al. Magnetic resonance imaging with diffusion-weighted imaging in the evaluation of thyroid-associated orbitopathy: Getting below the tip of the iceberg. *Eur Radiol* (2014) 24(5):1118–26. doi: 10.1007/s00330-014-3103-3

26. Feeney C, Lingam RK, Lee V, Rahman F, Nagendran S. Non-EPI-DWI for detection, disease monitoring, and clinical decision-making in thyroid eye disease. *AJNR Am J Neuroradiol* (2020) 41(8):1466–72. doi: 10.3174/ajnr.A6664

27. Das T, Roos JCP, Patterson AJ, Graves MJ, Murthy R. T2-relaxation mapping and fat fraction assessment to objectively quantify clinical activity in thyroid eye disease: an initial feasibility study. *Eye (Lond)* (2019) 33(2):235–43. doi: 10.1038/s41433-018-0304-z

28. Matsuzawa K, Izawa S, Kato A, Fukaya K, Matsumoto K, Okura T, et al. Low signal intensities of MRI T1 mapping predict refractory diplopia in graves' ophthalmopathy. *Clin Endocrinol (Oxf)* (2020) 92(6):536–44. doi: 10.1111/cen.14178

29. Ma R, Geng Y, Gan L, Peng Z, Cheng J, Guo J, et al. Quantitative T1 mapping MRI for the assessment of extraocular muscle fibrosis in thyroid-associated ophthalmopathy. *Endocrine* (2021) 75 (2):456–64. doi: 10.1007/s12020-021-02873-0

30. Gagliardo C, Radellini S, Morreale Bubella R, Falanga G, Richiusa P, Vadala M, et al. Lacrimal gland herniation in graves ophthalmopathy: A simple and useful MRI biomarker of disease activity. *Eur Radiol* (2020) 30(4):2138–41. doi: 10.1007/s00330-019-06570-5

31. Hu H, Xu XQ, Wu FY, Chen HH, Su GY, Shen J, et al. Diagnosis and stage of graves' ophthalmopathy: Efficacy of quantitative measurements of the lacrimal gland based on 3-T magnetic resonance imaging. *Exp Ther Med* (2016) 12(2):725–9. doi: 10.3892/etm.2016.3389

32. Wu D, Zhu H, Hong S, Li B, Zou M, Ma X, et al. Utility of multi-parametric quantitative magnetic resonance imaging of the lacrimal gland for diagnosing and staging graves' ophthalmopathy. *Eur J Radiol* (2021) 141:109815. doi: 10.1016/j.ejrad.2021.109815

33. Zou M, Wu D, Zhu H, Huang X, Zhao X, Zhao J, et al. Multiparametric quantitative MRI for the evaluation of dysthyroid optic neuropathy. *Eur Radiol* (2021) 32(3):1931–8. doi: 10.1007/s00330-021-08300-2

34. Wu H, Luo B, Yuan G, Wang Q, Liu P, Zhao Y, et al. The diagnostic value of the IDEAL-T2WI sequence in dysthyroid optic neuropathy: A quantitative analysis of the optic nerve and cerebrospinal fluid in the optic nerve sheath. *Eur Radiol* (2021) 31(10):7419–28. doi: 10.1007/s00330-021-08030-5

35. Satterfield KR, Chambers CB. Orbital anatomy. In: DM Albert, JW Miller, DT Azar and LH Young, editors. *Albert And jakobiec's principles and practice of ophthalmology*. Cham: Springer International Publishing (2022). p. 5021–47.

36. Bremond-Gignac D, Copin H, Cussenot O, Lassau JP, Henin D. Anatomical histological and mesoscopic study of the adipose tissue of the orbit. *Surg Radiol Anat* (2004) 26(4):297–302. doi: 10.1007/s00276-004-0223-5

37. Wolfram-Gabel R, Kahn JL. Adipose body of the orbit. *Clin Anat* (2002) 15 (3):186–92. doi: 10.1002/ca.10011

38. Potgieser PW, Wiersinga WM, Regensburg NI, Mourits MP. Some studies on the natural history of graves' orbitopathy: Increase in orbital fat is a rather late phenomenon. *Eur J Endocrinol* (2015) 173(2):149–53. doi: 10.1530/EJE-14-1140

39. Regensburg NI, Wiersinga WM, Berendschot TT, Potgieser P, Mourits MP. Do subtypes of graves' orbitopathy exist? *Ophthalmology* (2011) 118(1):191–6. doi: 10.1016/j.ophtha.2010.04.004

40. Prummel MF, Bakker A, Wiersinga WM, Baldeschi L, Mourits MP, Kendall-Taylor P, et al. Multi-center study on the characteristics and treatment strategies of patients with graves' orbitopathy: The first European group on graves' orbitopathy experience. *Eur J Endocrinol* (2003) 148(5):491–5. doi: 10.1530/eje.0.1480491

41. Bartalena L, Wiersinga WM. Proposal for standardization of primary and secondary outcomes in patients with active, moderate-to-Severe graves' orbitopathy. *Eur Thyroid J* (2020) 9(Suppl 1):3–16. doi: 10.1159/000510700

42. European Group on Graves O, Wiersinga WM, Perros P, Kahaly GJ, Mourits MP, Baldeschi L, et al. Clinical assessment of patients with graves' orbitopathy: The European group on graves' orbitopathy recommendations to generalists, specialists and clinical researchers. *Eur J Endocrinol* (2006) 155(3):387–9. doi: 10.1530/eje.1.02230

43. Tachibana S, Murakami T, Noguchi H, Noguchi Y, Nakashima A, Ohyabu Y, et al. Orbital magnetic resonance imaging combined with clinical activity score can improve the sensitivity of detection of disease activity and prediction of response to immunosuppressive therapy for graves' ophthalmopathy. *Endocr J* (2010) 57(10):853–61. doi: 10.1507/endocrj.K10E-156

44. Choi KJ, Lee MJ. Comparison of exophthalmos measurements: Hertel exophthalmometer versus orbital parameters in 2-dimensional computed tomography. *Can J Ophthalmol* (2018) 53(4):384–90. doi: 10.1016/j.jcjo.2017.10.015

45. Wu D, Liu X, Wu D, Di X, Guan H, Shan Z, et al. Normal values of hertel exophthalmometry in a Chinese han population from shenyang, northeast China. *Sci Rep* (2015) 5:8526. doi: 10.1038/srep08526

46. Dijkstal JM, Bothun ED, Harrison AR, Lee MS. Normal exophthalmometry measurements in a united states pediatric population. *Ophthalmic Plast Reconstr Surg* (2012) 28(1):54–6. doi: 10.1097/IOP.0b013e3182392f05

47. Bilen H, Gullulu G, Akcay G. Exophthalmometric values in a normal Turkish population living in the northeastern part of Turkey. *Thyroid* (2007) 17 (6):525–8. doi: 10.1089/thy.2006.0279

48. Kashkouli MB, Nojomi M, Parvaresh MM, Sanjari MS, Modarres M, Noorani MM. Normal values of hertel exophthalmometry in children, teenagers, and adults from Tehran, Iran. *Optom Vis Sci* (2008) 85(10):1012–7. doi: 10.1097/OPX.0b013e3181890dc7

49. Beden U, Ozarslan Y, Ozturk HE, Sonmez B, Erkan D, Oge I. Exophthalmometry values of Turkish adult population and the effect of age, sex, refractive status, and hertel base values on hertel readings. *Eur J Ophthalmol* (2008) 18(2):165–71. doi: 10.1177/112067210801800201

50. Frueh WT, Frueh BR. Errors of single-mirror or prism hertel exophthalmometers and recommendations for minimizing the errors. *Ophthalmic Plast Reconstr Surg* (2007) 23(3):197–201. doi: 10.1097/IOP.0b013e3180500d70

51. Sleep TJ, Manners RM. Interinstrument variability in hertel-type exophthalmometers. *Ophthalmic Plast Reconstr Surg* (2002) 18(4):254–7. doi: 10.1097/00002341-200207000-00004

52. Schmidt P, Kempin R, Langner S, Beule A, Kindler S, Koppe T, et al. Association of anthropometric markers with globe position: A population-based MRI study. *PloS One* (2019) 14(2):e0211817. doi: 10.1371/journal.pone.0211817

53. Bingham CM, Sivak-Callcott JA, Gurka MJ, Nguyen J, Hogg JP, Feldon SE, et al. Axial globe position measurement: A prospective multicenter study by the international thyroid eye disease society. *Ophthalmic Plast Reconstr Surg* (2016) 32 (2):106–12. doi: 10.1097/IOP.0000000000000437

54. Nishida Y, Tian S, Isberg B, Hayashi O, Tallstedt L, Lennerstrand G. Significance of orbital fatty tissue for exophthalmos in thyroid-associated ophthalmopathy. *Graefes Arch Clin Exp Ophthalmol* (2002) 240(7):515–20. doi: 10.1007/s00417-002-0498-3

55. Tian S, Nishida Y, Isberg B, Lennerstrand G. MRI Measurements of normal extraocular muscles and other orbital structures. *Graefes Arch Clin Exp Ophthalmol* (2000) 238(5):393–404. doi: 10.1007/s004170050370

56. Wiersinga WM, Regensburg NI, Mourits MP. Differential involvement of orbital fat and extraocular muscles in graves' ophthalmopathy. *Eur Thyroid J* (2013) 2(1):14–21. doi: 10.1159/000348246

57. Jain AP, Gellada N, Ugradar S, Kumar A, Kahaly G, Douglas R. Teprotumumab reduces extraocular muscle and orbital fat volume in thyroid eye disease. *Br J Ophthalmol* (2020) 106(2):165–71. doi: 10.1136/bjophthalmol-2020-317806

58. Douglas RS, Kahaly GJ, Patel A, Sile S, Thompson EHZ, Perdok R, et al. Teprotumumab for the treatment of active thyroid eye disease. *N Engl J Med* (2020) 382(4):341–52. doi: 10.1056/NEJMoa1910434

59. Chévez-Barrios P, Cykowski MD. Pathology of the optic nerve and extraocular muscle. In: DM Albert, JW Miller, DT Azar and LH Young, editors. *Albert And jakobiec's principles and practice of ophthalmology*. Cham: Springer International Publishing (2022). p. 6489–524.

60. Bakalova R, Georgieva E, Ivanova D, Zhelev Z, Aoki I, Saga T. Magnetic resonance imaging of mitochondrial dysfunction and metabolic activity, accompanied by overproduction of superoxide. *ACS Chem Neurosci* (2015) 6 (12):1922–9. doi: 10.1021/acschemneuro.5b00220

61. Keene KR, van Vught L, van de Velde NM, Ciggaar IA, Notting IC, Genders SW, et al. The feasibility of quantitative MRI of extra-ocular muscles in myasthenia gravis and graves' orbitopathy. *NMR BioMed* (2021) 34(1):e4407. doi: 10.1002/nbm.4407

62. Just M, Kahaly G, Higer HP, Rosler HP, Kutzner J, Beyer J, et al. Graves ophthalmopathy: role of MR imaging in radiation therapy. *Radiology* (1991) 179 (1):187–90. doi: 10.1148/radiology.179.1.2006276

63. Hiromatsu Y, Kojima K, Ishisaka N, Tanaka K, Sato M, Nonaka K, et al. Role of magnetic resonance imaging in thyroid-associated ophthalmopathy: Its predictive value for therapeutic outcome of immunosuppressive therapy. *Thyroid* (1992) 2(4):299–305. doi: 10.1089/thy.1992.2.299

64. Szucs-Farkas Z, Toth J, Balazs E, Galuska L, Burman KD, Karanyi Z, et al. Using morphologic parameters of extraocular muscles for diagnosis and follow-up of graves' ophthalmopathy: Diameters, areas, or volumes? *AJR Am J Roentgenol* (2002) 179(4):1005–10. doi: 10.2214/ajr.179.4.1791005

65. Higashiyama T, Nishida Y, Ohji M. Changes of orbital tissue volumes and proptosis in patients with thyroid extraocular muscle swelling after methylprednisolone pulse therapy. *Jpn J Ophthalmol* (2015) 59(6):430–5. doi: 10.1007/s10384-015-0410-4

66. Weis E, Heran MK, Jhamb A, Chan AK, Chiu JP, Hurley MC, et al. Quantitative computed tomographic predictors of compressive optic neuropathy in patients with thyroid orbitopathy: A volumetric analysis. *Ophthalmology* (2012) 119(10):2174–8. doi: 10.1016/j.ophtha.2012.04.021

67. Nagy EV, Toth J, Kaldi I, Damjanovich J, Mezosi E, Lenkey A, et al. Graves' ophthalmopathy: eye muscle involvement in patients with diplopia. *Eur J Endocrinol* (2000) 142(6):591–7. doi: 10.1530/eje.0.1420591

68. Kim HC, Yoon SW, Lew H. Usefulness of the ratio of orbital fat to total orbit area in mild-to-moderate thyroid-associated ophthalmopathy. *Br J Radiol* (2015) 88(1053):20150164. doi: 10.1259/bjr.20150164

69. Lota AS, Gatehouse PD, Mohiaddin RH. T2 mapping and T2* imaging in heart failure. *Heart Fail Rev* (2017) 22(4):431–40. doi: 10.1007/s10741-017-9616-5

70. Marinelli NL, Haughton VM, Munoz A, Anderson PA. T2 relaxation times of intervertebral disc tissue correlated with water content and proteoglycan content. *Spine (Phila Pa 1976)*. (2009) 34(5):520–4. doi: 10.1097/BRS.0b013e318195dd44

71. Kasar S, Ozturk M, Polat AV. Quantitative T2 mapping of the sacroiliac joint cartilage at 3T in patients with axial spondyloarthropathies. *Eur Radiol* (2021) 32(2):1395–403. doi: 10.1007/s00330-021-08357-z

72. Kotecha T, Martinez-Naharro A, Treibel TA, Francis R, Nordin S, Abdel-Gadir A, et al. Myocardial edema and prognosis in amyloidosis. *J Am Coll Cardiol* (2018) 71(25):2919–31. doi: 10.1016/j.jacc.2018.03.536

73. Albano D, Bignone R, Chianca V, Cuocolo R, Messina C, Sconfienza LM, et al. T2 mapping of the sacroiliac joints in patients with axial spondyloarthritis. *Eur J Radiol* (2020) 131:109246. doi: 10.1016/j.ejrad.2020.109246

74. Gold GE, Han E, Stainsby J, Wright G, Brittain J, Beaulieu C. Musculoskeletal MRI at 3.0 T: Relaxation times and image contrast. *AJR Am J Roentgenol* (2004) 183(2):343–51. doi: 10.2214/ajr.183.2.1830343.

75. Del Grande F, Santini F, Herzka DA, Aro MR, Dean CW, Gold GE, et al. Fat-suppression techniques for 3-T MR imaging of the musculoskeletal system. *Radiographics* (2014) 34(1):217–33. doi: 10.1148/rg.341135130

76. Hoh HB, Laitt RD, Wakeley C, Kabala J, Goddard P, Potts MJ, et al. The STIR sequence MRI in the assessment of extraocular muscles in thyroid eye disease. *Eye (Lond)* (1994) 8(Pt 5):506–10. doi: 10.1038/eye.1994.126

77. Laitt RD, Hoh B, Wakeley C, Kabala J, Harrad R, Potts M, et al. The value of the short tau inversion recovery sequence in magnetic resonance imaging of thyroid eye disease. *Br J Radiol* (1994) 67(795):244–7. doi: 10.1259/0007-1285-67-795-244

78. Kirsch EC, Kaim AH, De Oliveira MG, von Arx G. Correlation of signal intensity ratio on orbital MRI-TIRM and clinical activity score as a possible predictor of therapy response in graves' orbitopathy–a pilot study at 1.5 T. *Neuroradiology* (2010) 52(2):91–7. doi: 10.1007/s00234-009-0590-z

79. Caglic I, Barrett T. Diffusion-weighted imaging (DWI) in lymph node staging for prostate cancer. *Transl Androl Urol* (2018) 7(5):814–23. doi: 10.21037/tau.2018.08.04

80. Messina C, Bignone R, Bruno A, Bruno A, Bruno F, Calandri M, et al. Diffusion-weighted imaging in oncology: An update. *Cancers (Basel)* (2020) 12 (6):1493. doi: 10.3390/cancers12061493

81. Ro SR, Asbach P, Siebert E, Bertelmann E, Hamm B, Erb-Eigner K. Characterization of orbital masses by multiparametric MRI. *Eur J Radiol* (2016) 85(2):324–36. doi: 10.1016/j.ejrad.2015.11.041

82. Sun B, Song L, Wang X, Li J, Xian J, Wang F, et al. Lymphoma and inflammation in the orbit: Diagnostic performance with diffusion-weighted imaging and dynamic contrast-enhanced MRI. *J Magn Reson Imaging* (2017) 45 (5):1438–45. doi: 10.1002/jmri.25480

83. Attye A, Jean C, Remond P, Peyrin C, Lecler A, Boudiaf N, et al. Track-weighted imaging for neuroretina: Evaluations in healthy volunteers and ischemic optic neuropathy. *J Magn Reson Imaging* (2018). doi: 10.1002/jmri.25941

84. Kilicarslan R, Alkan A, Ilhan MM, Yetis H, Aralasmak A, Tasan E. Graves' ophthalmopathy: The role of diffusion-weighted imaging in detecting involvement of extraocular muscles in early period of disease. *Br J Radiol* (2015) 88 (1047):20140677. doi: 10.1259/bjr.20140677

85. Qayyum A. Diffusion-weighted imaging in the abdomen and pelvis: Concepts and applications. *Radiographics* (2009) 29(6):1797–810. doi: 10.1148/rg.296095521

86. Khemani S, Singh A, Lingam RK, Kalan A. Imaging of postoperative middle ear cholesteatoma. *Clin Radiol* (2011) 66(8):760–7. doi: 10.1016/j.crad.2010.12.019

87. Benson JC, Carlson ML, Lane JI. Non-EPI versus multishot EPI DWI in cholesteatoma detection: Correlation with operative findings. *AJNR Am J Neuroradiol* (2021) 42(3):573–7. doi: 10.3174/ajnr.A6911

88. Lingam RK, Mundada P, Lee V. Novel use of non-echo-planar diffusion weighted MRI in monitoring disease activity and treatment response in active grave's orbitopathy: An initial observational cohort study. *Orbit* (2018) 37(5):325–30. doi: 10.1080/01676830.2017.1423343

89. Marique L, Senou M, Craps J, Delaigle A, Van Regemorter E, Werion A, et al. Oxidative stress and upregulation of antioxidant proteins, including adiponectin, in extraocular muscular cells, orbital adipocytes, and thyrocytes in graves' disease associated with orbitopathy. *Thyroid* (2015) 25(9):1033–42. doi: 10.1089/thy.2015.0087

90. Daumerie C, Duprez T, Boschi A. Long-term multidisciplinary follow-up of unilateral thyroid-associated orbitopathy. *Eur J Intern Med* (2008) 19(7):531–6. doi: 10.1016/j.ejim.2008.01.013

91. Jiang H, Chen HC, Lafata KJ, Bashir MR. Week 4 liver fat reduction on MRI as an early predictor of treatment response in participants with nonalcoholic steatohepatitis. *Radiology* (2021) 300(2):361–8. doi: 10.1148/radiol.2021204325

92. Bacher S, Hajdu SD, Maeder Y, Dunet V, Hilbert T, Omoumi P. Differentiation between benign and malignant vertebral compression fractures using qualitative and quantitative analysis of a single fast spin echo T2-weighted Dixon sequence. *Eur Radiol* (2021) 31(12):9418–27. doi: 10.1007/s00330-021-07947-1

93. Wieser K, Joshy J, Filli L, Kriechling P, Sutter R, Furnstahl P, et al. Changes of supraspinatus muscle volume and fat fraction after successful or failed arthroscopic rotator cuff repair. *Am J Sports Med* (2019) 47(13):3080–8. doi: 10.1177/0363546519876289

94. Cohen LM, Liou VD, Cunnane ME, Yoon MK. Radiographic analysis of fatty infiltration of the extraocular muscles in thyroid eye disease. *Orbit* (2022) 41 (1):53–8. doi: 10.1080/01676830.2020.1817100

95. Byun JS, Moon NJ, Lee JK. Quantitative analysis of orbital soft tissues on computed tomography to assess the activity of thyroid-associated orbitopathy.

Graefes Arch Clin Exp Ophthalmol (2017) 255(2):413–20. doi: 10.1007/s00417-016-3538-0

96. Regensburg NI, Wiersinga WM, Berendschot TT, Saeed P, Mourits MP. Densities of orbital fat and extraocular muscles in graves orbitopathy patients and controls. *Ophthalmic Plast Reconstr Surg* (2011) 27(4):236–40. doi: 10.1097/IOP.0b013e31820365d5

97. Bhatti MT, Dutton JJ. Thyroid eye disease: therapy in the active phase. *J Neuroophthalmol* (2014) 34(2):186–97. doi: 10.1097/WNO.0000000000000128

98. Utech CI, Khatibnia U, Winter PF, Wulle KG. MR T2 relaxation time for the assessment of retrobulbar inflammation in graves' ophthalmopathy. *Thyroid* (1995) 5(3):185–93. doi: 10.1089/thy.1995.5.185

99. Taylor AJ, Salerno M, Dharmakumar R, Jerosch-Herold M. T1 mapping: Basic techniques and clinical applications. *JACC Cardiovasc Imaging* (2016) 9 (1):67–81. doi: 10.1016/j.jcmg.2015.11.005

100. Jiang K, Ferguson CM, Lerman LO. Noninvasive assessment of renal fibrosis by magnetic resonance imaging and ultrasound techniques. *Transl Res* (2019) 209:105–20. doi: 10.1016/j.trsl.2019.02.009

101. Haaf P, Garg P, Messroghli DR, Broadbent DA, Greenwood JP, Plein S. Cardiac T1 mapping and extracellular volume (ECV) in clinical practice: A comprehensive review. *J Cardiovasc Magn Reson* (2016) 18(1):89. doi: 10.1186/s12968-016-0308-4

102. Robinson AA, Chow K, Salerno M. Myocardial T1 and ECV measurement: Underlying concepts and technical considerations. *JACC Cardiovasc Imaging* (2019) 12(11 Pt 2):2332–44. doi: 10.1016/j.jcmg.2019.06.031

103. Wang Z, Xiong B, Kang N, Pan X, Wang C, Su L, et al. The value of MR-DWI and T1 mapping in indicating radiation-induced soft tissue injury. *Front Oncol* (2021) 11:651637. doi: 10.3389/fonc.2021.651637

104. Verdijk RM, Pecorella I, Mooy CM. The orbit, including the lacrimal gland and lacrimal drainage system. In: S Heegaard and H Grossniklaus, editors. *Eye pathology: An illustrated guide*. Berlin, Heidelberg: Springer Berlin Heidelberg (2015). p. 547–731.

105. Walcott B, Cameron RH, Brink PR. The anatomy and innervation of lacrimal glands. In: DA Sullivan, editor. *Lacrimal gland, tear film, and dry eye syndromes: Basic science and clinical relevance*. Boston, MA: Springer US (1994). p. 11–8.

106. Bahn RS. Graves' ophthalmopathy. *N Engl J Med* (2010) 362(8):726–38. doi: 10.1056/NEJMra0905750

107. Han JS, Kim SE, Jin JQ, Park NR, Lee JY, Kim HL, et al. Tear-derived exosome proteins are increased in patients with thyroid eye disease. *Int J Mol Sci* (2021) 22(3):1115. doi: 10.3390/ijms22031115

108. Xu N, Cui Y, Fu D, Sun F. Tear inflammatory cytokines and ocular surface changes in patients with active thyroid eye disease treated with high-dose intravenous glucocorticoids. *J Endocrinol Invest* (2020) 43(7):901–10. doi: 10.1007/s40618-019-01174-8

109. Du B, Wang Y, Yang M, He W. Clinical features and clinical course of thyroid-associated ophthalmopathy: A case series of 3620 Chinese cases. *Eye (Lond)* (2021) 35(8):2294–301. doi: 10.1038/s41433-020-01246-7

110. Vehof J, Snieder H, Jansonius N, Hammond CJ. Prevalence and risk factors of dry eye in 79,866 participants of the population-based lifelines cohort study in the Netherlands. *Ocul Surf* (2021) 19:83–93. doi: 10.1016/j.jtos.2020.04.005

111. Dolman PJ. Grading severity and activity in thyroid eye disease. *Ophthalmic Plast Reconstr Surg* (2018) 34(4S Suppl 1):S34–40. doi: 10.1097/IOP.0000000000001150

112. Trokel SL, Jakobiec FA. Correlation of CT scanning and pathologic features of ophthalmic graves' disease. *Ophthalmology* (1981) 88(6):553–64. doi: 10.1016/S0161-6420(81)34993-8

113. Harris MA, Realini T, Hogg JP, Sivak-Callcott JA. CT dimensions of the lacrimal gland in graves orbitopathy. *Ophthalmic Plast Reconstr Surg* (2012) 28 (1):69–72. doi: 10.1097/IOP.0b013e31823c4a3a

114. Bingham CM, Harris MA, Realini T, Nguyen J, Hogg JP, Sivak-Callcott JA. Calculated computed tomography volumes of lacrimal glands and comparison to clinical findings in patients with thyroid eye disease. *Ophthalmic Plast Reconstr Surg* (2014) 30(2):116–8. doi: 10.1097/IOP.0000000000000015

115. Nugent RA, Belkin RI, Neigel JM, Rootman J, Robertson WD, Spinelli J, et al. Graves orbitopathy: Correlation of CT and clinical findings. *Radiology* (1990) 177(3):675–82. doi: 10.1148/radiology.177.3.2243967

116. Rosenbaum JT, Choi D, Wilson DJ, Grossniklaus HE, Harrington CA, Dailey RA, et al. Fibrosis, gene expression and orbital inflammatory disease. *Br J Ophthalmol* (2015) 99(10):1424–9. doi: 10.1136/bjophthalmol-2015-306614

117. Liu X, Ma J, Wang N. Optic nerve. In: N Wang, X Liu and N Fan, editors. *Optic disorders and visual field*. Singapore: Springer Singapore (2019). p. 11–5.

118. Blandford AD, Zhang D, Chundury RV, Perry JD. Dysthyroid optic neuropathy: update on pathogenesis, diagnosis, and management. *Expert Rev Ophthalmol* (2017) 12(2):111–21. doi: 10.1080/17469899.2017.1276444

119. Khong JJ, Finch S, De Silva C, Rylander S, Craig JE, Selva D, et al. Risk factors for graves' orbitopathy; the Australian thyroid-associated orbitopathy research (ATOR) study. *J Clin Endocrinol Metab* (2016) 101(7):2711–20. doi: 10.1210/jc.2015-4294

120. Dolman PJ. Dysthyroid optic neuropathy: Evaluation and management. *J Endocrinol Invest* (2021) 44(3):421–9. doi: 10.1007/s40618-020-01361-y

121. Pau D, Al Zubidi N, Yalamanchili S, Plant GT, Lee AG. Optic neuritis. *Eye (Lond)* (2011) 25(7):833–42. doi: 10.1038/eye.2011.81

122. Rose GE, Vahdani K. Optic nerve stretch is unlikely to be a significant causative factor in dysthyroid optic neuropathy. *Ophthalmic Plast Reconstr Surg* (2020) 36(2):157–63. doi: 10.1097/IOP.0000000000001501

123. Soni CR, Johnson LN. Visual neuropraxia and progressive vision loss from thyroid-associated stretch optic neuropathy. *Eur J Ophthalmol* (2010) 20(2):429–36. doi: 10.1177/112067211002000226

124. Saeed P, Tavakoli Rad S, Bisschop P. Dysthyroid optic neuropathy. *Ophthalmic Plast Reconstr Surg* (2018) 34(4S Suppl 1):S60–S7. doi: 10.1097/IOP.0000000000001146

125. Johnson BT, Jameyfield E, Aakalu VK. Optic neuropathy and diplopia from thyroid eye disease: Update on pathophysiology and treatment. *Curr Opin Neurol* (2021) 34(1):116–21. doi: 10.1097/WCO.0000000000000894

126. Garip-Kuebler A, Halfter K, Reznicek L, Klingenstein A, Priglinger S, Hintschich CR. Subclinical dysthyroid optic neuropathy: Tritan deficiency as an early sign of dysthyroid optic neuropathy. *Br J Ophthalmol* (2021) 105(7):1019–23. doi: 10.1136/bjophthalmol-2020-316433

127. Wu Y, Tu Y, Wu C, Bao L, Wang J, Lu F, et al. Reduced macular inner retinal thickness and microvascular density in the early stage of patients with dysthyroid optic neuropathy. *Eye Vis (Lond)* (2020) 7:16. doi: 10.1186/s40662-020-00180-9

128. Barrett L, Glatt HJ, Burde RM, Gado MH. Optic nerve dysfunction in thyroid eye disease: CT. *Radiology* (1988) 167(2):503–7. doi: 10.1148/radiology.167.2.3357962

129. Rutkowska-Hinc B, Maj E, Jablonska A, Milczarek-Banach J, Bednarczuk T, Miskiewicz P. Prevalence of radiological signs of dysthyroid optic neuropathy in magnetic resonance imaging in patients with active, moderate-to-Severe, and very severe graves orbitopathy. *Eur Thyroid J* (2018) 7(2):88–94. doi: 10.1159/000486828

130. Wang L, Yuan J, Zhang SJ, Gao M, Wang YC, Wang YX, et al. Myocardial T1 rho mapping of patients with end-stage renal disease and its comparison with T1 mapping and T2 mapping: A feasibility and reproducibility study. *J Magn Reson Imaging* (2016) 44(3):723–31. doi: 10.1002/jmri.25188

131. Zhai L, Wang Q, Liu P, Luo B, Yuan G, Zhang J. T2 mapping with and without fat-suppression to predict treatment response to intravenous glucocorticoid therapy for thyroid-associated ophthalmopathy. *Korean J Radiol* (2022) 23(6):664–73. doi: 10.3348/kjr.2021.0627

132. Hu H, Chen HH, Chen W, Wu Q, Chen L, Zhu H, et al. T2 mapping histogram at extraocular muscles for predicting the response to glucocorticoid therapy in patients with thyroid-associated ophthalmopathy. *Clin Radiol* (2021) 76 (2):159 e1– e8. doi: 10.1016/j.crad.2020.09.005

133. Song X, Liu Z, Li L, Gao Z, Fan X, Zhai G, et al. Artificial intelligence CT screening model for thyroid-associated ophthalmopathy and tests under clinical conditions. *Int J Comput Assist Radiol Surg* (2021) 16(2):323–30. doi: 10.1007/s11548-020-02281-1

134. Lin C, Song X, Li L, Li Y, Jiang M, Sun R, et al. Detection of active and inactive phases of thyroid-associated ophthalmopathy using deep convolutional neural network. *BMC Ophthalmol* (2021) 21(1):39. doi: 10.1186/s12886-020-01783-5

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Long-term follow-up of surgical treatment of thyroid-associated orbitopathy restrictive strabismus

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Objective: Thyroid-associated orbitopathy (TAO) is the most frequent cause of extraocular muscle enlargement, with consecutive restrictive strabismus. The main muscles involved are inferior and medial rectus, resulting in horizontal esotropia and/or vertical strabismus. Surgery may either establish or improve binocular single vision. The aim of the present study is to describe long-term follow-up of patients who underwent horizontal or vertical TAO strabismus surgery.

Methods: This observational retrospective study included 29 patients suffering from either vertical or horizontal TAO strabismus and diplopia, of whom 11 underwent bilateral medial recti muscle recession (Group A) and 18 underwent unilateral inferior rectus muscle recession (Group B). The endpoint of the study was the assessment of changes in deviation angle and diplopia across four time points (baseline, 7 days, 6 months, and 24 months) in each group.

Results: In Group A, the horizontal deviation angle significantly decreased 7 days after intervention ($p < 0.001$), without modifications overtime. In Group B, both deviation angles in primary and down-gaze position significantly decreased from baseline, both 7 days after surgery ($p < 0.001$) and at 6 months ($p = 0.040$). An overcorrection, with an inversion of vertical deviation angle, was observed across the different time points.

Conclusions: Horizontal TAO strabismus correction leads to significant improvements of deviation angle and diplopia, with a stable undercorrection overtime. Inferior rectus recession leads to more unstable results, with a trend towards overcorrection limited to the first 6 months after surgery.

KEYWORDS

thyroid associated orbitopathy, muscle recession, diplopia, strabismus in TAO surgery, restrictive strabismus treatment

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Introduction

Thyroid-associated orbitopathy (TAO) is the most frequent cause of either single or multiple extraocular muscle (EOM) enlargement at the core of restrictive strabismus (1).

Active TAO is characterized by inflammation and infiltration of orbital tissues by immune cells (T lymphocytes, mast cells, and B lymphocytes) and orbital remodeling, which gradually stabilizes and leads to the inactive phase of the disease (2).

EOMs are the major site of the disease process, and the impairment of ocular motility is caused by inflammation, followed by relatively rapid fibrosis of the involved muscles, with subsequent reduced elasticity and usually preserved muscle contractility (3).

The inferior rectus and medial rectus muscles are the most commonly involved, resulting in horizontal esotropia and/or vertical strabismus.

Surgery mainly aims either to establish or to improve the binocular single vision field (BSVF) in primary gaze and reading position. In addition, the evaluation of fusional vergences would be useful to predict the chance of postoperative compensation of possible hypo- or hypercorrection (4).

Unfortunately, achieving an optimal outcome may be challenging, especially in patients with combined horizontal and vertical deviations (5–8). The success rate of strabismus surgery in TAO patients is extremely variable and reported reoperation rate is approximately 45% of cases (7, 9, 10).

Undercorrection is the most common reported complication of horizontal strabismus correction (11, 12), and late overcorrection may occur after inferior rectus recession (8, 13).

Only a few studies have assessed the long-term effects of surgical treatment of TAO associated with strabismus in subsets of patients with thyroid function within the reference ranges, although they separately assess horizontal and vertical treatment (9, 11). The aim of the present study is to describe the long-term follow-up of patients submitted to either horizontal or vertical TAO strabismus surgery. Postoperative motor and sensory outcomes, and margin reflex distance 2 (MRD2) in patients submitted to inferior rectus weakening were also assessed.

Materials and methods

Study design and population

This observational retrospective cohort study included all patients suffering from either vertical or horizontal TAO strabismus and diplopia and surgically treated at the Ophthalmology Unit of the Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome (Italy), between 1 January 2011 and 31 January 2016.

Patients previously medically or surgically treated, decompressed, with a follow-up period of less than 48 months, as well as subjects with either missing or incomplete records were excluded.

All patients signed a written informed consent to use their data for research aims. Photographs were obtained in selected cases with patients' permission. The study was carried out with approval from the Head and Neck Institutional Review Board (approval ID; 18/2020) and in accordance with the 1976 Declaration of Helsinki and its later amendments.

Procedures

All patients underwent a complete orthoptic and ophthalmological assessment, including best-corrected visual acuity (BCVA) measurement, near (33 cm) and far (6 m) prism and alternating cover test (PACT), and ocular motility evaluation.

Divergence and convergence fusional amplitudes (FAs) were measured, when possible, at distance and at near fixation through the full optical correction. An accommodative target was used first at distance (6 m) and then at near (33 cm). Starting from the base-out or base-up or down prisms totally compensating the deviation, base-out prisms of decreasing power and of increasing power were used to measure divergence and convergence FA, respectively. All surgical procedures were performed in our clinic by two experienced surgeons (GS and AS).

Forced duction test (FDT) was performed intraoperatively, before surgery, under general anesthesia. The eye was moved with two-toothed forceps applied to the conjunctiva at the limbus towards the opposite direction to that in which mechanical restriction was suspected. To evaluate the presence of mechanical restriction involving the inferior rectus, forceps were applied at the 3- and 9-o'clock positions, and the eye was moved in sursumduction (i.e., upward rotation of an eye).

All patients underwent intraoperative relaxed muscle positioning technique. Muscles were recessed to the positions where they rested freely on the globe without tension; absorbable not adjustable sutures were placed. The conjunctiva was further recessed. Moreover, an infratarsal lower eyelid retractor lysis was performed at the same time as inferior rectus muscle recession to reduce the chance of lower eyelid retraction.

Endpoints

The primary endpoint of the study was the assessment of deviation angle modifications at a 2-year follow-up, across four time points (baseline, 7 days, 6 months, and 24 months) in the two subgroups, i.e., patients who underwent bilateral medial rectus recession (Group A) and patients who underwent

unilateral inferior rectus recession (Group B). As secondary endpoints, changes in postoperative motor and sensory outcomes (i.e., all types of diplopia) were assessed. Also, only in patients submitted to inferior rectus weakening (Group B) were MRD2 changes at 6 months also evaluated.

Statistical analysis

All variables were first analyzed by descriptive statistic techniques. In-depth, qualitative variables were described as absolute and percentage frequencies. The Shapiro–Wilk test was applied to assess the distribution of quantitative variables. Data were then expressed either as mean and standard deviation (SD), whether normally distributed, or as median and interquartile range (IQR), otherwise.

Between groups, differences were assessed by the Fisher exact test or the Chi-squared test, with Yates correction, as appropriate, on qualitative variables. Quantitative data, indeed, were evaluated, either by the Student's *t*-test or the non-parametric Mann–Whitney *U* test.

Changes in the deviation angle across the four time points (baseline, 7 days, 6 months, and 24 months) in each subgroup were instead analyzed either by an ANOVA for repeated measures or Friedman test. MRD2 modification at 6 months from pre-surgery in Group B was instead assessed by a paired Student's *t*-test, due to the Gaussian distribution of the data. Finally, modifications in all forms of diplopia since the immediate post-surgery (7 days *vs*. 6 months and 7 days *vs*. 24 months) in each subgroup were instead assessed by the McNemar or the Cochran *Q* tests, as appropriate. Data of pre-surgery were not considered, as all of the patients had diplopia.

A p-value <0.05 was considered as statistically significant. All analyses were performed by using R software version 4.1.2 (CRAN ®, R Core 2021) and STATA version 16 (STATA Corp).

Results

Twenty-nine patients were included in the study: 11 underwent bilateral medial recti muscle recession and 18 underwent unilateral inferior rectus muscle recession.

The two subgroups were homogeneously distributed as for age and sex, as well as for smoking habit and hormonal compensation. Thyroid hormone levels were within the normal range in 72.7% of patients of Group A and in 94.4% patients of Group B. All patients had thyroidectomy/radioactive iodine treatment, except from three in Group A, treated with anti-thyroid drugs.

As for diplopia, this was present in all patients in the constant form. Focusing on Group B, diplopia associated with vertical inferior deviation angle was constant in 14 of 18 cases (77.8%).

At 7 days since operation, divergence and convergence FA for near and for distance were measured, with insignificant difference between the two subgroups. All data are reported in Table 1.

Looking at deviation angle modifications across the four time points, as for Group A, the horizontal angle deviation in primary position (P.P.) significantly reduced from baseline ($p < 0.001$). A significant reduction occurred 7 days after surgery (46 ± 23.7 *vs*. 14.9 ± 14.3, $p < 0.001$), while the reduction then leveled off at 6 and 24 months, respectively. In Group B, instead, the vertical angle in P.P. also significantly decreased from baseline ($p < 0.001$). A significant reduction occurred both 7 days after surgery (24.3 ± 8.3 *vs*. 2.2 ± 3.2, $p < 0.001$) and between 7 days and 6 months (2.2 ± 3.2 *vs*. 0.6 ± 3.3, $p = 0.040$). As for the down-gaze position (D.P.), we observed a similar behavior. An inversion (right/left or left/right) of deviation angle in P.P. was observed in two patients at 7 days, in five patients at 6 months, and in seven patients at 24 months. In D.P., at 7 days, 5 patients showed an inversion of the vertical angle of deviation; at 6 months, 11 patients; and at 24 months, 12 patients. The whole data are reported in Table 2 and Figure 1. Moreover, in this latter subgroup, MRD2 significantly increased 6 months after operation as compared to pre-surgery (mean 5.9 mm ± 0.8 *vs*. 3.5 ± 1.1, $p < 0.001$), as reported in Figure 2.

At baseline, as aforementioned, all patients were characterized by diplopia, independent from the type of treatment. In Group A, in all cases, diplopia at baseline was constant, as well as in P.P. in Group B, while as for D.P., diplopia was inconstant in 4 of 18 cases. Diplopia cases reduced in both subgroups throughout the different time points, even though, as reported in Tables 3 and 4, no significant difference emerged at 6 and 24 months as compared to immediately post-surgery (Figure 3).

In Group A, postoperative constant diplopia was observed in six patients, in two of whom, diplopia was treatable with prisms at 7 days; in the remaining four cases, the diplopia in three cases was treatable with prisms at 24 months. In Group B, constant diplopia did not occur at 7 days while six patients complained about inconstant diplopia in P.P. and in D.P., all of them corrigible with prisms. Two patients showed constant diplopia in D.P. at 6 and 24 months, corrigible with prisms. In P.P., one patient complained about constant diplopia, treatable with prisms at 6 months, which improved over time (at 24 months) (see Tables 3, 4, Figure 3).

Discussion

Approximately 0.6%–20% of patients with TAO will require strabismus surgery (6, 7). Although strabismus surgery aims to restore binocular single vision (BSV), an optimal outcome would be challenging to obtain (6, 7, 14).

TABLE 1 Baseline general characteristics of the study cohort (n = 29).

	Group A(n = 11)	Group B(n = 18)	p
Age (years), mean (SD)	56.9 (12.4)	53.4 (13.5)	
Sex, n (%) M F	5 (45.5) 6 (54.5)	6 (33.3) 12 (66.7)	0.514
Smoking habit, n (%)	5 (45.5)	7 (38.9)	0.728
Hormonal compensation, n (%)	8 (72.7)	17 (94.4)	0.100
Treatment with tapazole, n (%)	3 (27.3)	–	0.019
Horizontal deviation angle, mean (SD)	46.0 (23.7)	–	n.a.
Diplopia, n (%) Constant Inconstant	11 (100) -	–	n.a.
Vertical angle deviation in P.P., mean (SD)	–	24.3 (8.3)	n.a.
Diplopia, n (%) Constant Inconstant	–	18 (100) -	n.a.
Vertical angle deviation in D.P., mean (SD)	–	15.8 (6.4)	n.a.
Diplopia, n (%) Constant Inconstant	- -	14 (77.8) 4 (22.2)	n.a.
7 days			
CFA for near	16.2 (5.8)	20.1 (7.2)	0.118
CFA for distance	9.5 (4.7)	12.9 (6.5)	0.111
DFA for near	5.3 (2.4)	5.1 (2.7)	0.868
DFA for distance	3.5 (3.0)	5.3 (3.9)	0.158

M, male; F, female; P.P., primary position; D.P., down-gaze position; SD, standard deviation; CFA, convergence fusional amplitude; DFA, divergence fusional amplitude. n.a. = not applicable.

Surgery is primarily focused on either establishing or improving BSVF in primary gaze and reading position. In such context, the evaluation of fusional vergences may be useful to predict the chance of postoperative compensation of potential hypo- or hypercorrection.

Prior to surgery, the angle of deviation should be stable for at least 4 to 6 months. Moreover, the thyroid function should be within the reference range and orbitopathy was inactive. In fact, operating during the active phase of TAO usually results in significant instability in surgical outcomes (15, 16).

Patients should be informed thoroughly to have realistic expectations. Likely more than one operation is needed. After strabismus surgery, BSV may be achieved only in primary and reading positions, proptosis may increase, and the lid lag might worsen (17). The frequency of reoperation in adults with TAO strabismus is relatively high, up to 26% (18, 19).

Undercorrection is the most common reported complication of horizontal strabismus correction, but simultaneous conjunctiva and Tenon's recession seems to improve the outcome (11, 12, 20). Late overcorrection may occur instead after inferior rectus recession. A postoperative mean drift toward overcorrection (from 1.9^{Δ} to 3^{Δ}) has been described (8, 13). Several elements have been reported as significant prognostic factors for postoperative overcorrection, including duration and severity of orbitopathy, impaired contralateral elevation, and underestimation of increased ipsilateral superior rectus tone

TABLE 2 Changes in angle deviation at the three time points after surgery in the two subgroups (n = 29).

Group A (n = 11)	**Baseline**	**7gg**	**6 months**	**24 months**	$p^{overall}$	$p^{(pre\text{-}7\ gg)}$	$p^{(7gg\text{–}6\ m)}$	$p^{(6m\text{–}24m)}$
Horizontal angle deviation in P.P., mean (SD)	46 (23.7)	14.9 (14.3)	13.6 (12.4)	8.4 (5.9)	<0.001	<0.001	0.381	0.055
Group B (n = 18)								
Vertical angle deviation in P.P., mean (SD)	24.3 (8.3)	2.2 (3.2)	0.6 (3.3)	−0.9 (3.2)	<0.001	<0.001	0.040	0.089
Vertical angle deviation in D.P., mean (SD)	15.8 (6.4)	0.3 (3.5)	−2.4 (3.7)	−3.4 (3.0)	<0.001	<0.001	0.002	0.453

P.P., primary position; D.P., down-gaze position; SD, standard deviation.

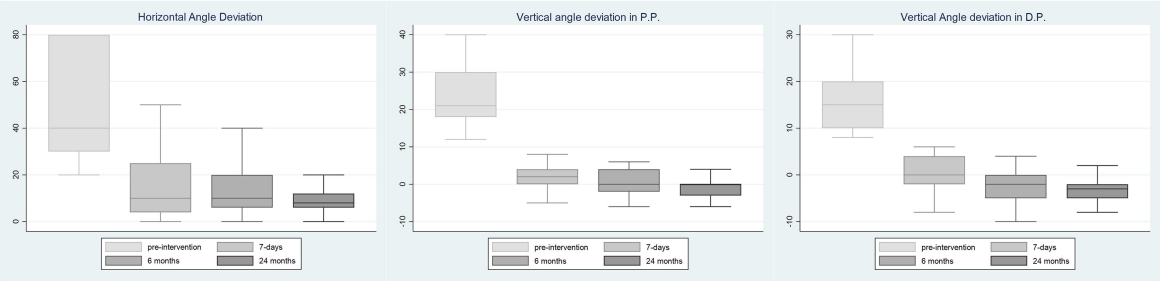

FIGURE 1
Deviation angle at four time points. Deviation angle modifications at 7 days, 6 months, and 24 months, with respect to pre-surgery in Group A and Group B, respectively. P.P., Primary Position; D.P., Down-Gaze Position.

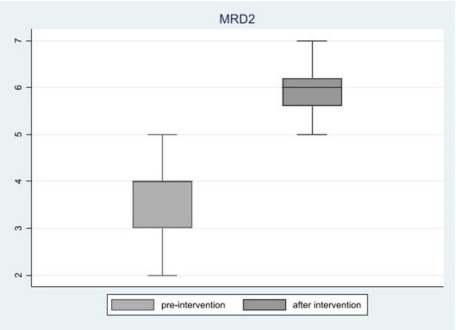

FIGURE 2
MRD2. MRD2 changes 6 months after surgery in Group B. MRD2: Margin Reflex Distance - 2.

(21). Moreover, the progression of underlying thyroid myopathy after strabismus surgery, even in cases with a stable angle of deviation for 6 months, may result in late postoperative instability of deviation. In addition, anatomical causes, as well as an inadequate muscle scleral fixation, may lead to either muscle slippage or posterior shifting of inferior rectus scleral insertion. Predisposing factors for these postoperative complications are the gravitational forces, the short arc of contact of inferior rectus muscle, and the thickened tenon beneath the inferior rectus muscle in TAO patients (22).

Down-gaze diplopia due to an early or late inferior rectus under-action, with vertical strabismus in down-gaze after inferior rectus weakening, is usually poorly tolerated. The reversal of angle deviation has been often related to an overlooked preoperative incomitance between primary position and down-gaze, often the result of the mechanical

TABLE 3 Changes in diplopia at 6 and 24 months as compared to 7 days after surgery in the two subgroups (n = 29).

Group A (n = 11)		**6 months**				**24 months**		
7 days	Absent	Constant	Inconstant	p	Absent	Constant	Inconstant	p
Diplopia, n (%)	2	0	1	0.368	2	-	1	0.223
Absent	0	5	1		0	4	2	
Constant	0	0	2		0	0	2	
Inconstant								
Group B (n = 18)								
P.P.								
Diplopia, n (%)	12	-	-	0.500	10	-	2	0.453
Absent	-	-	-		-	-	-	
Constant	2	1	3		5	-	1	
Inconstant								
D.P.								
Diplopia, n (%)	9	1	2	1.000	9	1	2	1.000
Absent	-	-	-		-	-	-	
Constant	4	1	1		4	1	1	
Inconstant								

P.P., primary position; D.P., down-gaze position.

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TABLE 4 Changes in diplopia treatable with prisms at 6 and 24 months as compared to 7 days after surgery in the two subgroups (n = 29).

Group A (n = 11)	**6 months**			**24 months**		
7 days	Yes	No	p	Yes	No	p
Diplopia treatable with prisms, n (%)	4	-	1.000	4	-	0.125
Yes	1	6		4	3	
No						
Group B (n = 18)						
P.P.						
Diplopia treatable with prisms, n (%)	4	2	0.500	1	5	0.219
Yes	-	12		1	11	
No						
D.P.						
Diplopia treatable with prisms, n (%)	1	4	1.000	1	4	1.000
Yes	3	10		4	9	
No						

P.P., primary position; D.P., down-gaze position.

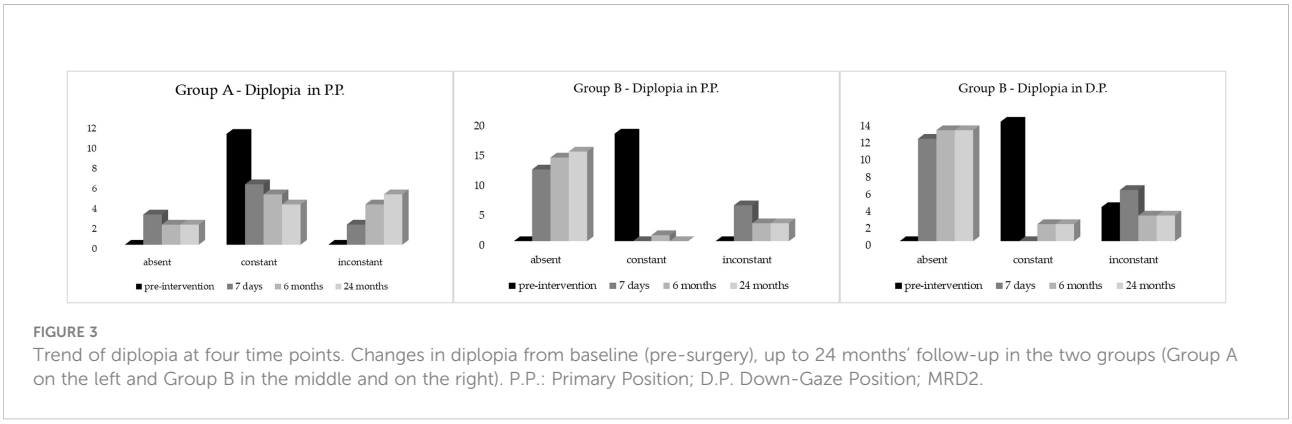

FIGURE 3
Trend of diplopia at four time points. Changes in diplopia from baseline (pre-surgery), up to 24 months' follow-up in the two groups (Group A on the left and Group B in the middle and on the right). P.P.: Primary Position; D.P. Down-Gaze Position; MRD2.

imbalance between opposing muscle groups (23). Moreover, inferior rectus muscle recession tends to retract the lower eyelid due to the anatomical connections with Lockwood ligament and lower eyelid retractors. Several surgical techniques have been recommended to correct lower lid retraction (24).

In Group A, an immediate significant improvement of the horizontal angle deviation was observed from baseline at 7 days from surgery without modification over time. A further but not significant decrease was, however, observed at 6 and 24 months. The result, in agreement with the data reported by some authors, and despite the simultaneous conjunctiva and Tenon's recession, is an undercorrection relatively stable over time (11, 12, 20). In Group B, a significant reduction of the angle of deviation in P.P. and in D.P. was observed 7 days after surgery, with a further significant reduction at 6 months with an overcorrection and an inversion right/left or left/right of the angle of deviation in some cases mainly in D.P. (Figure 1). The angle leveled off 6 months after surgery without significant further modification at 24 months in P.P. and D.P. The tendency toward overcorrection, as already reported after inferior rectus recession, seems limited to the first 6 months post-surgery with subsequent stabilization of the angle of deviation.

Despite the infratarsal lower eyelid retractor lysis, performed simultaneously with inferior rectus muscle recession, a significant increase in MRD2 was observed at 6 months after surgery with a significant lower eyelid ptosis and scleral show. The preoperative values are nevertheless below the normal range (4–5 mm) as a result of a forced down-gaze eye position (25).

As expected, a significant post-surgical treatment improvement of diplopia was observed in both groups and, in Group B, also in D.P. Often the diplopia after surgery was absent or inconstant and treatable with prisms without significant modification over time except for four cases in Group A that complained of constant diplopia at 24 months; of these, three were treatable with prisms, and two cases in Group B that showed constant diplopia were treatable with prisms.

The patients with constant diplopia were later reoperated on and the reoperation rate was of 4 out 11 (36.6%) cases in Group A and 2 out 18 (11.1%) cases in Group B (constant diplopia in D.P.) according to other reports (18, 19).

In conclusion, when we look at the horizontal and vertical surgery of TAO strabismus separately, the result is an undercorrection relatively stable over time for horizontal surgery and a good immediate response with an overcorrection, within and not later than 6 months, for vertical strabismus. The horizontal surgery has a higher reoperation rate and the lower eyelid ptosis is a significant functional and aesthetic complication of inferior rectus weakening. This study has some limitations, mainly the retrospective nature of the study and its relatively small sample size. Further prospective and hopefully multicentric studies are needed to validate our results.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: https://github.com/piaclarapafundi/TAO-STRABISMUS.git.

Ethics statement

The studies involving human participants were reviewed and approved by the Head and Neck Institutional Review Board (approval ID; 18/2020). The patients/participants provided their written informed consent to participate in this study.

Author contributions

GS conceived and designed the work, played an important role in interpreting the results, revised the manuscript, and approved the final version. RM acquired data, drafted the manuscript, and approved the final version. AS acquired data, drafted the manuscript, and approved the final version. CF acquired data, played an important role in interpreting the results, revised the manuscript, and approved the final version. PP designed the work, revised the manuscript, and approved the final version. All authors contributed to the article and approved the submitted version.

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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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References

1. Savino G, Petrone G, Volpe G, Midena G, Grimaldi G, Fiorentino V, et al. Vertical restrictive strabismus associated with proptosis: Similar clinical signs, different etiopathogenetic causes. *A Rep three patients Eur J Ophthalmol* (2020) 28:1120672120946929. doi: 10.1177/1120672120946929

2. Garrity JA, Bahn RS. Pathogenesis of graves ophthalmopathy: implications for prediction, prevention, and treatment. *Am J Ophthalmol* (2006) 142(1):147–53. doi: 10.1016/j.ajo.2006.02.047

3. Bahn RS. Current insights into the pathogenesis of graves' ophthalmopathy. *Horm Metab Res* (2015) 47(10):773–8. doi: 10.1055/s-0035-1555762

4. Eckstein A, Esser J, Oeverhaus M, Saeed P, Jellema HM. Surgical treatment of diplopia in graves orbitopathy patients. *Ophthalmic Plast Reconstr Surg* (2018) 34 (4S Suppl 1):S75–84. doi: 10.1097/IOP.0000000000001148

5. Akbari MR, Mirmohammadsadeghi A, Mahmoudzadeh R, Veisi A. Management of thyroid eye disease-related strabismus. *J Curr Ophthalmol* (2020) 32(1):1–13. doi: 10.1016/j.joco.2019.10.002

6. Rajendram R, Bunce C, Adams GG, Dayan CM, Rose GE. Smoking and strabismus surgery in patients with thyroid eye disease. *Ophthalmology* (2011) 118 (12):2493–7. doi: 10.1016/j.ophtha.2011.06.003

7. Jellema HM, Saeed P, Mombaerts I, Dolman PJ, Garrity J, Kazim M, et al. Objective and subjective outcomes of strabismus surgery in graves' orbitopathy: a prospective multicentre study. *Acta Ophthalmol* (2017) 95(4):386–91. doi: 10.1111/aos.13367

8. Honglertnapakul W, Cavuoto KM, McKeown CA, Capó H. Surgical treatment of strabismus in thyroid eye disease: characteristics, dose-response, and outcomes. *J AAPOS.* (2020) 24(2):72.e1–7. doi: 10.1016/j.jaapos.2019.12.014

9. Volpe NJ, Mirza-George N, Binenbaum G. Surgical management of vertical ocular misalignment in thyroid eye disease using an adjustable suture technique. *J AAPOS.* (2012) 16(6):518–22. doi: 10.1016/j.jaapos.2012.08.010

10. Laezza MP, Concilio M, Giordano M, Lanni V, Iuliano A, Strianese D. Outcomes and risk factors of surgical management of thyroid eye disease-related diplopia. *Eur J Ophthalmol* (2022) 32(6):3679–84. doi: 10.1177/11206721221083836

11. Lyu IJ, Lee JY, Kong M, Park KA, Oh SY. Surgical responses of medial rectus muscle recession in thyroid eye disease-related esotropia. *PloS One* (2016) 11(1): e0146779. doi: 10.1371/journal.pone.0146779

12. Jellema HM, Saeed P, Braaksma-Besselink Y, Schuit A, Kloos R, Mourits MP, et al. Unilateral and bilateral medial rectus recession in graves'

orbitopathy patients. *Strabismus* (2014) 22(4):182–7. doi: 10.3109/09273972.2014.962749

13. Jimenez-Chobillon MA, Lopez-Oliver RD. Transnasal endoscopic approach in the treatment of graves ophthalmopathy: the value of a medial periorbital strip. *Eur Ann Otorhinolaryngol Head Neck Dis* (2010) 127(3):97–103. doi: 10.1016/j.anorl.2010.04.005

14. Bartley GB, Fatourechi V, Kadrmas EF, Jacobsen SJ, Ilstrup DM, Garrity JA, et al. The treatment of graves' ophthalmopathy in an incidence cohort. *Am J Ophthalmol* (1996) 121(2):200–6. doi: 10.1016/s0002-9394(14)70585-9

15. Coats DK, Paysse EA, Plager DA, Wallace DK. Early strabismus surgery for thyroid ophthalmopathy. *Ophthalmology* (1999) 106(2):324–9. doi: 10.1016/S0161-6420(99)90071-4

16. Thomas SM, Cruz OA. Comparison of two different surgical techniques for the treatment of strabismus in dysthyroid ophthalmopathy. *J AAPOS.* (2007) 11(3):258–61. doi: 10.1016/j.jaapos.2006.10.021

17. Gomi CF, Yang SW, Granet DB, Kikkawa DO, Langham KA, Banuelos LR, et al. Change in proptosis following extraocular muscle surgery: effects of muscle recession in thyroid-associated orbitopathy. *J AAPOS.* (2007) 11(4):377–80. doi: 10.1016/j.jaapos.2007.01.115

18. Mocan MC, Ament C, Azar NF. The characteristics and surgical outcomes of medial rectus recessions in graves' ophthalmopathy. *J Pediatr Ophthalmol Strabismus* (2007) 44(2):93–119. doi: 10.3928/01913913-20070301-02

19. Ha SG, Kim SH. Initial postoperative alignment in strabismus related to thyroid eye disease. *J Pediatr Ophthalmol Strabismus* (2021) 58(1):23–7. doi: 10.3928/01913913-20200910-04

20. Scofield-Kaplan SM, Dunbar K, Stein G, Kazim M. Improvement in both primary and eccentric ocular alignment after thyroid eye disease-strabismus surgery with tenon's recession. *Ophthalmic Plast Reconstr Surg* (2018) 34(4S Suppl 1):S85–9. doi: 10.1097/IOP.0000000000001143

21. De Hoog J, Stravers S, Kalmann R. Recession of the inferior rectus muscle in graves' orbitopathy. *Eye (Lond)* (2010) 24(6):1011–7. doi: 10.1038/eye.2009.267

22. Chatzistefanou KI, Kushner BJ, Gentry LR. Magnetic resonance imaging of the arc of contact of extraocular muscles: implications regarding the incidence of slipped muscles. *J AAPOS.* (2000) 4(2):84–93. doi: 10.1067/mpa.2000.103434

23. Kushner BJ. Management of diplopia limited to down gaze. *Arch Ophthalmol* (1995) 113(11):1426–30. doi: 10.1001/archopht.1995.01100110086030

24. Akbari MR, Raygan F, Ameri A, Jafari A, Eshraghi B, Fard MA. Lower eyelid retractor lysis versus Lockwood advancement to minimize lower eyelid retraction resulting from inferior rectus muscle recession. *J AAPOS* (2013) 17(4):445–7. doi: 10.1016/j.jaapos.2013.04.003

25. Koka K, Patel BC. Ptosis correction. In: *StatPearls*. Treasure Island (FL: StatPearls Publishing (2021). p. 30969650.

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Thyroid eye disease or Graves' orbitopathy: What name to use, and why it matters

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There is currently no universally accepted name for inflammatory disease of the eye and orbit associated with thyroid autoimmune disease. Variability in terminology impedes the evaluation of scientific literature and clinical collaboration and can affect patients' understanding of a disease process. The goals of this perspective article are 1. To compare the frequency of different terms used for eye disease associated with autoimmune thyroid disease in the scientific literature between 2000, 2010 and 2020 publications; 2. To investigate potential associations of terminology with author and journal specialty, and multidisciplinary vs. mono-disciplinary author teams; 3. To determine preferential terms used by professional societies; and 4. To propose standardized terminology based on our data analysis. The methods for this study included review of all English language articles listed in PubMed, with publication dates in the years 2000, 2010 and 2020, that included one of 6 terms currently used to describe eye disease associated with autoimmune thyroid disease. Characteristics pertaining to authors, journals, and article type were recorded. Results showed that the most used term in the 2000 literature was Graves' Ophthalmopathy (61%). In the 2010 literature, Graves' Orbitopathy (31%) became most common, followed by Graves' Ophthalmopathy (30%). Between 2010 and 2020, thyroid eye disease (37%) became the most common term, followed by Graves' Orbitopathy (35%). This perspective article proposes "thyroid eye disease" (TED) as the preferred name for this entity and discusses supporting terminology patterns and trends over time in scientific literature and in professional societies.

KEYWORDS

thyroid eye disease, graves, orbitopathy, ophthalmopathy, TED

Introduction

Standardization of medical terminology is crucial to facilitate the evaluation of scientific literature, ensure accuracy of diagnostic parameters and reported outcomes, and allow for multi-center collaboration. In addition, patients' understanding of a disease process and treatment decisions can be impacted by terminology changes (1). Results of

standardization efforts are frequently published as practice guidelines or consensus reports by large specialty groups (2, 3). There are little published data on terminology for inflammatory disease of the eye and orbit associated with thyroid autoimmune disease. Currently used terms include thyroid eye disease (TED), Graves' orbitopathy, thyroid-associated orbitopathy, Graves' ophthalmopathy, Graves eye disease and Basedow disease.

Ideally, terminology for a medical condition appropriately describes the involved anatomical structures and disease process, allows clinicians to differentiate the diagnosis from similar entities, and can be understood by patients and other specialties alike. This perspective article summarizes terminology patterns in the existing body of scientific literature and proposes the adoption of "Thyroid Eye Disease" (TED) as standardized terminology for the inflammatory disease of the eye and orbit associated with thyroid autoimmunity.

Methods

To determine the terminology use in the scientific literature for the inflammatory disease of the eye and orbit associated with thyroid autoimmunity, we searched all 2000, 2010 and 2020 publications indexed in the PubMed database for 6 keywords. The keywords were: Thyroid eye disease, thyroid ophthalmopathy, thyroid orbitopathy, Graves or Graves' ophthalmopathy, Graves or Graves' orbitopathy, and Graves' eye disease. The search was performed with temporal limits and two 10-year intervals in order to generate a trend for the utilization of these terms. In addition to the predominant terminology used in the title and abstract, we then recorded authors' characteristics including primary specialty, as well as the composition of the team as single specialty or multidisciplinary. We also recorded journal specialty and article type. Articles where these variables could not be determined were excluded.

We then also reviewed the terminology used by the professional societies that have a dedicated interest in this field (AAO, ATA, EUGOGO, ETA, ITEDS), and identified the terms that they have used in their official statements or guidelines over the same period.

IRB review was not needed since no protected health information was involved in this study.

Results

- Terminology trends in the literature from 2000 to 2020:

The overall number of search results included in analysis increased from 77 in 2000 to 299 in 2020 (Figure 1), an increase of 388%. The 3 most commonly used terms in the 2000 literature were Graves' Ophthalmopathy (61%), Graves' Orbitopathy (12%) and Thyroid- (Associated) Ophthalmopathy (9%). This changed in 2010 to Graves' Orbitopathy (31%), Graves' Ophthalmopathy (30%) and Thyroid Eye Disease (22%). Popularity of the 3 most commonly used terms changed again from 2010 to 2020, when the predominantly used term was TED (37%), followed by Graves' Orbitopathy (35%) and Graves' Ophthalmopathy (20%).

- Impact of author specialty and journal-intended audience:

In endocrinology journals, Graves' Ophthalmopathy was the predominant term in 2000 (84%), taken over by Graves' Orbitopathy in 2010 (47%) and 2020 (67%) as shown in Table 1. Use of Graves' Ophthalmopathy decreased at those 2 more recent time points (32% and 18%), and TED was used infrequently in 2000, 2010 and 2020 (8%, 2.6% and 12%, respectively). Similarly, the most commonly used term in ophthalmology journals in 2000 was Graves' Ophthalmopathy (46%). In 2010 and 2020, this changed to TED (30% and 57%), followed by Graves' Orbitopathy (25% and 16%) and Graves' Ophthalmopathy (23% and 16%). In publications with endocrinologist and ophthalmologist senior authors, respective terminology trends were similar to patterns in journals of those specialties (Table 1 and Figures 1B, C). Publications by multidisciplinary author teams showed a steady increase in use of TED from 2000 to 2010 and 2020 (9% to 23% to 32%), an initial large drop with recent stabilization for Graves' Ophthalmopathy (64% to 21% to 25%) and predominant but in the recent decade decreasing use of Graves' Orbitopathy (11% to 42% to 38%).

- Changes in terminology used by professional societies:

To determine consensus trends, we studied terminology use in publications and on websites of 5 large professional societies: AAO, ATA, EUGOGO, ETA, ITEDS. Detailed data are displayed in Supplementary Table 1. In the most recently published statements and guidelines, 4 out of the 5 societies used TED, while EUGOGO used Graves' Orbitopathy. The AAO, ATA and ETA used Graves' orbitopathy and Graves ophthalmopathy in earlier publications. In some cases, multiple terms are used in the same paragraph on current websites, which underscores the lack of consistency even within a single professional organization.

Discussion

Our review of the literature shows that there is a trend for increasing use of TED by medical societies and ophthalmologists, while Graves' orbitopathy remains the most likely used term by endocrinologists. Medical terminology is determined by convention and practice guideline recommendations, and may be modified based on new research findings, better understanding of the disease process, or to improve communication between specialties and with patients.

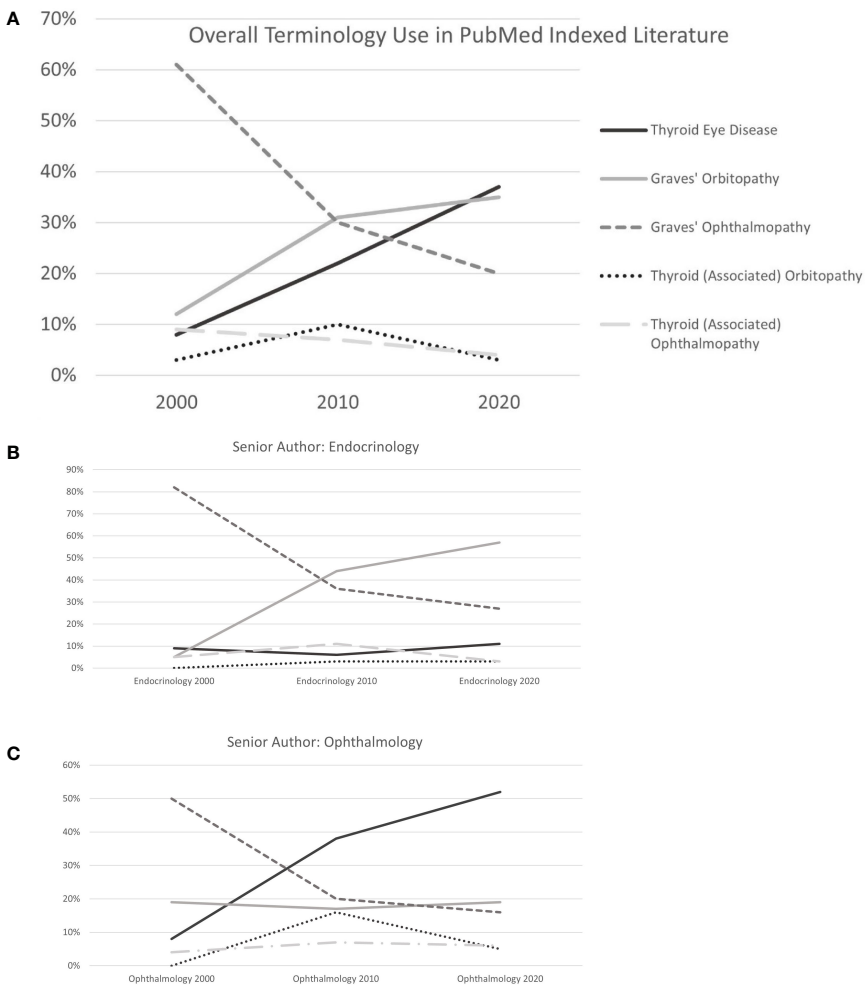

FIGURE 1
(A) Terminology Use Overall. **(B)** Terminology Use by Endocrinologists. **(C)** Terminology Use by Ophthalmologists.

Why Graves orbitopathy or ophthalmopathy is a problematic term:

The inflammatory disease of the eye and orbit associated with thyroid autoimmunity is a complex condition that mainly affects orbital tissues including extraocular muscles and fat, but can also cause pathology of eyelids, conjunctiva, cornea, optic nerve and retina (4–6). While most cases occur in the setting of the autoimmune hyperthyroidism caused by Graves' disease, about 10% of patients will not be hyperthyroid at the time of the ophthalmic diagnosis (7), either because of sequential onset of eye and thyroid involvement, complete lack of functional thyroid abnormalities or in patients who develop eye disease associated with autoimmune hypothyroidism (8). In contrast to this reality, the eponym "Graves" as part of terminology for eye disease implies a hyperthyroid state, as the defining characteristic of Graves' disease. Studies have shown confusion among patients regarding the possibility of eye disease occurring without hyperthyroidism (9). The authors have experienced similar variability in medical knowledge among referring providers in their clinical practice. Many patients referred to our multidisciplinary TED clinic have experienced a delay in diagnosis, because it was felt that normal thyroid hormone levels and TSH can rule out active eye disease. Some patients were calling their eye disease Graves' disease, and thus opening the door for miscommunication when discussing prior evaluation and treatment geared towards thyroid or eye pathology.

A recently published correspondence describes the great variation of nomenclature that can be found even within a single journal issue, and makes a recommendation based on the authors' opinion regarding scientific and clinical accuracy

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TABLE 1

Journal or Senior Author (SA) specialty	Thyroid Eye Disease	Graves' orbitopathy	Graves' ophthalmopathy	Thyroid-(associated) orbitopathy	Thyroid-(associated) ophthalmopathy	Other	Total(2000: 77) (2010: 134)(2020: 299)
Endocrinology Journals 2000	2 8%	–	21 84%	–	1 4%	1	25 (32%)
Endocrinology Journals 2010	1 2.6%	18 47%	12 32%	3 8%	4 11%	–	38 (27%)
Endocrinology Journals 2020	9 12%	52 67%	14 18%	3 4%		–	78 (26%)
Ophthalmology Journals 2000	2 7%	3 11%	13 46%	1 4%	4 14%	4	28 (36%)
Ophthalmology Journals 2010	21 30%	17 25%	16 23%	7 10%	8 12%	–	69 (50%)
Ophthalmology Journals 2020	77 57%	22 16%	22 16%	6 4%	8 6%	1	136 (45%)
Endocrinology SA 2000	2 9%	1 5%	18 82%	–	1 5%	–	22 (29%)
Endocrinology SA 2010	2 6%	16 44%	13 36%	1 3%	4 11%	–	36
Endocrinology SA 2020	9 11%	45 57%	21 27%	2 3%	2 3%	–	79
Ophthalmology SA 2000	2 8%	5 19%	13 50%	–	1 4%	4	26 (34%)
Ophthalmology SA 2010	23 38%	12 17%	12 20%	10 16%	4 7%	–	61
Ophthalmology SA 2020	81 52%	30 19%	25 16%	7 5%	9 6%	–	155

(10). While the existing conundrum is adequately described, the study was limited to reporting the respective number of search results for 11 keyword synonyms in different electronic databases, but did not further analyze trends over time, or association with author and journal specific factors. Our review of TED related literature from 2000, 2010 and 2020 showed that TED narrowly surpassed Graves' orbitopathy as the most used term in more recent publications (Figure 1). Use of "Graves Ophthalmopathy", as well as other less common terms including "thyroid-(associated) orbitopathy" and "thyroid- (associated) ophthalmopathy", decreased during this 10-year period. While articles using TED and Graves' orbitopathy together made up 20% in 2000, this number increased to 53% in 2010 and 72% in 2020. These findings indicate the ability of the medical and scientific community to change predominant terminology use over a relatively short period, as well as a general trend towards standardization. There is a clear specialty-dependent preference between those two most used terms: Endocrinology journals and senior authors mainly use Graves' orbitopathy, while ophthalmology journals and senior authors prefer TED. This may reflect familiarity with the broader manifestations that ophthalmologists treat in patients with TED, aside from inflammation of orbital tissues. The term "Graves' orbitopathy" is integrated in the name of the European Group on Graves' Orbitopathy (EUGOGO), who has led several landmark clinical trials and developed widely accepted practice guidelines. However, on their website, the term TED is introduced immediately following GO, and multidisciplinary centers of excellence are described as "Combined Thyroid Eye Clinics (11).

The current real-world usage of different terms outside of scientific literature, which reflects what patients and other lay people encounter when researching periocular inflammatory disease associated with thyroid autoimmune disease, can be estimated by completing a Google search: The term "thyroid eye disease" yields over 83 million results, compared to 323,000 for Graves' ophthalmopathy and only 124,000 for Graves' orbitopathy (accessed from a U.S. server, Sep 12, 2022).

Conclusion

We propose Thyroid Eye Disease (TED) as the preferred term for eye and periocular inflammatory disease associated with thyroid autoimmune disease. We base this recommendation on the increasing use by ophthalmologists as well as endocrinologists, and the better encompassing of the associated clinicopathologic processes. TED can be understood much more easily by patients, and for clinicians it eliminates the

confusion about hyperthyroid state as a diagnostic criterium. Terminology trends in multidisciplinary publications and professional societies support this recommendation and highlight potential beneficial effects for collaborative care.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Author contributions

LW (first and corresponding author) - drafting the manuscript, generating analysis, and creating final manuscript. MS (senior author) - generating hypothesis, support in analysis and critical review of manuscript. EB and AT - critical review of the manuscript. YR – data collection, analysis, and review of manuscript. KR – analysis and review of manuscript. All authors contributed to the article and approved the submitted version.

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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Supplementary material

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References

1. Nickel B, Barratt A, McGeechan K, Brito JP, Moynihan R, Howard K, et al. Effect of a change in papillary thyroid cancer terminology on anxiety levels and treatment preferences: A randomized crossover trial. *JAMA Otolaryngol Head Neck Surg* (2018) 144(10):867–74. doi: 10.1001/jamaoto.2018.1272

2. Levey AS, Eckardt KU, Dorman NM, Christiansen SL, Hoorn EJ, Ingerfinger JR. Nomenclature for kidney function and disease: report of a kidney disease: Improving global outcomes (KDIGO) consensus conference. *Kidney Int* (2020) 97 (6):1117–29. doi: 10.1016/j.kint.2020.02.010

3. Jabs DA, Nussenblatt RB, Rosenbaum JT. Standardization of uveitis nomenclature (SUN) working group. standardization of uveitis nomenclature for reporting clinical data. results of the first international workshop. *Am J Ophthalmol* (2005) 140(3):509–16. doi: 10.1016/j.ajo.2005.03.057

4. Park J, Baek S. Dry eye syndrome in thyroid eye disease patients: The role of increased incomplete blinking and meibomian gland loss. *Acta Ophthalmol* (2019) 97(5):e800–6. doi: 10.1111/aos.14000

5. Jamshidian Tehrani M, Mahdizad Z, Kasaei A, Fard MA. Early macular and peripapillary vasculature dropout in active thyroid eye disease. *Graefes Arch Clin Exp Ophthalmol* (2019) 257(11):2533–40. doi: 10.1007/s00417-019-04442-8

6. Naik MN, Vasanthapuram VH, Joseph J, Murthy SI. Microbial keratitis in thyroid eye disease: Clinical features, microbiological profile, and treatment outcome. *Ophthalmic Plast Reconstr Surg* (2019) 35(6):543–8. doi: 10.1097/IOP.0000000000001361

7. Bartley GB B, Fatourechi V, Kadrmas EF, Jacobsen SJ, Ilstrup DM, Garrity JA, et al. Clinical features of graves' ophthalmopathy in an incidence cohort. *Am J Ophthalmol* (1996) 121(3):284–90. doi: 10.1016/S0002-9394(14)70276-4

8. Muñoz-Ortiz J, Sierra-Cote MC, Zapata-Bravo E, Valenzuela-Vallejo L, Marin-Noriega MA, Uribe-Reina P, et al. Prevalence of hyperthyroidism, hypothyroidism, and euthyroidism in thyroid eye disease: a systematic review of the literature. *Syst Rev* (2020) 9(1):201. doi: 10.1186/s13643-020-01459-7

9. Edmunds MR E, Boelaert K. Knowledge of thyroid eye disease in graves' disease patients with and without orbitopathy. *Thyroid* (2019) 29(4):557–62. doi: 10.1089/thy.2018.0665

10. Ing EB, Madjedi K, Hurwitz JJ, Nijhawan N, Oestreicher J, Torun N. Nomenclature: thyroid-associated orbitopathy, graves ophthalmopathy, or thyroid eye disease? *Can J Ophthalmol* (2021) 56(1):e22–4. doi: 10.1016/j.jcjo.2020.06.004

11. European Group on Graves' Orbitopathy. Graves' Orbitopathy. Available at: https://www.eugogo.eu/en/home/ (Accessed May 17, 2022).

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Observation study of using a small dose of rituximab treatment for thyroid-associated ophthalmopathy in seven Chinese patients: One pilot study

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Objective: To report the efficacy, long-term safety, and tolerability of using a small dose (125 mg/m2 weekly for 4 weeks) of rituximab to treat Chinese patients with thyroid-associated ophthalmopathy (TAO).

Methods: Seven patients with active moderate-to-severe TAO were prospectively recruited in this study. A small dose of rituximab (125mg/m2 body surface area) was given weekly with a duration of four weeks. Thyroid function, thyrotropin receptor antibody (TRAb), B cell and T cell subsets, ophthalmological examination, magnetic resonance imaging derived parameters, and adverse reactions were recorded at each visit.

Results: Seven patients were followed for an average of 224 weeks. B-cell depletion was observed in all patients following rituximab infusion. The clinical activity score (CAS) decreased from 4.86 $\pm$ 0.69 to 3.00 $\pm$ 0.82 at 5 weeks after treatment (P = 0.033) and remained significantly lower than baseline values at the end of follow-up (P = 0.001). Compared to baseline values, significant decreases in exophthalmos of the right eye, the thickness of extraocular muscles with maximum signal intensity, and the highest signal intensity ratio (SIR) of extraocular muscle to ipsilateral temporal muscle values were observed at the last follow-up (all P < 0.05). Disease progressions or recurrences were not observed during follow-up. Only mild fatigue was observed after the first infusion as a side effect (n = 1).

Conclusion: Small dose of rituximab may be a promising option with adequate safety, tolerability, and long-term efficacy for patients with active moderate-to-severe TAO.

KEYWORDS

thyroid-associated ophthalmopathy, treatment, rituximab, small dose, magnetic resonance imaging

Introduction

Thyroid-associated ophthalmopathy (TAO) is the most common and serious extra-thyroid manifestation of Graves' disease. Signs and symptoms of active TAO include eyelid contracture, exophthalmos, diplopia, corneal ulcerations, and even loss of vision (1). Intravenous glucocorticoids (GC) therapy is suggested as a first-line treatment for active and moderate-to-severe TAO. However, a proportion of patients cannot achieve remission and are defined as refractory TAO (2). Besides that, high-dose GC therapy is not always suitable for all TAO patients due to the contraindications and complications (e.g., weight gain, diabetes, high blood pressure, peptic ulcer, femoral head necrosis) (3). Thus, besides the conventional intravenous GC treatment, finding an effective alternative treatment strategy for patients with TAO was needed in clinical practice.

Although detailed pathogenesis has not been fully elucidated, the immunologic cross-activity between thyroid and orbital tissue antigens is deemed to play an important role in the occurrence and progress of TAO (4). Thyroid-stimulating hormone receptor (TSHR) is the most common pathogenic antigen in TAO (5). B cells in affected tissues can recognize TSHR and produce insulin-like growth factor-1 receptor (IGF-1R). The combination of TSHR and IGF-1R on the orbit releases cytokines, recruiting more immune cells into the orbit, causing hyaluronic acid accumulation, and expansion of orbital adipose tissue which contributes to the development of TAO (6). Teprotumumab is a complete human IgG1kappa monoclonal antibody that targets insulin-like growth factor I receptor (IGF-IR). It can reduce hyaluronan production and cytokine stimulation, thus can effectively control inflammation, and improve the exophthalmos and diplopia of patients (7). However, the expensive medical cost and uncertainty of long-term efficacy preclude its wide application. Therefore, B cells deserve consideration as a promising new therapeutic target in TAO.

Rituximab (RTX) is a chimeric human and mouse monoclonal antibody, which is expressed on pre-B cells and mature B cells. It has been proven to be useful in the treatment of autoimmune diseases such as rheumatoid arthritis, membranous nephropathy, and antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (8–10). Recently, increasing results have been reported on the RTX treatment of TAO (11–15), however, a high dose of RTX (such as 500 mg or 1000 mg twice, 2 weeks apart, 375 mg/m^2 weekly for 4 weeks) is usually used, and therefore side effects (e.g., infusion reactions, arthralgias, optic neuropathy, abdominal pain) have been reported in about one-third of patients (16–18). Given this, some studies have tried to use low doses of RTX in eliminating B cells and reducing inflammation (14, 19). Du et al. treated 15 patients with refractory TAO using low-dose RTX (cumulative dose, 100-400mg), and clinical improvement was achieved in 87% of the patients within 2 months (14). Insull et al. found that treatment with 100 mg RTX in combination with glucocorticoids (mean dose 2.3g) or other immunosuppressive agents (methotrexate or ciclosporin) was effective in reducing clinical activity in 12 TAO patients (19). However, the follow-up period was limited in above mentioned studies, therefore the long-term effect of a small dose RTX treatment in TAO patients was still unclear.

Therefore, the purpose of this study was to investigate the long-term efficacy, safety, and tolerability of using a small dose (125 mg/m^2 weekly for 4 weeks) of rituximab to treat Chinese patients with TAO.

Materials and methods

Patients

The study was approved by the ethics committees of our hospital (No. 2011-SR-032). Written informed consent was all obtained before patients recruit. Inclusion criteria were as follows: (1) age ranged from 18 to 75 years; (2) active moderate-to-severe disease defined according to the clinical activity score (CAS) (CAS ≥ 3/7) and European Group on Graves' Orbitopathy (EUGOGO) severity assessment (20, 21); (3) normal or near-normal thyroid function (no more than twice the upper limit of normal); (4) with evidence of disease progression during the previous 2 months or no improvement in the past 6 months; (5) discontinue previous steroid treatment for at least 3 months. (6) no contraindications to MRI scanning. Exclusion criteria were as follows: (1) vision-threatening TAO; (2) medically unfit to receive RTX (history of pulmonary tuberculosis, hepatitis B carrier, hepatitis C positive, human immunodeficiency virus (HIV), absolute neutrophil count < 1.5×10^9/L); (3) pregnant or breastfeeding.

Study design

All individuals were treated with RTX weekly infusions of 125 mg/m^2 of body surface area for four weeks, and dexamethasone (5 mg) was given before dosing to prevent possible allergic reactions. During the infusion, heart rate and blood pressure were monitored. Patients were evaluated before and after treatment at designated follow-up visits (5, 8, 16, 28, 52, and 224 weeks) by laboratory tests, clinical manifestation, and ophthalmic examination. Orbital magnetic resonance imaging (MRI) was performed before treatment, and at 52, 224 weeks after RTX injection. Adverse events that were reasonably or probably related to RTX were documented throughout the study period.

Clinical assessments

Baseline assessment included medical history, concomitant medications, physical examination (by an endocrinologist with 10 years of experience), ophthalmic evaluation including proptosis, visual acuity, and intraocular pressure (by an ophthalmologist with 5 years of experience), orbital MRI, and laboratory data. The laboratory data included the thyroid-stimulating hormone (TSH), free triiodothyronine (FT_3) free thyroxine (FT_4), thyrotropin receptor antibody (TRAb), lymphocyte subsets ($CD3^+$, $CD3^+CD4^+$, $CD3^+CD8^+$, $CD19^+$, and $CD20^+$), and serum immunoglobulin (IgG, IgA, IgM).

Imaging techniques and analysis

MRI scans were performed on a 3.0-T MRI system (Magnetom Skyra; Siemens Healthcare, Erlangen, Germany) with a 12-channel head coil. Patients were instructed to take a comfortable supine position with eyes closed to reduce motion-related errors. Imaging protocols included axial T1- weighted image (repetition time/echo

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time, 635/6.7 ms), and axial, coronal, and sagittal T2-weighted image with fat suppression (FS) (repetition time/echo time, 4000/75–117 ms). Image analysis was performed by two dedicated radiologists (with 10 and 3 years of experience on head and neck radiology, respectively). Specific MRI-derived parameters and their measurement methods were showed as follows: (1) Exophthalmos: vertical distances from the apex of cornea to the interzygomatic line on axial T2-weighted image with FS. (2) The thickness of orbital fat (OF): the maximum distance between the medial wall of the eyeball and the medial wall of the orbit on axial T1-weighted image was measured. (3) The highest signal intensity ratio (SIR) of extraocular muscle to ipsilateral temporal muscle: on the coronal image of T2WI temporal FS, the signal intensity of extraocular muscle and ipsilateral temporal muscle with the highest T2 signal was measured by region of interest (ROI) method, and the signal intensity ratio of extraocular muscle and temporal muscle was taken as SIR. (4) The volume of extraocular muscle (EOM): the cross-sectional area of the extraocular muscle with the highest T2 signal was measured using the calculation method reported in a previous study (22). The superior rectus must be assessed along with the levator palpebrae because of the difficulty in separating them on the magnetic resonance images. The volume of EOM was obtained by the sum of the cross-sectional areas with a slice thickness of 3.5mm. The average of the measurements of two radiologists was adopted for future statistical analysis.

Statistical analyses

Statistical analyses were performed using the SPSS software (version 23.0, SPSS, Inc., Chicago, IL) and GraphPad Prism (version 8.0.0, GraphPad Software, Inc. San Diego, CA). Continuous data were presented as the mean ± standard deviation. The repeated measures analysis of variance (ANOVA) was applied for the comparison of data at different time points. Statistical significance was defined as a two-sided P value less than 0.05.

Results

Patients

Seven patients (two males, and five females; age range of 43-62 years) were finally enrolled in the study. Among all patients, two male patients had a long history of smoking before treatment, and one female patient occasionally had a history of passive smoking. One patient had quit smoking before the treatment of rituximab, and the other patient could not quit smoking. None of the other patients had active or passive smoking during the follow-up period. Baseline patient characteristics are displayed in Table 1. At the time of RTX treatment, three patients were subclinical hyperthyroid, and two of them received methimazole treatment. Three were euthyroid, and one of whom was treated with levothyroxine. One patient developed hypothyroidism after radioactive iodine treatment and was then supplied with levothyroxine. During the follow-up period, five patients had normal thyroid function (71.4%), one patient had hypothyroid (14.3%), and one patient had hyperthyroidism followed by transient hypothyroidism (14.3%). After adjusting the drug dosage, the thyroid function of the patient returned to normal. Two patients did not receive intravenous glucocorticoids before RTX treatment: patient 2 because of uncontrolled diabetes, and patient 5 was reluctant to receive high-dose GC therapy because of concerns about side effects. Four patients were treated with glucocorticoids and discontinued three months before the treatment of RTX. The mean follow-up period was 224 weeks (range: 44-78 months).

Effects of RTX treatment on lymphocyte subgroup and serum immunoglobulin

All patients showed significant reductions in $CD19^+$ and $CD20^+$ cells at weeks 5 and 8 compared to baseline after RTX treatment (all $P < 0.05$), and began to increase at week 16. Until the study ended,

TABLE 1 Demographics and clinical characteristics of seven patients treated with rituximab.

Patient number	1	2	3	4	5	6	7
Age (years)	46	55	62	59	44	43	49
Sex (F/M)	F	F	M	M	F	F	F
Smoking history	No	No	Yes	Yes	No	No	No
Thyroid status	Euthyroid	Euthyroid	Subclinical hyperthyroidism	Hypothyroidism	Subclinical hyperthyroidism	Subclinical hyperthyroidism	Euthyroid
Therapy for thyroid dysfunction	–	L-T4 after radioiodine	MMI	L-T4 after radioiodine	–	MMI	–
Previous treatment	Somatostatin	None	GC	GC	None	GC	GC
Clinical response to GS	Progression	–	Progression	Progression	–	Progression	Progression
Duration of TAO (Months)	7	1	1	11	1	3	9
CAS	5	4	5	5	4	6	5
Involved of EOM	All	IR	All	All	All	All	All

F, female; M, male; GC, glucocorticoid; MMI, methimazole; L-T4, L-thyroxine; CAS, clinical activity scores; EOM, extraocular muscle; IR, inferior rectus; TAO, thyroid-associated ophthalmopathy.

peripheral B cells had not returned to baseline (Table 2 and Figure 1A). The percentages of T lymphocyte subsets, C3 complement, C4 complement and the number of serum immunoglobulin remained stable throughout the study (Table 2).

Effect of RTX treatment on thyroid function and ophthalmic indexes

No significant differences were observed in FT_3, FT_4, and TSH levels from baseline to each follow-up time point (Table 3). TRAb showed an insignificant downward trend throughout the follow-up period (Table 3 and Figure 1B). Meanwhile, an increase in intraocular pressure was observed at week 8 after RTX treatment, followed by a decline, but there was no statistical difference (Table 3 and Figure 1C). At the end of follow-up, the visual acuity of the patient's right eye was significantly improved compared with that before treatment (P = 0.037) (Table 3).

Effect of RTX treatment on disease activity

The mean CAS was 4.86 ± 0.69 at baseline, decreased to 3.00 ± 0.82 at 5 weeks (P = 0.033), and remained at low levels throughout the follow-up period. At the end of the follow-up, the mean CAS value (0.86 ± 0.90) was still significantly lower than the initial value (P = 0.001) (Table 3 and Figure 1D). Among those 7 patients, 5/7 (71.4%) had disease inactivation (CAS<3) at week 28, and 6/7 (85.7%) were inactive at week 52. There were no cases of relapse at 224 weeks of follow-up.

Effect of RTX treatment on imaging parameters

The volume of extraocular muscles with maximum signal intensity before therapy was 1279.65 ± 277.07 mm^3, which decreased to 853.15 ± 178.54 and 790.46 ± 295.30 mm^3at 52 weeks after treatment and the last follow-up (P = 0.003 and 0.015, respectively) (Table 4 and Figure 2A). The highest SIR of extraocular muscle to ipsilateral temporal muscle values significantly decreased at 52 weeks (1.989 ± 0.639) and the last follow-up (1.508 ± 0.364), compared to those observed at baseline (3.495 ± 1.420) (P = 0.030 and 0.029, respectively) (Table 4 and Figure 2B). In addition, the exophthalmos of the right eye also significantly decreased at 52 weeks and the last follow-up (all P = 0.013) (Table 4 and Figure 2C). We did not observe significant changes in the exophthalmos of the left eye and the thickness of orbital fat after RTX treatment (all P > 0.05) (Table 4 and Figures 2C, D). Figure 3 shows the MRI images of SIR in a representative case at pre-treatment and follow-up examinations.

Side effect

Only one patient experienced fatigue after the first infusion, but it did not recur in subsequent infusions. There were no other side effects of the RTX infusions during a 224-week follow-up observation period.

Discussion

In this study, we found that a low dose sustained RTX (125 mg/m^2 weekly for 4 weeks) was feasible and effective for Chinese patients with TAO. Four of seven TAO patients were refractory to GC therapy before RTX treatment, however marked improvement was obtained within a very short period after RTX infusion. It is noteworthy that none of the patients experienced late recurrence during a long-term follow-up period of more than 4 years. To our knowledge, our study was the first one reporting the effectiveness of a small dose of RTX in achieving effective peripheral B-cell depletion and long-term remission of TAO in the Chinese population.

Most of the previous studies used RTX by the protocol of rheumatoid arthritis protocol (1 g with 2-week intervals) or lymphoma (375 mg/m^2

TABLE 2 Changes of B and T cell subsets and immunoglobulins in TAO patients after rituximab treatment during the follow-up period.

Parameters	Time points						
	0 (baseline)	5 weeks	8 weeks	16 weeks	28 weeks	52 weeks	224 weeks
CD19	14.26 ± 7.00	0.37 ± 0.96*	0.02 ± 0.04*	1.11 ± 2.56	1.99 ± 3.74*	6.15 ± 4.63	5.99 ± 3.54
CD20	14.39 ± 7.04	0.04 ± 0.09*	0.00 ± 0.00*	0.99 ± 2.61	1.36 ± 1.86*	3.93 ± 2.32	5.70 ± 3.36
CD4 (%)	34.54 ± 10.05	35.61 ± 8.28	33.64 ± 11.62	38.80 ± 9.63	37.31 ± 12.66	36.43 ± 6.10	33.26 ± 6.97
CD8 (%)	25.37 ± 7.44	28.59 ± 6.89	28.22 ± 9.59	30.68 ± 4.47	27.33 ± 12.07	25.92 ± 5.86	21.85 ± 5.31
CD3 (%)	62.98 ± 14.92	67.99 ± 14.18	66.76 ± 19.76	72.59 ± 10.71	66.91 ± 24.85	65.93 ± 9.53	58.96 ± 10.21
IgG (g/L)	10.86 ± 2.00	12.32 ± 2.14	12.80 ± 2.85	12.21 ± 1.98	12.17 ± 1.72	12.61 ± 1.57	14.89 ± 1.60
IgA (g/L)	1.91 ± 0.69	2.10 ± 0.75	2.12 ± 0.69	2.09 ± 0.84	2.11 ± 0.74	2.14 ± 0.87	2.33 ± 0.70
IgM (g/L)	1.12 ± 0.38	1.20 ± 0.47	1.17 ± 0.43	1.16 ± 0.43	1.11 ± 0.47	0.91 ± 0.34	1.02 ± 0.38
C3 (g/L)	0.98 ± 0.28	1.07 ± 0.25	1.00 ± 0.27	1.00 ± 0.27	1.03 ± 0.22	1.02 ± 0.26	1.08 ± 0.27
C4 (g/L)	0.26 ± 0.09	0.25 ± 0.09	0.29 ± 0.09	0.27 ± 0.10	0.26 ± 0.08	0.25 ± 0.06	0.26 ± 0.07

The numeric data are reported as the mean ± standard deviation.
IgA, Immunoglobulin A; IgG, Immunoglobulin G; IgM, Immunoglobulin M; C3, C3 complement; C4, C4 complement.
*P < 0.05 versus baseline values.

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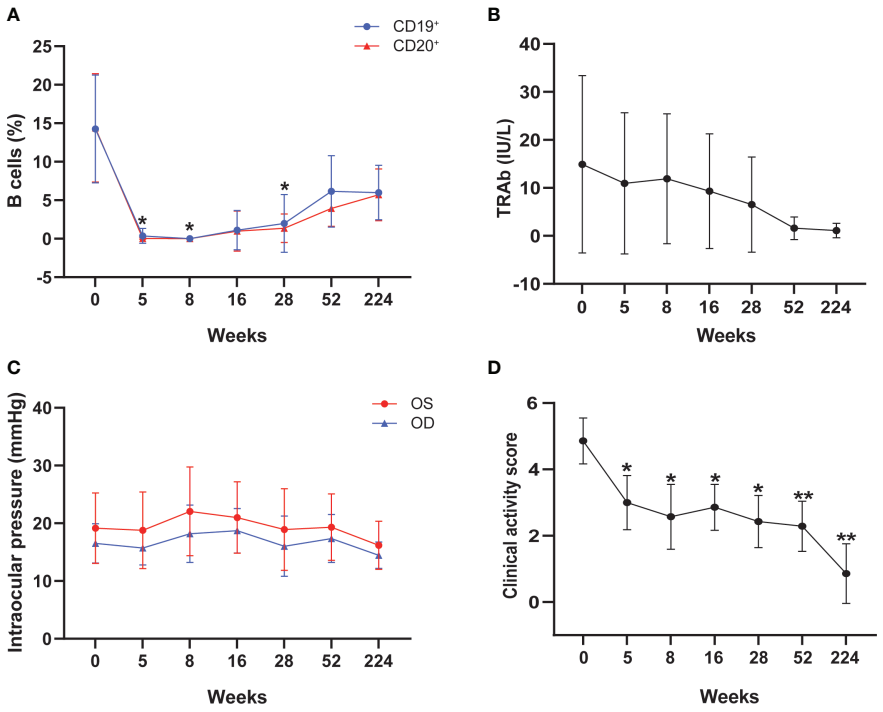

FIGURE 1
Changes of peripheral B cells **(A)**, TRAb levels **(B)**, intraocular pressure **(C)**, and clinical activity score **(D)** during the treatment of rituximab. TRAb, thyrotropin receptor antibody; The asterisk indicated significant differences (*$P < 0.05$, **$P < 0.01$).

weekly for 4 weeks) (12, 23–25). However, the optimal dose of RTX has not been clarified. Previously, Maloney et al. reported that the use of weekly infusions times four of 125 mg/m^2, 250 mg/m^2, and 375 mg/m^2 of RTX in patients with relapsed lymphoma could cause B-cell depletion (26). In autoimmune disease, where the prognosis is less severe than in lymphoproliferative disease, we consider lower doses for TAO patients. Our results suggest that B cells were rapidly and effectively depleted by RTX injection at 125kg/m^2 per week for 4 weeks.

An important finding from our study is that sustained long-term remissions can be achieved in patients with TAO after this small dose of RTX treatment. A previous study found that 5 patients with refractory TAO following a 4-week course of weekly rituximab (375 mg/m^2), and the CAS decreased significantly within one month, but there was no further change in the subsequent 5 years of follow-up (17). In our study, a decrease in CAS was observed in all patients at the first week after treatment and remained stably low during the follow-up, with a further significant decrease from baseline after an average of 224 weeks of follow-up. The observed improvement in CAS seemed to correlate with the onset of B-cell depletion (23). It is worth noting that we did not observe disease relapse after B cell

TABLE 3 Changes of clinical and laboratory parameters in TAO patients after rituximab treatment during the follow-up period.

Parameters	Time points						
	0 (baseline)	5 weeks	8 weeks	16 weeks	28 weeks	52 weeks	224 weeks
FT3 (pmol/L)	5.54 ± 3.17	6.62 ± 3.63	5.68 ± 3.14	4.63 ± 0.70	3.66 ± 1.30	4.69 ± 0.41	5.24 ± 1.00
FT4 (pmol/L)	17.08 ± 4.83	18.36 ± 3.84	20.15 ± 8.10	18.69 ± 6.62	14.75 ± 7.20	16.37 ± 2.89	19.47 ± 5.89
TSH (mIU/L)	8.39 ± 21.33	4.08 ± 9.07	2.75 ± 5.80	1.71 ± 2.91	15.62 ± 37.22	3.45 ± 4.37	6.38 ± 14.26
TRAb (IU/L)	14.92 ± 18.48	10.94 ± 14.72	11.89 ± 13.55	9.32 ± 11.96	6.54 ± 9.92	1.58 ± 2.33	1.11 ± 1.51
CAS	4.86 ± 0.69	3.00 ± 0.82*	2.57 ± 0.98*	2.86 ± 0.69*	2.43 ± 0.79*	2.29 ± 0.76**	0.86 ± 0.90**
IOP (OD)	16.51 ± 3.40	15.73 ± 2.94	18.19 ± 4.98	18.70 ± 3.84	16.03 ± 5.21	17.36 ± 4.14	14.46 ± 2.28
IOP (OS)	19.16 ± 6.09	18.77 ± 6.64	22.06 ± 7.68	20.99 ± 6.18	18.93 ± 7.07	19.33 ± 5.75	16.19 ± 4.15
Visual acuity (OD)	0.71 ± 0.31	0.74 ± 0.27	0.77 ± 0.24	0.77 ± 0.24	0.77 ± 0.24	0.77 ± 0.24	0.89 ± 0.23
Visual acuity (OS)	0.71 ± 0.27	0.71 ± 0.27	0.79 ± 0.22	0.79 ± 0.22	0.79 ± 0.22	0.80 ± 0.20	0.93 ± 0.13*

The numeric data are reported as the mean ± standard deviation.
FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid-stimulating hormone; TRAb, thyrotropin receptor antibody; IOP, intraocular pressure; OD, right eye; OS, left eye; CAS, clinical activity scores;
*$P < 0.05$, **$P < 0.01$ versus baseline values.

TABLE 4 Changes of imaging parameters in TAO patients after rituximab treatment during the follow-up period.

Parameters	Time points			*P*-value	
	0 (baseline)	52 weeks	224 weeks	$P_{0\text{-}52}$	$P_{0\text{-}224}$
Exophthalmos (OD)	20.51 ± 1.89	18.93 ± 2.27	17.97 ± 2.08	0.013*	0.013*
Exophthalmos (OS)	20.17 ± 2.48	18.83 ± 2.05	17.64 ± 1.54	0.345	0.093
OF (OD)	6.74 ± 0.63	7.31 ± 0.78	7.20 ± 0.76	0.133	0.087
OF (OS)	6.69 ± 1.13	6.33 ± 0.82	6.17 ± 0.87	0.305	0.226
SIR	3.50 ± 1.42	1.99 ± 0.64	1.51 ± 0.36	0.030*	0.029*
EOM (mm^3)	1279.65 ± 277.07	853.15 ± 178.54	790.46 ± 295.30	0.003**	0.015*

The numeric data are reported as the mean ± standard deviation.
OD, right eye; OS, left eye; OF, the thickness of orbital fat; EOM, the volume of extraocular muscle with maximum signal intensity. SIR, the highest signal intensity ratio of extraocular muscle to ipsilateral temporal muscle.
*$P < 0.05$, **$P < 0.01$ versus baseline values.

reconstitution. Thus, these findings offer strong clinical evidence of the usage of small dose of RTX for TAO treatment.

Though a downward trend was observed in TRAb after the whole follow-up course, it was not statistically significant. Our findings are consistent with previous studies that showed no significant effect on TRAb with either low-dose or high-dose RTX treatment (13, 27). This might be due to RTX targeting only immature B cells, leaving the mature plasma cells that produce TRAb unharmed (28). Conversely, some studies have shown a significant reduction of TRAb in RTX-treated patients (11, 29). These studies suggested that the changes in TRAb may be attributed to the direct effect on TRAb or remission of hyperthyroidism after long-term antithyroid drug therapy. None of the seven patients had a recurrence of ocular inflammation after RTX treatment, despite the fact that the drug did not affect TRAb in our study. These initial findings warrant further investigation to fully elucidate the underlying mechanism.

Additionally, this study presented that the right eye protrusion of TAO patients decreased significantly after treatment. Some studies

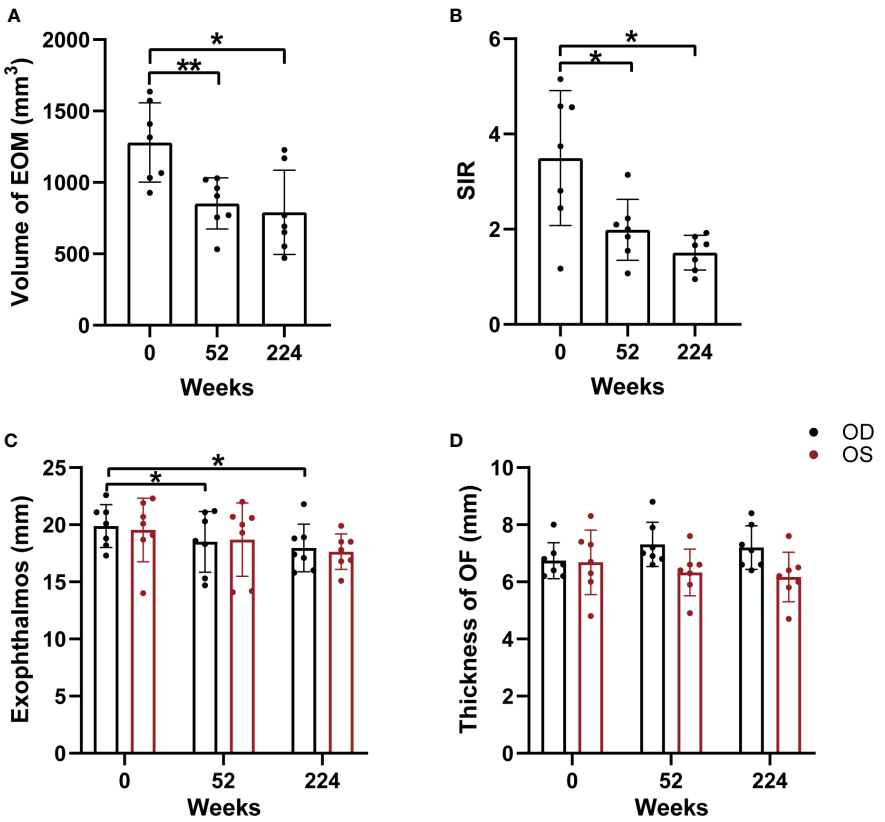

FIGURE 2
Comparisons of orbital MRI-based parameters during follow-up, including the volume of extraocular muscles with maximum signal intensity **(A)**, the highest SIR of extraocular muscle to ipsilateral temporal muscle **(B)**, the exophthalmos **(C)** and the thickness of orbital fat **(D)**. EOM, extraocular muscle; OF, orbital fat; OD, right eye; OS, left eye; SIR, the highest signal intensity ratio of extraocular muscle to ipsilateral temporal muscle. Asterisk indicated significant differences (*P < 0.05, **P < 0.01).

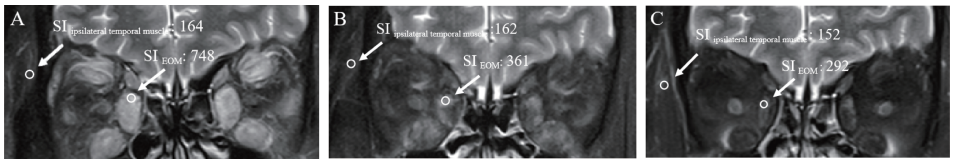

FIGURE 3
Orbital images of a patient with TAO at baseline **(A)**, 52 weeks **(B)**, and 224 weeks **(C)** after rituximab treatment. EOM, extraocular muscle; SI: signal intensity.

have shown similar results (15), whereas others reported no effect of RTX on proptosis and can cause a transient increase in protrusion (11, 30). The similarities of these studies are the use of large doses of RTX (1000 mg twice), Stan and Salvi have pointed out that high-dose of RTX can cause an increase in the volume of orbital tissue and proptosis in some patients, followed by volume displacement due to massive dissolution of B cells and may increase the risk of dysthyroid optic neuropathy (DON) (18). This can also explain the transient increase in intraocular pressure observed at week 8 of our study, accompanied by the complete depletion of B cells. Although no changes in protrusions were observed under a very low dose of RTX (100mg), the occurrence of DON cannot be avoided and patients required prompt surgical orbital decompression (19, 31). By contrast, no such case was noted in our study. In addition, we found that a small dose of RTX had a long-term positive effect on visual acuity in patients with TAO, although with the limitation of small subjects. The results of the 224 weeks of data on the patients that continued per protocol suggest the RTX dose of 125 mg/m^2 weekly for 4 weeks may prevent the progression of DON. This is a promising finding, given that the optimal dose has not as yet been fully determined, further research with a larger sample size is warranted to confirm the findings.

In this study, we applied an objective approach to dynamically evaluate the long-term efficacy of RTX treatment in TAO patients. The increased signal intensity of enlarged EOM on T2-weighted images and the volume of EOM reflected the edematous changes in the active inflammation stage (22, 32). It has been previously confirmed that SIR of extraocular muscle to temporalis muscle showed significant positive correlations with CAS values, and could be used as an indicator to evaluate the inflammation activity of TAO (33). We observed a significant decrease in SIR and the volume of EOM with maximum signal intensity at weeks 52 and 224 after RTX treatment, compared to the baseline value. In addition, the thickness of EOM with maximum signal intensity was significantly reduced from baseline to the end of follow-up. These results highlight the ability of a small dose of RTX to produce long-term sustained relief of inflammatory edema in patients with TAO.

However, our analysis may have been limited by several factors. First, small numbers of subjects, non-randomized studies, and the lack of a double-blind, placebo-controlled design. Second, the favorable long-term outcomes seen after RTX treatment cannot rule out the influence of the natural history of the disease. Further well-designed and large-scale randomized controlled studies are needed to determine the optimal dose regimen, long-term benefits, and possible side effects. Finally, only the changes in clinical serological, immunological, ophthalmological, and imaging indicators were analyzed. Further research on the assessment of patients' quality of life (QOL), may provide clinicians with important information about the psychosocial functions of those patients, which will help to understand more comprehensively the impact of RTX on patients with TAO.

Conclusions

In our study, we found that a small dose of RTX (125 mg/m^2 weekly for four doses) was safe and long-term efficacious for patients with TAO. Besides the conventional intravenous GC treatment, a small dose of RTX might be an alternative treatment strategy for patients with active moderate-to-severe TAO.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by the First Affiliated Hospital of Nanjing Medical University (No. 2011-SR-032). The patients/participants provided their written informed consent to participate in this study.

Author contributions

Conceptualization, YW; methodology, YW and HH; investigation, LC; resources, TY; data curation, HZ; writing-original draft preparation, YW; writing-review and editing, HC and XX; supervision, HC. All authors contributed to the article and approved the submitted version.

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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.

Publisher's note

References

1. Antonelli A, Fallahi P, Elia G, Ragusa F, Paparo SR, Ruffilli I, et al. Graves' disease: Clinical manifestations, immune pathogenesis (cytokines and chemokines) and therapy. *Best Pract Res Clin Endocrinol Metab* (2020) 34(1):101388. doi: 10.1016/j.beem.2020.101388

2. Zang S, Ponto KA, Kahaly GJ. Clinical review: Intravenous glucocorticoids for graves' orbitopathy: efficacy and morbidity. *J Clin Endocrinol Metab* (2011) 96(2):320–32. doi: 10.1210/jc.2010-1962

3. Moleti M, Giuffrida G, Sturniolo G, Squadrito G, Campenni A, Morelli S, et al. Acute liver damage following intravenous glucocorticoid treatment for graves' ophthalmopathy. *Endocrine* (2016) 54(1):259–68. doi: 10.1007/s12020-016-0928-3

4. Paik JS, Kim SE, Kim JH, Lee JY, Yang SW, Lee SB. Insulin-like growth factor-1 enhances the expression of functional TSH receptor in orbital fibroblasts from thyroid-associated ophthalmopathy. *Immunobiology* (2020) 225(2):151902. doi: 10.1016/j.imbio.2019.151902

5. Smith TJ. TSH-receptor-expressing fibrocytes and thyroid-associated ophthalmopathy. *Nat Rev Endocrinol* (2015) 11(3):171–81. doi: 10.1038/nrendo.2014.226

6. Shen S, Chan A, Sfikakis PP, Hsiu Ling AL, Detorakis ET, Boboridis KG, et al. B-cell targeted therapy with rituximab for thyroid eye disease: closer to the clinic. *Surv Ophthalmol* (2013) 58(3):252–65. doi: 10.1016/j.survophthal.2012.10.006

7. Douglas RS, Kahaly GJ, Patel A, Sile S, Thompson EHZ, Perdok R, et al. Teprotumumab for the treatment of active thyroid eye disease. *N Engl J Med* (2020) 382(4):341–52. doi: 10.1056/NEJMoa1910434

8. Fervenza FC, Appel GB, Barbour SJ, Rovin BH, Lafayette RA, Aslam N, et al. Rituximab or cyclosporine in the treatment of membranous nephropathy. *N Engl J Med* (2019) 381(1):36–46. doi: 10.1056/NEJMoa1814427

9. Humby F, Durez P, Buch MH, Lewis MJ, Rizvi H, Rivellese F, et al. Rituximab versus tocilizumab in anti-TNF inadequate responder patients with rheumatoid arthritis (R4RA): 16-week outcomes of a stratified, biopsy-driven, multicentre, open-label, phase 4 randomised controlled trial. *Lancet* (2021) 397(10271):305–17. doi: 10.1016/S0140-6736(20)32341-2

10. Geetha D, Specks U, Stone JH, Merkel PA, Seo P, Spiera R, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis with renal involvement. *J Am Soc Nephrol* (2015) 26(4):976–85. doi: 10.1681/ASN.2014010046

11. Salvi M, Vannucchi G, Curro N, Campi I, Covelli D, Dazzi D, et al. Efficacy of b-cell targeted therapy with rituximab in patients with active moderate to severe graves' orbitopathy: A randomized controlled study. *J Clin Endocrinol Metab* (2015) 100 (2):422–31. doi: 10.1210/jc.2014-3014

12. Salvi M, Vannucchi G, Campi I, Curro N, Dazzi D, Simonetta S, et al. Treatment of graves' disease and associated ophthalmopathy with the anti-CD20 monoclonal antibody rituximab: an open study. *Eur J Endocrinol* (2007) 156(1):33–40. doi: 10.1530/eje.1.02325

13. Eid L, Coste-Verdier V, Longueville E, Ribeiro E, Nicolescu-Catargi B, Korobelnik JF. The effects of rituximab on graves'orbitopathy: A retrospective study of 14 patients. *Eur J Ophthalmol* (2020) 30(5):1008–13. doi: 10.1177/1120672119845224

14. Du Pasquier-Fediaevsky L, Andrei S, Berche M, Leenhardt L, Heron E, Riviere S. Low-dose rituximab for active moderate to severe graves' orbitopathy resistant to conventional treatment. *Ocul Immunol Inflamm* (2019) 27(5):844–50. doi: 10.1080/09273948.2018.1453078

15. Salvi M, Vannucchi G, Beck-Peccoz P. Potential utility of rituximab for graves' orbitopathy. *J Clin Endocrinol Metab* (2013) 98(11):4291–9. doi: 10.1210/jc.2013-1804

16. El Fassi D, Nielsen CH, Hasselbalch HC, Hegedus L. Treatment-resistant severe, active graves' ophthalmopathy successfully treated with b lymphocyte depletion. *Thyroid* (2006) 16(7):709–10. doi: 10.1089/thy.2006.16.709

17. Erdei A, Paragh G, Kovacs P, Karanyi Z, Berenyi E, Galuska L, et al. Rapid response to and long-term effectiveness of anti-CD20 antibody in conventional therapy resistant graves' orbitopathy: A five-year follow-up study. *Autoimmunity* (2014) 47(8):548–55. doi: 10.3109/08916934.2014.939266

18. Stan MN, Salvi M. MANAGEMENT OF ENDOCRINE DISEASE: Rituximab therapy for graves' orbitopathy - lessons from randomized control trials. *Eur J Endocrinol* (2017) 176(2):R101–R9. doi: 10.1530/EJE-16-0552

19. Insull EA, Sipkova Z, David J, Turner HE, Norris JH. Early low-dose rituximab for active thyroid eye disease: An effective and well-tolerated treatment. *Clin Endocrinol (Oxf)* (2019) 91(1):179–86. doi: 10.1111/cen.13970

20. Mourits MP, Prummel MF, Wiersinga WM, Koornneef L. Clinical activity score as a guide in the management of patients with graves' ophthalmopathy. *Clin Endocrinol (Oxf)* (1997) 47(1):9–14. doi: 10.1046/j.1365-2265.1997.2331047.x

21. Bartalena L, Kahaly GJ, Baldeschi L, Dayan CM, Eckstein A, Marcocci C, et al. The 2021 European group on graves' orbitopathy (EUGOGO) clinical practice guidelines for the medical management of graves' orbitopathy. *Eur J Endocrinol* (2021) 185(4):G43–67. doi: 10.1530/EJE-21-0479

22. Higashiyama T, Nishida Y, Ohji M. Changes of orbital tissue volumes and proptosis in patients with thyroid extraocular muscle swelling after methylprednisolone pulse therapy. *Jpn J Ophthalmol* (2015) 59(6):430–5. doi: 10.1007/s10384-015-0410-4

23. El Fassi D, Nielsen CH, Bonnema SJ, Hasselbalch HC, Hegedus L. B lymphocyte depletion with the monoclonal antibody rituximab in graves' disease: a controlled pilot study. *J Clin Endocrinol Metab* (2007) 92(5):1769–72. doi: 10.1210/jc.2006-2388

24. Silkiss RZ, Reier A, Coleman M, Lauer SA. Rituximab for thyroid eye disease. *Ophthalmic Plast Reconstr Surg* (2010) 26(5):310–4. doi: 10.1097/IOP.0b013e3181c4dfde

25. Khanna D, Chong KK, Afifiyan NF, Hwang CJ, Lee DK, Garneau HC, et al. Rituximab treatment of patients with severe, corticosteroid-resistant thyroid-associated ophthalmopathy. *Ophthalmology* (2010) 117(1):133–9 e2. doi: 10.1016/j.ophtha.2009.05.029

26. Maloney DG, Grillo-Lopez AJ, Bodkin DJ, White CA, Liles TM, Royston I, et al. IDEC-C2B8: results of a phase I multiple-dose trial in patients with relapsed non-hodgkin's lymphoma. *J Clin Oncol* (1997) 15(10):3266–74. doi: 10.1200/JCO.1997.15.10.3266

27. Vannucchi G, Campi I, Bonomi M, Covelli D, Dazzi D, Curro N, et al. Rituximab treatment in patients with active graves' orbitopathy: effects on proinflammatory and humoral immune reactions. *Clin Exp Immunol* (2010) 161(3):436–43. doi: 10.1111/j.1365-2249.2010.04191.x

28. Struja T, Kutz A, Fischli S, Meier C, Mueller B, Recher M, et al. Is graves' disease a primary immunodeficiency? new immunological perspectives on an endocrine disease. *BMC Med* (2017) 15(1):174. doi: 10.1186/s12916-017-0939-9

29. Mitchell AL, Gan EH, Morris M, Johnson K, Neoh C, Dickinson AJ, et al. The effect of b cell depletion therapy on anti-TSH receptor antibodies and clinical outcome in glucocorticoid-refractory graves' orbitopathy. *Clin Endocrinol (Oxf)* (2013) 79(3):437–42. doi: 10.1111/cen.12141

30. Stan MN, Garrity JA, Carranza Leon BG, Prabin T, Bradley EA, Bahn RS. Randomized controlled trial of rituximab in patients with graves' orbitopathy. *J Clin Endocrinol Metab* (2015) 100(2):432–41. doi: 10.1210/jc.2014-2572

31. Vannucchi G, Campi I, Covelli D, Curro N, Lazzaroni E, Palomba A, et al. Efficacy profile and safety of very low-dose rituximab in patients with graves' orbitopathy. *Thyroid* (2021) 31(5):821–8. doi: 10.1089/thy.2020.0269

32. Yokoyama N, Nagataki S, Uetani M, Ashizawa K, Eguchi K. Role of magnetic resonance imaging in the assessment of disease activity in thyroid-associated ophthalmopathy. *Thyroid* (2002) 12(3):223–7. doi: 10.1089/105072502753600179

33. Higashiyama T, Nishida Y, Morino K, Ugi S, Nishio Y, Maegawa H, et al. Use of MRI signal intensity of extraocular muscles to evaluate methylprednisolone pulse therapy in thyroid-associated ophthalmopathy. *Jpn J Ophthalmol* (2015) 59(2):124–30. doi: 10.1007/s10384-014-0365-x

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Factors related to steroid treatment responsiveness in thyroid eye disease patients and application of SHAP for feature analysis with XGBoost

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Introduction: The primary treatment for active thyroid eye disease (TED) is immunosuppressive therapy with intravenous steroids. In this study, we attempted to predict responsiveness to steroid treatment in TED patients using eXtreme Gradient Boosting (XGBoost). Factors associated with steroid responsiveness were also statistically evaluated.

Methods: Clinical characteristics and laboratory results of 89 patients with TED who received steroid treatment were retrospectively reviewed. XGBoost was used to explore responsiveness to steroid treatment, and the diagnostic performance was evaluated. Factors contributing to the model output were investigated using the SHapley Additive exPlanation (SHAP), and the treatment response was investigated statistically using SPSS software.

Results: The eXtra Gradient Boost model showed high performance, with an excellent accuracy of 0.861. Thyroid-stimulating hormone, thyroid-stimulating immunoglobulin (TSI), and low-density lipoprotein (LDL) cholesterol had the highest impact on the model. Multivariate logistic regression analysis showed that less extraocular muscle limitation and high TSI levels were associated with a high risk of poor intravenous methylprednisolone treatment response. As a result of analysis through SHAP, TSH, TSI, and LDL had the highest impact on the XGBoost model

Conclusion: TSI, extraocular muscle limitation, and LDL cholesterol levels may be useful in predicting steroid treatment response in patients with TED. In terms of machine learning, XGBoost showed relatively robust and reliable results for small datasets. The machine-learning model can assist in decision-making for further treatment of patients with TED.

KEYWORDS

extreme gradient boost, XGBoost, machine learning, graves orbitopathy, thyroid eye disease, novel risk factors

1 Introduction

Thyroid eye disease (TED) is a condition in which an immunological response to soft tissue in orbit creates severe patient discomfort, necessitating anti-inflammatory treatment if necessary. The current understanding of the underlying mechanism suggests that the interactions between the autoimmune response and thyroid-stimulating hormone (TSH) receptor-expressing orbital fibroblasts in orbit are the primary pathogenesis of TED. Recent research indicates that insulin-like growth factor-1 receptors play a synergistic role in TSH receptor (TSHR)-initiated signaling, in addition to TSHR activation (1, 2).

Immunosuppressive treatment with intravenous steroids has been the major treatment for active TED, and pulsed intravenous methylprednisolone has been shown to be effective. Radiation and immune modulators, such as rituximab and teprotumumab, can be employed to manage TED (3). However, as recommended by a recent consensus statement issued by the European Group on Graves Orbitopathy (EUGOGO), intravenous methylprednisolone (IVMP) remains the first-line treatment for moderate-to-severe and active TED (4).

According to previous research, up to 20%–25% of clinically active, moderate-to-severe TED patients may not respond to steroids and/or relapse after treatment discontinuation (5). The clinical activity score (CAS), TSHR antibody (TRAb) level, triglyceride level, and disease duration are reportedly associated with responsiveness to IVMP treatment (6, 7). However, the effect of these factors on IVMP remains controversial. Furthermore, systemic steroid medication may be advantageous in patients with TED; however, it should be used with caution because of possible systemic side effects (4). Moreover, the mechanism of action of high-dose steroids is unknown and must be weighed against its harmful effects (8). Therefore, predicting the steroid response in patients should be strongly considered.

In this study, we used eXtreme Gradient Boosting (XGBoost), a scalable machine-learning system for tree boosting, to predict steroid treatment responses in patients with TED. The XGBoost system is an open-source package. The usefulness and superiority of the system have been widely recognized in several machine-learning challenges (9). It uses a gradient-boosting framework to create machine learning with excellent efficiency, flexibility, and probability (9). To improve our model, we applied the synthetic minority oversampling technique (SMOTE) and feature selection (FS) to detect essential features for classification. Finally, the FS-based XGBoost model proposed the feature importance associated with responsiveness in detail with SHapley Additive exPlanations (SHAP).

To the best of our knowledge, this is the first time that the gradient boosting machine, the XGBoost system, has been used in this field. According to this study, despite the small amount of data utilized for training, the FS-based XGBoost model showed stable and high performance. Factors related to steroid responsiveness were investigated using univariate and multivariate statistical methods.

2 Methods

2.1 Patient recruitment

This retrospective study was conducted in accordance with the principles of the Declaration of Helsinki. This study was approved by the Institutional Review Board (IRB) of Pusan National University Hospital (IRB No. 2112-006-109), South Korea. Owing to the retrospective nature of the study, the IRB waived the need for patient consent.

In this study, patients with TED were enrolled at the Oculoplasty Clinic of Pusan National University Hospital between March 1, 2016 and December 31, 2020. When both eyes of a participant were eligible, the more severe eye was chosen for inclusion and data analysis.

Among 287 patients diagnosed with TED, 89 were enrolled and divided into two groups. One group showed responsiveness to steroid treatment (responsive) and the other showed no response to steroid treatment (unresponsive). Patients who were enrolled in this study satisfied all the following conditions: (1) a TED diagnosis based on the EUGOGO consensus and (2) patients who were in the active phase and moderate to severe category based on the CAS. The exclusion criteria were as follows: (1) treatment with other immunosuppressive therapies, decompression surgery, or radiotherapy within the previous 3 months or during IVMP therapy; (2) not having completed the full course of the IVMP treatment regimen; (3) incomplete ophthalmic assessment data and/or essential laboratory tests including free T4, T3, TSH, TRAb, and thyroid-stimulating immunoglobulin (TSI); and (4) patients with a previous medical history of glaucoma, diabetic retinopathy, maculopathy, or strabismus.

The treatment protocol was as follows: IVMP was administered by an endocrinologist for 12 weeks. MP was injected weekly on the same day at a 0.5-g dose and a 0.25-g dose for the remaining 6 weeks. We monitored liver function and blood glucose levels regularly. Anti-thyroid drugs or thyroxine were used to restore and maintain euthyroidism. Individuals who smoked were advised to abstain from smoking.

2.2 Data collection and outcome evaluation

One ophthalmologist in the oculoplastic division described all ophthalmic examinations in the medical records. Two investigators in the oculoplastic division analyzed the electronic medical records of these patients to determine their eligibility for the study. Demographic and biochemical data and additional pertinent clinical data were evaluated. TRAb levels were measured using the third-generation thyrotropin-binding inhibitor immunoglobulin assay, which inhibits the binding of labeled thyroid-stimulating autoantibody (TSAb) (monoclonal Ab clone #M22) to the TSH receptor. The TSI was measured using a thyroid-stimulating immunoglobulin (TSI) bioassay, which measures cyclic adenosine monophosphate production after TSAb binds to the TSH receptor. Smoking status was categorized as never smoked, ex-smoker, or

current smoker. In the statistical analysis, we classified ex-smokers and never-smokers as nonsmokers.

The presence of at least two of the following five ophthalmic parameters was defined as the response after full doses of IVMP treatment: 1) a reduction of at least 2 mm in proptosis; 2) a reduction of CAS by at least 2 points or <3/7; 3) an increase in visual acuity of at least one Snellen line; 4) improvement in diplopia (decrease in Gorman degree); and 5) no recurrence or additional radiation therapy at least 6 months after IVMP treatment. Based on these assessments, we divided the patients into "responsive" and "unresponsive groups." Patients who received additional radiation therapy after IVMP treatment or decompression surgery during IVMP treatment were classified as "unresponsive." Detailed patient recruitment flow charts are illustrated in Figure 1.

2.3 Data preparation: SMOTE and FS

We applied the synthetic minority oversampling technique and FS method to overcome the shortage of datasets and minimize computational complexity. We constructed a supervised machine-learning classification model using XGBoost in the following manner: 1) columns in the dataset were selected using the statistical hypothesis test (categorical variable: chi-squared or the Fisher exact test; continuous data: t-test or the Mann–Whitney U test). This eliminates redundant and irrelevant features to simplify the training model. 2) Next, FS was performed based on feature importance using a combination of random forest and XGBoost. Random forest and XGBoost FS methods have been applied in various studies and have shown good performance (10–12). We collected 17 top-ranked features in descending order of importance to describe responsiveness. Data preparation is performed by reducing data dimensionality and creating a model with only important features. 3) Finally, we applied SMOTE to increase the number of under-presented cases, as reported in another study (13). SMOTE takes each data point from a minority class and generates new members along a line that connects them to their k-nearest neighbors (13, 14). We did not employ data normalization and one-hot encoding in our model to prevent performance degradation (9).

In our experiments, the scikit-learn machine-learning framework was used to implement the XGBoost. During the 10-fold cross-validation, we optimized the parameters of the model. The hyperparameter values selected in our model are as follows: booster: gbtree; n_estimators: 300; max depth: 5; loss function binary: logistic; subsample = 1; lambda = 0.7; alpha = 0.15; and learning rate = 0.03. A flowchart of the experimental design is shown in Figure 2.

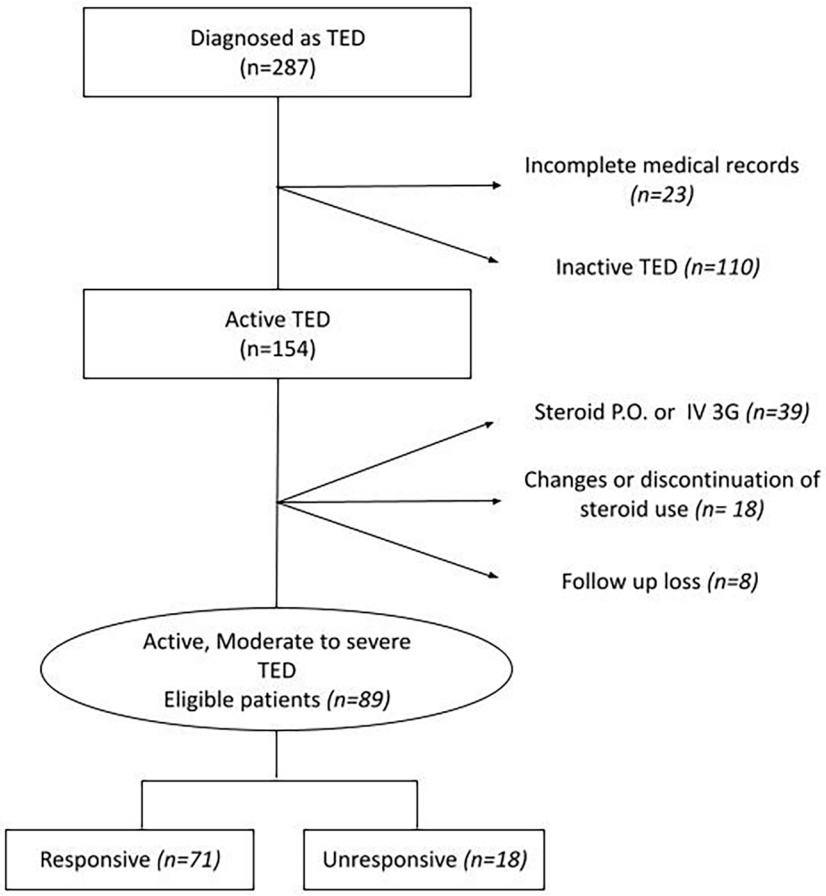

FIGURE 1
Flow chart of the data extraction. P.O., per oral; TED, thyroid eye disease; IV, intravenous; 3G, 3 grams.

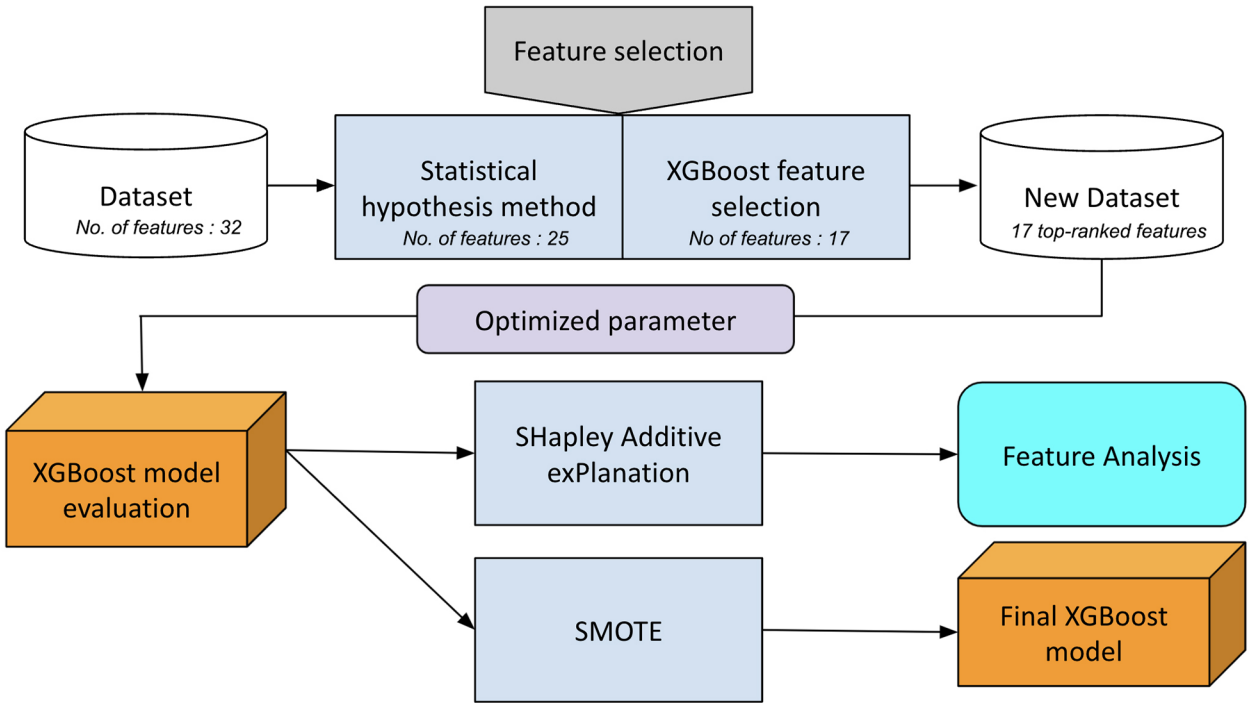

FIGURE 2
Flow chart of the hybrid feature selection to construct the final XGBoost predictive model.

2.4 XGBoost classifier

We underwent training for the state-of-the-art scalable boosting machine-learning method called XGBoost (9). Python language version 3.8 was used, and the hardware environment was an AMD Ryzen 7 8-core processor with 32 GB RAM and GeForce 2070Ti video cards (NVIDIA, Santa Clara, CA, USA). XGBoost is a tree-boosting technique that is highly scalable and accurate. Traditional gradient boosting incorporates the following components: (1) a regularization term into the objective function, (2) an approximate split using a weighted quantile sketch, (3) a sparsity-aware split function for parallel tree learning, and (4) out-of-core computation and cache-aware learning.

All participants were randomly assigned to either the training set (80%, 71 of 89 patients) or the test set (20%, 18 of 89 patients). The training dataset was not large, but XGBoost had significant adaptations to reduce overfitting and was applied to a wide range of issues. Other regularization approaches, such as shrinkage and column subsampling, were also included. Shrinkage reduces the impact of individual trees while allowing subsequent trees to improve the model. Column subsampling was initially widely utilized in random forests, although it has never been employed for tree boosting (15). According to feedback, column sub-sampling was applied, preventing overfitting compared to row sub-sampling. Furthermore, it also accelerates the parallel technique detailed in the subsequent sections of this paper.

2.5 Model evaluation and interpretation

The CV mean accuracy was used to evaluate the prediction performance of our model. To interpret the results and importance of each feature, we applied SHAP. This allowed us to provide a powerful and insightful measure of the relevance of a feature in a model. XGBoost model was compared with other machine learning algorithms and linear regression model which is traditional statistical model. We compared the XGboost model before and after the SMOTE statistically with CV mean accuracies.

2.6 Statistical analysis

The Kolmogorov–Smirnov test was used to determine the normality of the data distribution. Continuous data were compared using Student's t-test or Mann–Whitney U test. Categorical variables were compared using the chi-square test or Fisher's exact test. Univariate logistic regression analysis was performed to determine the significance of each variable. Significant variables identified in the univariate analysis were then subjected to multivariate logistic regression analysis to identify the independent factors associated with responsiveness to IVMP treatment. Statistical Package for the Social Sciences (SPSS) software (version 22.0; SPSS, Chicago, IL, USA) was used for all statistical analyses. Statistical significance was set at $P<0.05$.

3 Results

3.1 Patients characteristics

All variables, including the demographic, clinical, and biochemical characteristics, are presented in Table 1. Among the 89 active, moderate-to-severe TED patients who were administered 4.5 g of methylprednisolone intravenously, 71 (79.8%) were included in the responsive group, and 18 (20.1%) were included in the responsive and unresponsive groups. When comparing never smokers to ex-smokers in the responsive group, the response rate was significantly higher in former smokers than in never smokers (P = 0.029, 100% vs. 71.2%). When we classified ex-smokers as never smokers, there was no difference in responsiveness between never-smokers and current smokers (P = 0.377) (data not shown). CAS was higher in the unresponsive group, but the difference was not statistically significant (P = 0.065), and extraocular movement limitation was more severe in the responsive group (P = 0.054). Overall, there were no significant differences between the two groups, except for the smoking status.

3.2 Results of the univariate and multivariate analysis

The summary statistics of the univariate and multivariate analyses between the responsive and unresponsive groups are shown in Table 2. As shown in Table 2, univariate logistic regression analysis showed that only extraocular movement limitation was significantly associated with responsiveness after IVMP treatment (odds ratio [OR] 0.632, 95% confidence interval [CI] 0.40 to 0.97; P = 0.044). After adjusting for confounding factors, extraocular muscle limitation and TSI were associated with the IVMP response. Less extraocular muscle limitation (OR 0.463, 95% CI 0.25 to 0.85, P = 0.014) and high TSI level were associated with a high risk of poor IVMP treatment response (OR 1.005, 95% CI 1.000 to 1.009, P = 0.038).

3.3 FS

Based on the results shown in Table 1, the least associated variables of age, height, type of TED, symmetry, vision, total cholesterol, and T3 were excluded from the original 32 variables in the first FS method (P = 0.910, P = 0.933, P = 0.791, P = 0.729, P = 0.959, P = 0.938, and P = 0.806, respectively). Second, we selected the final 17 top-ranked features (TSI, low-density lipoprotein [LDL] cholesterol, body mass index [BMI], TSH, Gorman score, Tg, TSHR ab, Visual field (VF) index, weight, high-density lipoprotein cholesterol, difference in exophthalmos, free T4, exophthalmos, duration of Graves' disease, and CAS) based on the random forest and XGBoost feature importance methods.

3.4 Results of XGBoost classifier

We analyzed the features to predict responsiveness to IVMP treatment using both the random forest classifier and XGBoost. Before we applied SMOTE, the cross-validation accuracies of both models were 0.84 and 080. Using SMOTE, 142 datasets were created, and the final performance of XGBoost is presented in Table 3. When evaluated using the confusion matrix, the relatively high false-positive of 14 cases in the first model and 82.9% positive predictive value (PPV) before applying SMOTE were noticeably improved after using SMOTE. The false-positive of the model after applying SMOTE were 8 and PPV was 88.8%.

3.5 Important features predicting responsiveness after IVMP treatment investigated by SHAP

The SHAP summary results are shown in Figure 3, which rank features according to their importance in predicting responsiveness to IVMP treatment. TSH, TSI, and LDL cholesterol levels had the greatest effects on the model. Among them, TSI and LDL cholesterol showed a specific pattern in which a higher TSI level was associated with a significant impact on the model and a lower LDL cholesterol level was associated with a significant impact on the model. Figure 4 shows the effect of TSI and LDL cholesterol on responsiveness. TSI levels lower than 400 decreased the predicted probability, while a high level of TSI increased the predicted treatment responsiveness probability. An LDL cholesterol level of 80–100 increases the predicted probability, and an LDL cholesterol level over 110 decreases the predicted probability. TSH showed no definite pattern on SHAP dependence analysis.

4 Discussion

In this study, we discovered that severe extraocular movement limitation indicated a better response to IVMP treatment. Concurrently, higher TSI levels have been linked to a poor response to IVMP treatment in patients with active moderate-to-severe TED. Ahn and Lee (16) reported that Extra ocular muscle(EOM) enlargement on CT is a predictor of a favorable steroid treatment response, and Xu et al. found that the thickness of the EOM on magnetic resonance imaging was considerably higher in the responsive group than in the unresponsive group. Moreover, Naik et al. (17) classified soft tissue involvement in TED as either fat growth or predominant muscle enlargement, with the latter being more susceptible to steroid treatment. Inflammation and edematous changes in the EOM cause EOM enlargement and limit motility, which is consistent with the results of several other studies. In the multivariate analysis excluding interference from other factors, we found an OR of 0.463 (p = 0.014) for patients with severe extraocular movement limitation in response to treatment. However, this finding does not indicate better extraocular movement after treatment, and the overall inflammatory symptoms resolved. Additional research is required to determine extraocular movements based on treatment.

Although there is limited research regarding TSI, in 1995, Mori et al. reported that TSAb could be a valuable marker for predicting the efficacy of methylprednisolone pulse therapy in TED patients. In nine TED patients treated with intravenous methylprednisolone in this study, they found that high levels of TSAb are expected to be a factor for good response to therapy. Conversely, our study showed that a

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TABLE 1 Demographic characteristics of the responsive and unresponsive group.

	Total	Response to steroid treatment		
		Responsive	Unresponsive	p-value
Number of patients (%)	89	71 (79.8)	18 (20.1)	
Age (years, mean ± SD)	51.34 ± 13.79	51.25 ± 13.67	51.67 ± 14.62	0.910[a]
Sex (male:female)	39:50	32:39	7:11	0.637[b]
Height (cm, mean ± SD)	163.35 ± 7.37	163.38 ± 7.26	163.22 ± 8.04	0.933[a]
Weight (kg, mean ± SD)	62.67 ± 10.18	62.45 ± 10.79	63.55 ± 7.46	0.683[a]
BMI (kg/m^2, mean ± SD)	23.39 ± 2.69	23.28 ± 2.89	23.81 ± 1.66	0.320[a]
Thyroid eye disease type (fat dominant: muscle dominant)	27:62	22:49	5:13	0.791[b]
Thyroid eye disease symmetry (both: asymmetric: unilateral)	57:28:4	44:23:4	13:5:0	0.729[d]
Graves' disease duration (months, mean ± SD)	32.01 ± 59.47	33.70 ± 59.87	25.33 ± 59.07	0.289[c]
Thyroid eye disease duration (months, mean ± SD)	17.00 ± 35.77	19.52 ± 39.61	7.06 ± 5.68	0.566[c]
Family history (present: absent)	20:69	15:56	5:13	0.540[d]
Smoking (never smoker: ex-smoker: current smoker)	52:13:24	38:13:20	14:0:4	
never smoker: current smoker		37:21	15:3	0.119[b]
never smoker: ex-smoker		37:13	15:0	*0.029[b]
ex-smoker: current smoker		13:21	0:3	0.538[b]
CAS (mean ± SD)	3.98 ± 1.02	3.87 ± 0.97	4.39 ± 1.14	0.065[c]
Gorman (mean ± SD)	1.22 ± 1.32	1.35 ± 1.32	0.72 ± 1.23	0.054[c]
Visual acuity (OD) (mean ± SD)	0.12 ± 0.20	0.12 ± 0.20	0.14 ± 0.23	0.672[c]
Visual acuity (OS) (mean ± SD)	0.12 ± 0.26	0.12 ± 0.28	0.12 ± 0.21	0.959[c]
Intraocular pressure (OD) (mmHg, mean ± SD)	16.16 ± 3.09	16.24 ± 3.20	15.83 ± 2.66	0.613[a]
Intraocular pressure (OS) (mmHg, mean ± SD)	16.23 ± 3.17	16.28 ± 3.20	16.02 ± 3.14	0.761[a]
Exophthalmos measurement (OD) (mm, mean ± SD)	18.12 ± 3.03	17.90 ± 3.13	18.97 ± 2.44	0.165[c]
Exophthalmos measurement (OS)(mm, mean ± SD)	18.19 ± 2.76	17.94 ± 2.80	19.19 ± 2.43	0.098[c]
Difference in proptosis (mm, mean ± SD)	1.28 ± 1.12	1.35 ± 1.15	1.00 ± 0.97	0.229[c]
Extraocular movement limitation (mean ± SD)	1.44 ± 1.44	1.60 ± 1.50	0.81 ± 0.99	0.054[c]
Visual field index (OD) (%, mean ± SD)	94.40 ± 11.91	95.10 ± 7.65	91.67 ± 21.98	0.450[c]
Visual field index (OS) (%, mean ± SD)	94.25 ± 13.97	94.67 ± 11.69	92.58 ± 21.07	0.484[c]
Free T4 (ng/dL, mean ± SD)	1.39 ± 0.61	1.41 ± 0.64	1.33 ± 0.45	0.818[c]
TSH (mIU/L, mean ± SD)	3.25 ± 10.03	2.50 ± 5.03	6.21 ± 20.13	0.072[c]
T3 (ng/dL, mean ± SD)	147.82 ± 87.07	148.71 ± 93.01	144.32 ± 60.08	0.806[c]
TSH receptor antibody (IU/mL, mean ± SD)	13.49 ± 13.40	12.72 ± 13.00	16.55 ± 14.88	0.299[c]
Thyroid-stimulating immunoglobulin (%, mean ± SD)	397.45 ± 166.31	383.15 ± 174.34	453.87 ± 117.46	0.107[a]
Total cholesterol (mg/dL, mean ± SD)	186.71 ± 35.38	186.85 ± 37.05	186.12 ± 28.70	0.938[a]
LDL cholesterol (mg/dL, mean ± SD)	114.84 ± 30.91	115.96 ± 32.83	110.43 ± 21.93	0.501[a]
HDL cholesterol (mg/dL, mean ± SD)	59.41 ± 19.14	58.40 ± 15.67	63.39 ± 29.38	0.980[c]
Triglyceride (mg/dL, mean ± SD)	165.31 ± 116.07	174.05 ± 125.52	130.83 ± 57.27	0.146[c]

BMI, body mass index; CAS, clinical activity score; TSH, thyroid-stimulating hormone; LDL, low-density lipoprotein; HDL, high-density lipoprotein; OD, oculus dexter; OS, oculus sinister; SD, standard deviation.
Values are presented as mean ± standard deviation
*Statistically significant values with p <0.05.
[a]Student's t-test,
[b]chi-squared test,
[c]Mann–Whitney U test,
[d]Fisher's exact test.

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TABLE 2 Factors associated with the response to the steroid treatment investigated by univariate and multivariate binary logistic regression analysis (for an unresponsive group).

Univariate analysis	P-value	Odds ratio	95% confidence interval	
			Lower	Upper
Age	0.909	1.002	0.965	1.041
Sex	0.637	1.289	0.448	3.709
BMI	0.459	1.076	0.887	1.305
Thyroid eye disease type (fat dominant: muscle dominant)	0.792	1.167	0.371	3.678
Graves' disease duration	0.595	0.997	0.987	1.007
Thyroid eye disease duration	0.254	0.970	0.920	1.022
Smoking status				
Never smoker	0.318	(ref)		
Ex-smoker	0.999	0.999	0	
Current smoker	0.130	0.352	0.091	1.360
CAS				
3	0.637	(ref)		
4	0.173	2.545	0.664	9.751
5	0.176	2.909	0.620	13.651
6	0.314	2.667	0.396	17.977
7	1.000	0	0	
Gorman				
No diplopia	0.260	(ref)		
Intermittent diplopia	0.329	0.439	0.084	2.288
Inconstant diplopia	0.467	0.537	0.101	2.862
diplopia	0.063	0.220	0.045	1.084
Exophthalmos measurement (OD)	0.181	1.132	0.944	1.357
Exophthalmos measurement (OS)	0.088	1.197	0.973	1.471
Difference in proptosis	0.236	0.724	0.424	1.235
Extraocular muscle limitation	*0.044	0.632	0.405	0.987
Visual field index (OD)	0.312	0.981	0.945	1.018
Visual field index (OS)	0.577	0.991	0.959	1.023
Free T4	0.647	0.799	0.306	2.086
TSH	0.234	1.029	0.982	1.078
T3	0.848	0.999	0.993	1.006
TSH receptor antibody	0.280	1.020	0.984	1.059
TSI	0.112	1.003	0.999	1.006
Total cholesterol	0.937	0.999	0.985	1.014
LDL cholesterol	0.497	0.994	0.978	1.011
HDL cholesterol	0.334	1.012	0.988	1.037
Triglyceride	0.166	0.995	0.987	1.002
Multivariate analysis				
Extraocular muscle limitation	*0.014	0.463	0.251	0.855

(Continued)

TABLE 2 Continued

Univariate analysis	P-value	Odds ratio	95% confidence interval	
			Lower	Upper
TSI	*0.038	1.005	1.000	1.009
CAS				
3	0.377	(ref)		
4	0.208	2.620	0.584	11.748
5	0.064	5.913	0.899	38.898
6	0.148	5.894	0.534	65.031
7	1.000			
Smoking status				
Never smoker	0.541	(ref)		
Ex-smoker	0.998	0.000	0.000	
Current smoker	0.268	0.415	0.088	1.965

BMI, body mass index; CAS, clinical activity score; TSH, thyroid-stimulating hormone; TSI, thyroid-stimulating immunoglobulin; LDL, low-density lipoprotein; HDL, high-density lipoprotein; OD, oculus dexter; OS, oculus sinister.
*Statistically significant values with p <0.05.
Model chi-squared test p=0.001, Nagelkerke R2 = 0.387, Hosmer and Lemeshow test p=0.707.

higher TSI level was significantly associated with poor responsiveness to treatment (OR, 1.005; p = 0.038) in the multivariate analysis. Furthermore, the TSI level analyzed with XGBoost was one of the most important features for predicting treatment responsiveness.

In terms of model interpretation, we applied SHAP to obtain a compelling and insightful measure of the importance of a feature in a model (18). SHAP is a method for estimating the contribution of each factor or characteristic, and it breaks down the prediction to show the impact of each feature (19). According to our SHAP results, we found specific patterns of TSI and LDL cholesterol levels. High TSI values over 400 and lower LDL cholesterol values under approximately 120 mg/dL enhanced the model prediction and significantly impacted the model. Both of these were the top two important features analyzed with permutation feature importance in the FS process.

The TSI has been reported as an excellent marker in patients with TED because of its sensitivity and specificity (20). TED was observed in TSI-positive but TRab-negative participants in one controlled trial, and TSI had a striking positive connection with the clinical activity and severity of TED. They also found that TSI causes TED pathogenesis even after anti-thyroid medication, and that TSI positivity was low in Graves' disease(GD) patients without TED. Moreover, several studies have emphasized the need for TSI monitoring throughout the disease follow-up and treatment (21, 22). From this point of view and from our research, TSI is useful for diagnosis and follow-up, and for predicting steroid therapy response prior to treatment. According to our study's SHAP analysis of TSI, when the TSI level exceeds approximately 400%, the impact on model output increases, and 400% serves as a critical

TABLE 3 Performance of models.

	CV mean accuracy		Standard deviation
Random Forest	0.805		0.282
Linear Support vector machine	0.709		0.140
KNN	0.776		0.084
Decision Tree	0.673		0.106
Naïve Bayes	0.688		0.155
Logistic regression	0.698		0.163
XGboost	0.808		0.101
XGboost (SMOTE)	0.861		0.093
	XGBoost	XGboost (SMOTE)	P-value
CV mean accuracy	0.808	0.861	0.019

XGBoost model showed higher accuracy than other classic machine learning algorithm and traditional statistical algorithm. After using SMOTE, the mean CV accuray of XGBoost was highly improved. Ten-fold cross-validation was applied for these algorithms and mean CV accuracies were expressed due to its shortage of dataset.
CV cross-validation; KNN k-nearest neighbor; SMOTE synthetic minority oversampling technique

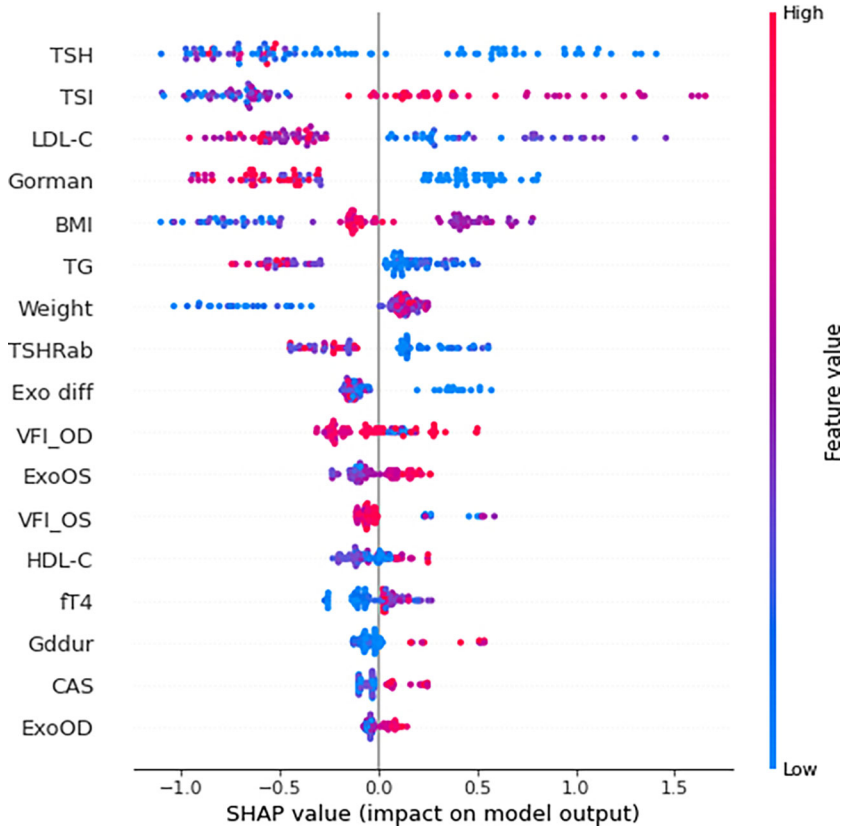

FIGURE 3
SHAP summary plot of feature importance to predict steroid responsiveness. SHAP, SHapley Additive exPlanations; TSH thyroid-stimulating hormone; TSI thyroid-stimulating immunoglobulin; LDL-C low-density lipoprotein cholesterol; BMI body mass index; TG triglyceride; TSHRab thyroid-stimulating hormone receptor antibody; Exo diff differences of exophthalmos; VFI_OD visual field index_oculus dexter; ExoOS exophthalmos in oculus sinister; VFI_OS visual field index_oculus sinister; HDL-C high-density lipoprotein cholesterol; Gddur disease duration of graves disease; CAS clinical activity score; ExoOD exophthalmos in oculus dexter.

pivot point for predicting responsiveness to IVMP treatment. When combined with statistical analyses, it is reasonable to assume that a TSI of 400% or above does not respond well to treatment. However, it is noteworthy that the AI model does not predict the outcome on the basis of this single attribute.

Several studies have been conducted to determine the relationship between lipid-lowering agents, LDL-cholesterol, and TED. According to Stein et al. (23), patients treated with statins had a 40% decreased risk of developing TED because of the anti-inflammatory action of statins. Sabini et al. (24) found a strong association between the presence of TED

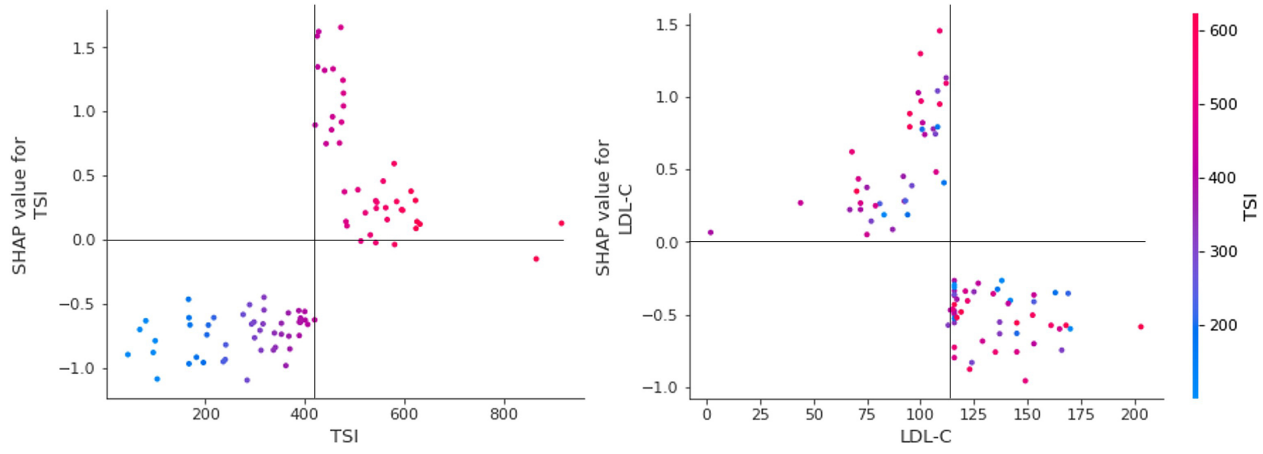

FIGURE 4
SHAP dependence plot for essential features. SHAP dependency analysis of TSI on the left and SHAP dependency analysis of LDL-cholesterol is described on the right. SHAP, SHapley Additive explanation; TSI thyroid-stimulating immunoglobulin; LDL-C low-density lipoprotein cholesterol.

and both total and LDL cholesterol in patients with newly diagnosed GD. Additionally, there is a considerable direct link between TED and LDL cholesterol levels. LDL cholesterol levels were shown to be considerably higher in individuals with TED, and cutoff values for LDL cholesterol were established at 118.4 mg/dL, with levels above these values significantly related to an elevated risk of TED. Surprisingly, a value of 115 mg/dL for LDL cholesterol in the artificial intelligence analysis in our study revealed a critical insight. Although LDL did not demonstrate any statistical significance in statistical analyses, including multiple regression, it had the greatest influence on the construction of the AI model; when the value was less than the reference point near 115–120 mg/dL, it had a higher impact on the model's prediction. Additional inflammation caused by a high LDL cholesterol may be taken to suggest that it adversely affects the prediction of steroid response, but once again, it is unreasonable to anticipate a patient's treatment response in the clinic based on this factor (25, 26).

Finally, a final XGBoost model with high performace was constructed using 17 factors, and a more trustworthy and useful model was constructed using the SMOTE technique to overcome the high false-positive rate.

5 Conclusion

Consequently, statistically, EOM limitation and TSI level had a significant effect on the prediction of treatment response, and among the factors proven using machine learning, TSH, TSI, and LDL-C were the top three features; however, in the case of TSH, there were difficulties in the interpretation.

Although the number of patients was limited and the study was retrospective, this is the first study to validate the steroid response factor *via* XGBoost. We believe that this study verifies the applicability of the gradient boosting model to a variety of ophthalmic diseases by demonstrating that noteworthy results were obtained.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: Due to its ethical concerns, supporting data cannot be made openly available. further inquiries can be directed to the corresponding author. Requests to access these datasets should be directed to Jungyul Park, ophjyp@naver.com.

Ethics statement

The studies involving human participants were reviewed and approved by The Institutional Review Board (IRB) of Pusan National University Hospital (IRB No. 2112-006-109), South Korea. Owing to the retrospective nature of the study, the IRB waived the need for patient consent. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

Conception and design of the study (JP, JK, HC); conduction of the study (JP, JK, HC); collection and management of data (JP, JK); data analysis (JP, JK); data interpretation (JP, D-MR, JK, HC); and preparation, review, and approval of the manuscript (JP, JK, D-MR, HC).

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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References

1. Hu S, Wang Y, He M, Zhang M, Ding X, Shi B. Factors associated with the efficacy of intravenous methylprednisolone in moderate-to-severe and active thyroid-associated ophthalmopathy: A single-centre retrospective study. *Clin endocrinology.* (2019) 90 (1):175–83. doi: 10.1111/cen.13855

2. Smith TJ. TSH-receptor-expressing fibrocytes and thyroid-associated ophthalmopathy. *Nat Rev Endocrinology.* (2015) 11(3):171–81. doi: 10.1038/nrendo.2014.226

3. Smith TJ, Kahaly GJ, Ezra DG, Fleming JC, Dailey RA, Tang RA, et al. Teprotumumab for thyroid-associated ophthalmopathy. *New Engl J Med* (2017) 376 (18):1748–61. doi: 10.1056/NEJMoa1614949

4. Bartalena L, Baldeschi L, Bodoridis K, Eckstein A, Kahaly GJ, Marcocci C, et al. The 2016 European thyroid Association/European group on graves' orbitopathy guidelines for the management of graves' orbitopathy. *Eur Thyroid J* (2016) 5(1):9–26. doi: 10.1159/000443828

5. Zang S, Ponto K, Kahaly G. Intravenous glucocorticoids for graves' orbitopathy: Efficacy and morbidity. *J Clin Endocrinol Metab* (2011) 96(2):320–32. doi: 10.1210/jc.2010-1962

6. Eckstein AK, Plicht M, Lax H, Neuhäuser M, Mann K, Lederbogen S, et al. Thyrotropin receptor autoantibodies are independent risk factors for graves' ophthalmopathy and help to predict severity and outcome of the disease. *J Clin Endocrinol Metab* (2006) 91(9):3464–70. doi: 10.1210/jc.2005-2813

7. Mourits MP, Prummel MF, Wiersinga WM, Koornneef L. Clinical activity score as a guide in the management of patients with graves' ophthalmopathy. *Clin endocrinology.* (1997) 47(1):9–14. doi: 10.1046/j.1365-2265.1997.2331047.x

8. Taylor PN, Zhang L, Lee RWJ, Muller I, Ezra DG, Dayan CM, et al. New insights into the pathogenesis and nonsurgical management of graves orbitopathy. *Nat Rev Endocrinology.* (2020) 16(2):104–16. doi: 10.1038/s41574-019-0305-4

9. Chen T, Guestrin C. Xgboost: A scalable tree boosting system. *Proc 22nd ACM sigkdd Int Conf knowledge Discovery Data mining.* (2016) 2016:785–94. doi: 10.1145/2939672.2939785

10. Al-Barakati HJ, Saigo H, Newman RH. RF-GlutarySite: A random forest based predictor for glutarylation sites. *Mol omics.* (2019) 15(3):189–204. doi: 10.1039/C9MO00028C

11. White C, Ismail HD, Saigo H. CNN-BLPred: A convolutional neural network based predictor for β-lactamases (BL) and their classes. *BMC Bioinf* (2017) 18(16):221–32. doi: 10.1186/s12859-017-1972-6

12. Yu J, Shi S, Zhang F, Chen G, Cao M. PredGly: Predicting lysine glycation sites for homo sapiens based on XGboost feature optimization. *Bioinformatics* (2019) 35 (16):2749–56. doi: 10.1093/bioinformatics/bty1043

13. Choi S, Park J, Park S, Byon I, Choi HY. Establishment of a prediction tool for ocular trauma patients with machine learning algorithm. *Int J Ophthalmol* (2021) 14(12):9. doi: 10.18240/ijo.2021.12.20

14. Parsa AB, Movahedi A, Taghipour H, Derrible S, Mohammadian AK. Toward safer highways, application of XGBoost and SHAP for real-time accident detection and feature analysis. *Accident Anal Prev* (2020) 136:105405. doi: 10.1016/j.aap.2019.105405

15. Chapelle O, Chang Y. Yahoo! learning to rank challenge overview. *Proc Learn to rank challenge* (2011) 14:1–24.

16. Ahn HY, Lee JK. Intravenous glucocorticoid treatment for Korean graves' ophthalmopathy patients. *J Korean Med Science.* (2020) 35(23):e177. doi: 10.3346/jkms.2020.35.e177

17. Naik VM, Naik MN, Goldberg RA, Smith TJ, Douglas RS. Immunopathogenesis of thyroid eye disease: Emerging paradigms. *Survey ophthalmology.* (2010) 55(3):215–26. doi: 10.1016/j.survophthal.2009.06.009

18. Ribeiro MT, Singh S, Guestrin C. " why should i trust you?" explaining the predictions of any classifier. *Proc 22nd ACM SIGKDD Int Conf knowledge Discovery Data Min* (2016) 1135–44. doi: 10.1145/2939672.2939778

19. Shapley LS. A Value for n-Person Games. In: Kuhn H., Tucker A., Eds., *Contributions to the Theory of Games II*, Princeton University Press, Princeton. (1953) p307–17.

20. Lytton SD, Ponto KA, Kanitz M, Matheis N, Kohn LD, Kahaly GJ. A novel thyroid stimulating immunoglobulin bioassay is a functional indicator of activity and severity of graves' orbitopathy. *J Clin Endocrinol Metab* (2010) 95(5):2123–31. doi: 10.1210/jc.2009-2470

21. Fassi DE, Banga JP, Gilbert JA, Padoa C, Hegedüs L, Nielen CH. Treatment of graves' disease with rituximab specifically reduces the production of thyroid stimulating autoantibodies. *Clin Immunol* (2009) 130(3):252–8. doi: 10.1016/j.clim.2008.09.007

22. Salvi M, Vannucchi G, Campi I, Currò N, Dazzi D, Simonetta S, et al. Treatment of graves' disease and associated ophthalmopathy with the anti-CD20 monoclonal antibody rituximab: An open study. *Eur J endocrinology.* (2007) 156(1):33–40. doi: 10.1530/eje.1.02325

23. Stein JD, Childers D, Gupta S, Talwar N, Nan B, Lee BJ, et al. Risk factors for developing thyroid-associated ophthalmopathy among individuals with graves disease. *JAMA ophthalmology.* (2015) 133(3):290–6. doi: 10.1001/jamaophthalmol.2014.5103

24. Sabini E, Mazzi B, Profilo MA, Mautone T, Casini G, Rocchi R, et al. High serum cholesterol is a novel risk factor for graves' orbitopathy: results of a cross-sectional study. *Thyroid* (2018) 28(3):386–94. doi: 10.1089/thy.2017.0430

25. Busnelli M, Manzini S, Froio A, Vargiolu A, Cerrito MG, Smolenski RT, et al. Diet induced mild hypercholesterolemia in pigs: Local and systemic inflammation, effects on vascular injury–rescue by high-dose statin treatment. *PloS One* (2013) 8(11):e80588. doi: 10.1371/journal.pone.0080588

26. Ponziani FR, Pecere S, Gasbarrini A, Ojetti V. Physiology and pathophysiology of liver lipid metabolism. *Expert Rev Gastroenterol hepatology.* (2015) 9(8):1055–67. doi: 10.1586/17474124.2015.1056156

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Update on the surgical management of Graves' orbitopathy

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Graves' orbitopathy (GO) is a complex autoimmune disorder of the orbit that causes the eye to appear disfigured. GO is typically associated with Graves' disease, an inflammatory autoimmune condition that is caused by thyrotropin receptor autoantibodies. Although our knowledge of the pathophysiology of GO has improved, its exact pathogenesis remains unclear. Some patients suffer from disfigurement, double vision, and even vision loss rather than hyperthyroidism. The disease severity and activity prompt different treatments, as the signs of GO are heterogeneous, so their management can be very complex. Despite medical advances, the first-line treatment for moderate-to-severe active GO is still glucocorticoids, while surgery can be critical for the treatment of chronic inactive GO. Surgery is sometimes required in the acute phase of the disease when there is an immediate risk to vision, such as in dysthyroid optic neuropathy. Most surgeries for GO are rehabilitative and subdivided into three categories: decompression, strabismus repair, and lid surgery. This review is a basic overview of the field, with up-to-date knowledge of the surgical techniques for GO. We review and summarize recent literature on the advances in surgery for GO to provide up-to-date insights on the optimal surgical treatment for GO.

KEYWORDS

surgery, Graves' orbitopathy (GO), decompression, strabismus, LID

Introduction

Graves' disease (GD) is an autoimmune disease of the thyroid gland; autoantibodies bind to the thyrotropin receptor on thyroid follicular cells. The annual incidence of GD is estimated to be 20-30 per 100,000 according to studies in Swedish populations (1–3) and approximately 20-50 per 100,000 according to more recent reviews (4, 5). The disease principally affects women aged 30 to 40 years, and the overall prevalence is 0.5% (6). Graves' orbitopathy (GO) is a complex inflammatory disorder of the orbit typically associated with GD. Limited data are available regarding GO incidence (7). A recent review clearly summarized what is known (7). According to Bartley (1994), the age-adjusted incidences of GO were 16 and 2.9 per 100,000 person-years in women and men, respectively (8). A recent Danish study investigated the nationwide incidence of thyroid eye disease (TED), a synonym of GO (9). The mean annual nationwide incidences of TED were 8.0 and 1.9 per 100,000 person-years in women and men, respectively; the mean incidence was 5.0 in the overall population, which included both women and men. Notably, GO develops in up to 50% of patients with GD (10–14). In a Swedish study, 75% of hyperthyroid patients had GD; 20% of these patients had thyroid-associated eye symptoms/signs (3). However, radiological orbital imaging revealed subtle abnormalities in 70% of patients with GD, although the patients reported no symptoms (15). The overall prevalence of GO is unclear. In 2013, a large Italian study reported that 73.7% of GD patients exhibited no ocular involvement, whereas > 20% of GD patients experienced mild, moderate-to-severe, and sight-threatening GO (16).

Most GO patients respond to conservative treatment and do not require surgery. However, approximately 5% of GO patients undergo surgery in the first year after diagnosis; up to 20% of GO patients undergo surgery within the first decade (17). When GO develops into dysthyroid optic neuropathy (DON), surgical intervention is required. In a British population, DON patients constituted approximately 2% of all GO patients; they initially received steroids, but nearly 50% of the patients required surgical orbital decompression within 9 months (18). In 2008, a nationwide cohort study in Denmark revealed that the incidence of diplopia in GO patients was approximately 17-51% (19). The 4-year cumulative incidence of strabismus was 10%, and 8% of such cases required surgery (9). A multidisciplinary approach combining medical and surgical strategies may benefit GO patients. Because signs of GO are heterogeneous, management can be complex. The European Group on Graves' orbitopathy (EUGOGO) recently stated that an optimal treatment has not been identified (20).

Typically, GO can be categorized into two phases: active and inactive. Active GO is associated with a progressive active inflammation over 6-24 months that expands the extraocular muscles (EOMs) and orbital fat. The presence of edema, inflammation, and accumulated interstitial glycosaminoglycan lead to the expansion of orbital contents. The condition can subsequently develop into proptosis; conjunctival chemosis; upper eyelid swelling; hyperemia of the eyelid, conjunctiva, and/or plica; strabismus; and (most seriously) a corneal ulcer or DON. When severe, the orbital apex can become crowded by the expansion of orbital soft tissues. These changes can trigger DON, a sight-threatening complication experienced by up to 4-8% of GO patients (8, 21, 22). A multicenter study regarding the clinical features of DON in Europe showed that orbital imaging could reveal apical muscle crowding in 88% of DON patients (23). However, the authors of the study noted that DON patients may lack severe proptosis and orbital inflammation (23). Most active GO is assumed to be self-limiting because, unlike the target organs of other human autoimmune diseases (e.g., the synovium in rheumatoid arthritis), most of the orbit lacks lymphoid tissue. Thus, lymphoid neogenesis may not occur within the orbit, which limits the duration of the autoimmune disease (24). However, the autoimmune process involves incapacitating sequelae that are usually initially active but then inactive (12, 25). Some patients experience disfigurement, double vision, and vision loss, rather than hyperthyroidism. Furthermore, in addition to causing daily physical discomfort, GO symptoms negatively impact mental health (26) and quality-of-life (27). Among patients with mild GO, 15-20% experience progression to greater severity, as reflected by a change in the clinical activity score (24). Laurberg et al. (28) reported that approximately 5% of GD patients developed moderate-to-severe GO; it was unclear whether their definition of moderate-to-severe GO included sight-threatening GO. Nevertheless, approximately 2-5% of patients with GO will progress to moderate-to-severe disease (13, 29–32). When sight-threatening GO is absent, but symptoms are seriously disabling in terms of significantly compromising daily life, EUGOGO recommends immunosuppression (if GO is active) and surgical intervention (if GO is inactive). Patients with moderate-to-severe GO usually have two or more of the following: lid retraction ≥ 2 mm, moderate or severe soft tissue involvement, exophthalmos ≥ 3 mm above the normal ethnicity- and sex-specific value, and constant or intermittent diplopia (33, 34). A small minority of patients require surgery when the self-limiting inflammatory phase has passed.

Thus far, first-line treatment to reduce orbital inflammation has involved high-dose glucocorticoids. In patients with moderate-to-severe GO, intravenous glucocorticoids are more effective and cause fewer adverse effects, compared with oral glucocorticoids (20). Immunosuppressants (azathioprine, cyclosporin) and orbital irradiation can be combined with oral or intravenous glucocorticoids as second-line treatments for moderate-to-severe GO (20). Recently, teprotumumab, a 150-kDa monoclonal antibody against IGF-1R, was reported to be effective and safe in patients with moderate-to-severe GO; the drug provides proptosis improvement similar to the result of

orbital decompression surgery (35, 36). Nevertheless, surgery plays an important role in the treatment of chronic inactive GO. Importantly, surgery is rarely performed in the acute phase, which may involve DON, despite clinical evidence that early orbital decompression can limit progression to more severe disease in patients with significant orbital congestion (24). According to the 2021 EUGOGO guidelines, among patients with active GO, orbital decompression is indicated for patients with severe exposure keratopathy, DON patients who do not respond to intravenous glucocorticoids within 1-2 weeks, and patients with recent eyeball subluxation (20). Most surgery is rehabilitative and can be subdivided into decompression, strabismus repair, and lid surgery. Generally, orbital decompression surgery is usually performed first, followed by strabismus surgery and then lid surgery (37, 38), because orbital decompression surgery may affect strabismus status. Additionally, decompression and/or strabismus surgery can affect the contours and/or heights of the upper and lower eyelids (39).

Overall, the surgical GO options are sparse, and the chosen method is determined on the basis of specific changes to the orbit. The procedure of choice when correcting globe proptosis is orbital wall decompression; squint surgery is often used to treat persistent diplopia. This surgery seeks to preserve binocular single vision in both the primary and downgaze positions; patients are thus likely to exhibit residual diplopia in other gaze directions (40). Blepharoplasty lowers the eyelids, lifts the midface, and reduces the brow fat pad; this surgery removes bags and tightens the skin. Upper lid retraction can be treated via levator advancement or Mueller muscle recession surgery (41).

This paper summarizes current knowledge regarding GO surgery; we systematically reviewed literature in the PubMed database. Thus, this is a basic overview of GO surgery, with up-to-date insights concerning optimal surgical treatments.

Orbital decompression

Orbital decompression is widely presumed to improve exophthalmos and DON. Orbital decompression may involve only fat removal; alternatively, it may involve one-, two-, three-, or four-wall bone decompression with or without orbital fat removal. The procedure is performed using an external or an endoscopic approach. Surgical orbital decompression involves the removal of fat and/or one or more of the bony walls to provide space for overgrown EOMs and orbital fat tissue. Although many studies have been conducted regarding orbital decompression, no consensus has emerged with respect to an optimal approach. Considering the absence of randomized controlled trials, no procedure is considered better than others. Additionally, a synthesis is difficult because studies vary in terms of surgeon expertise, patient disease stage, surgical indications, and evaluation methods (42).

In 1911, Dollinger was the first to introduce orbital decompression with lateral wall decompression (43). Subsequently, the Walsh-Ogura technique was established for use in removing the ocular floor and medial orbital wall (44). Orbital decompression for GO management has further evolved over the past 30 years; several approaches have been combined to simultaneously remove multiple walls, and an endoscopic approach has been introduced in conjunction with a navigation system. Recently, the surgical indications for proptosis have expanded to include esthetic improvement. The mean decrease in the Hertel exophthalmometric value after surgery was 4.56 mm (45). Furthermore, GO activity and severity were alleviated by orbital decompression, but the clinical activity score and the modified NOSPECS [No physical signs or symptoms, Only signs, Soft tissue involvement, Proptosis, Extraocular muscle involvement, Corneal involvement and Sight loss (due to optic nerve compression)] classification were associated with significant postoperative decline (46). Visual acuity significantly improved in DON patients who underwent decompression surgery, and postoperative visual acuity increased in 82-88% of such patients (47).

After fat decompression alone, the short/intermediate-term and long-term decreases were 4.2 mm and 5.9 mm, respectively (48). A few reports have indicated that orbital fat removal is safer than, but as effective as, bone wall decompression (49–51). When fat and bone are simultaneously removed, fat removal generally leads to 2-4 mm of reduction in ocular protrusion (47). However, one study revealed that although fat removal increased the effectiveness of surgery, statistical significance was only attained for three-wall decompression (42). Fat decompression was associated with a limited incidence of new-onset diplopia, and cerebrospinal fluid leakage was not reported, in contrast to the findings after lateral wall decompression (48). Periocular fat removal relieved intraorbital pressure and was effective in DON patients (52–54). Medial orbital wall decompression effectively treated mild-to-moderate exophthalmos accompanied by diplopia (17). Several studies showed that medial decompression provided a mean postoperative Hertel difference of 4.36 mm (45). Various surgical methods have been used to approach the medial wall, including transantral, transcutaneous, transconjunctival, intranasal, and transcaruncular routes (55–59). Notably, the transcaruncular approach enables optimal exposure and safe access to the medial periosteal space. In DON patients with mild ocular protrusions, the transcaruncular approach is recommended to relieve optic nerve compression. The medial orbit wall can also be accessed using an endoscopic nasal approach, thereby improving operative performance and safety when engaging in posterior decompression (47). The combination of medial and inferior wall decompressions enables a slightly greater reduction of 4 to 6 mm (47, 60, 61). However, this approach may be associated with marginally greater rates of regression and new-onset double vision, compared with balanced two-wall decompression (17).

An endoscopic approach to the orbital wall was first described by Kennedy et al. in the early 1990s (58). Studies in recent decades have shown that endoscopy can regress exophthalmos by 3.2-4.7 mm (62). Further recession is possible with the addition of an external approach, such as lateral orbital wall removal (62). Although the endoscopic approach did not improve protrusion to the degree achieved using the transconjunctival approach, the postoperative diplopia rate was lower with the endoscopic approach (42).

Lateral orbital wall decompression, first described by Kronlein in the late 19th century, remains a common method for treatment of GO (63). Generally, single lateral wall decompression is preferred when treating exophthalmos with a moderate protrusion (3-7 mm) (64). The effectiveness of such an approach in DON patients remains controversial; the posterior effect may be less than the effect of medial wall decompression in terms of decompressing the orbital apex. However, lateral wall decompression reduces proptosis by 2.7-4.8 mm (45, 65–67). Recently, deep lateral decompression has become more popular (45, 67) because it provides satisfactory decompression with minimal complications, along with the potential for use in combination with other techniques (e.g., medial wall decompression and fat removal) (68–71). The removal of thin bone above the temporalis muscle can trigger some complications. Specifically, medial movement of the temporalis muscle may cause the muscle to occupy the newly decompressed space, thus displacing soft orbital soft tissue back into the orbit. One study indicated that the use of polyethylene-coated titanium implants may be promote sidewall decompression (72). The postoperative diplopia rate after deep lateral decompression is 0-8.6% (67). Other complications include dry eye syndrome, vibration, temporal hollowing, rectus muscle injury, cerebrospinal fluid leakage, and hemorrhage (17, 64, 67). Balanced decompression (i.e., concurrent removal of medial and lateral walls) is recommended for patients with severe proptosis who do not exhibit diplopia (17). Balanced decompression may significantly improve mild-to-moderate proptosis in patients lacking diplopia. The mean proptosis reduction was 3.1 to 5.6 mm (45, 73–75); this reduction was statistically significant, and the extent of reduction was greater in double-wall groups than in single-wall groups (76). Proptosis reduction was more evident in patients with higher preoperative Hertel values; significantly lower reductions were apparent in patients with less preoperative proptosis (75). Balanced decompression may be maximally effective; it is safe in terms of causing minimal complications (61, 77–79).

For patients with severe exophthalmos, three-wall decompression is preferred (47). Because more extensive wall removal improves ocular proptosis, such decompression minimizes the orbital symptoms. A few nonrandomized studies have revealed that three-wall decompression may maximally improve exophthalmos, but it carries an increased risk of complications (61, 80–83). Decompression of the medial, inferior, and lateral walls considerably reduced ocular protrusion by 4.5-7.5 mm (45, 74, 79, 84). The mean reduction was significantly greater after three-wall decompression than after two-wall decompression, although three-wall decompression is most effective for patients with more severe preoperative exophthalmos (42). After three-wall decompression, new-onset diplopia and orbital complications are not uncommon. The results of multiple (non-controlled) descriptive studies have suggested that although three-wall decompression most effectively improves exophthalmos, it increases the rates of complications (mainly diplopia and hypoglobus) (61, 85, 86). Notably, three-wall decompression maximally reduced ocular proptosis and normalized the Hertel values, even in extreme cases (75). Some clinicians suggest that avoidance of post-orbital diplopia should not be the only goal; it is important to achieve normal Hertel values and eye symmetry. If three-wall decompression does not relieve DON, orbital roof decompression can be considered (47). Another option is four-wall decompression, which constitutes an extreme form of decompression. This complex procedure can trigger brain herniation via the orbital roof opening, thereby reducing the orbital volume associated with a pulsatile eye or eyeball (45). This technique is not recommended unless the exophthalmos is extremely severe. Recently, image-guided navigation has been used during orbital decompression surgery to further improve pronounced exophthalmos. This approach reduces the operating time, as well as the incidences of postoperative complications (e.g., diplopia and strabismus) (87, 88). The types of decompression are summarized in Table 1.

Few papers have adequately reported the rates of orbital complications. Leong et al. stated that the global incidence of complications was 9.3%, whereas the global incidence of serious complications with long-term sequelae was 0.12% (89). Diplopia is the most common postoperative complication of decompression surgery. The primary cause of diplopia after such surgery is EOM misalignment (90). After surgery, patients with preoperative diplopia were more likely to experience primary gaze diplopia regardless of the surgical technique used; thus, it was essential to preoperatively measure any primary positional misalignment (81). New-onset postoperative diplopia developed in a mean of 18-29% patients (64, 91); however, after fat decompression alone, the proportion was as low as 3.3% (48). Medial wall decompression triggered diplopia in 0-35% of patients (56, 60, 61, 64, 82), whereas the rate after lateral wall decompression was 0-6% (70, 92–95). New-onset diplopia was less common after lateral decompression than after other types of bone decompression (64). One study showed that lateral decompression did not increase the risk of diplopia, but bilateral surgery did (96). The incidences of diplopia after medial and inferior wall resection could reach 50% (97). Patients who undergo balanced medial and lateral wall decompressions may experience shifts in the symmetrical medial and lateral rectus values, theoretically reducing the risk of

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TABLE 1 Types of decompression.

	Decompressed wall	Indication	Effect	Features
Only fat	None	Mild to moderate	4.2 to 5.9 mm	· Effective in DON patients, relieves IOP. · Complications usually include diplopia. · When combined with bony decompression, fat removal improves protrusion by 2 to 4 mm.
Single wall (med.)	Med	Mild to moderate	4.36 mm	· Transcaruncular approach is generally recommended · Endoscopic approach remains available
Single wall (lat.)	Lat	Moderate	2.7 to 4.8 mm	· Easily accompanied with med. wall decompression · Effect on DON is controversial
Two-Wall (med. & inf.)	Med. & Lat.	Moderate	4 to 6 mm (3.2 to 4.7 mm for endoscopic approach)	· Ext. approach - more effective improvement · Endoscopic approach - lesser postoperative diplopia · Higher rate of postoperative diplopia compared to balanced two -wall decompression
Balanced Two-wall	Med. & Lat.	Mild to moderate or severe	3.1 to 5.6 mm	· Usually effective and safe; leads to fewer complications.
Three-Wall	Med., Lat., Inf.	Severe	4.5 to 7.5 mm	· Most effective in terms of improving protrusion, but leads to higher rate of postoperative complications (e.g., diplopia and hypoglobus).
Four-Wall	Med, Lat., Inf., Sup.	Severe	More effective than three-wall decompression	· Usually not recommended unless exophthalmos is extremely severe or three-wall decompression has failed.

diplopia (98). However, several studies have revealed diplopia rates of 10-20% (61, 81). One study demonstrated that balanced decompression increased the risk of new-onset diplopia (96). It has been suggested patients who underwent balanced medial and lateral wall decompression surgery were likely to have shifted symmetric medial and lateral rectus, which in theory reduces the risk of postoperative diplopia (98). However, in several studies the incidence rate of diplopia is reported to be in the range of 10-20% (61, 81). One study found balanced decompression increased the risk of developing new diplopia after surgery (96). The "balancing effect" of sidewall and medial wall decompressions may limit diplopia (78, 99, 100), although some studies have shown no change in the incidence of diplopia (101, 102). The highest diplopia rate was observed after three-wall decompression of the medial, medial inferior, and lateral walls (75). In several studies, three-wall decompression was associated with a 14-57% incidence of diplopia (17, 64). Some researchers have suggested that the association between lateral orbital wall decompression and postoperative strabismus is weaker than the associations of other wall decompressions with postoperative strabismus (103). One nonrandomized retrospective study compared lateral orbital wall decompression to balanced medial and lateral wall decompression; it revealed a relationship between lateral wall removal and a higher resolution rate in patients with preoperative strabismus (78).

The facial numbness rate after lateral surgery is 24%, but the numbness is generally mild and transient (< 3 months) (64). Lateral decompression tends to exhibit an association with a higher rate of postoperative numbness, compared with other types of bone decompression, but the differences are not statistically significant (64). In one study, numbness was recorded in 35% of 98 patients who underwent lateral wall decompression surgery; it persisted in 14% of those patients for 2 years (104). Other adverse effects include transient or permanent paresthesia of the suborbital nerve area in approximately 24% of patients (74), as well as immediate periorbital ecchymosis and edema, postoperative bleeding and infection, corneal erosion, sinusitis, cerebrospinal fluid leakage, abscesses, hematomas, and acute subdural hemorrhages (64, 74, 94, 105). The most common complications of endoscopic procedures are sinusitis, frontal or maxillary mucus production, cerebrospinal fluid fistular leakage, nasolacrimal duct lesions, strabismus, and diplopia. Strabismus may spontaneously disappear within 3-4 weeks but reappear during subsequent disease progression; correction is then necessary (62). Vision loss is rare after various orbital surgeries, including tumor resection, post-traumatic reconstruction, and GO decompression (42, 106). Vision loss can be triggered by tissue expansion and compression by a hematoma, the onset of hypotension while under general anesthesia, vasospasm, and/or the onset of optic nerve mechanical damage/ischemia caused by arterial occlusion (42). Among the many types of orbital surgery, orbital GO decompression exhibits the lowest risk of vision loss (42, 106); the prevalence ranges from 0.09% to 0.52% (73, 107, 108). One study showed that orbital decompression surgery for

GO patients triggered a significant decline in retinal nerve fiber layer thickness (109). Most patients undergo a single orbital decompression procedure; the reoperation rate after first decompression ranged from 1.7% to 13.8% (110). Thus, there is minimal literature concerning repeat orbital decompression. The reasons for reoperation include persistent protrusion and/or optic neuropathy, as well as recurring optic neuropathy with a GO flare (110). Reoperation status has been associated with younger age, normal thyroid function, high-level preoperative orbital protrusion, and preoperative steroid treatment (111).

Many of the studies mentioned above were nonrandomized, retrospective case series; thus, the results are not directly comparable. No evidence-based conclusions can be drawn regarding an optimal decompression procedure (i.e., the procedure with the lowest complication rate). Well-planned, prospective/longitudinal, randomized clinical trials are required to compare the surgical methods used for orbital decompression of GO patients. Such trials would yield reliable empirical evidence.

Squint surgery

During the late phase of GO inflammation, orbital fibrotic changes tighten the EOMs and thus restrict their movements (112). The most commonly affected muscle is the inferior rectus (IR; the bulkiest and most tonically active muscle), followed by the medial rectus (MR) and superior rectus (SR) (113). Affected muscles exhibit enlarged bellies on computed tomography; the tendons are typically spared (114).

Observation only is recommended when a patient lacks symptoms of diplopia in the primary gaze or the reading position. In such situations, conservative treatment options (e.g., Botox or a Fresnel prism) may aid acute-phase patients and patients with small deviations. Because the IR muscle is most commonly affected, restricted motility triggers binocular diplopia and advanced upgaze positioning. Most patients adopt chin-up postures to avoid diplopia. Additionally, most patients are not concerned about small vertical diplopia angles; the fusional amplitude is narrower on vertical deviation than on horizontal deviation. Ongoing inflammation and elastic changes in EOMs increase the numbers of affected muscles; binocular diplopia then spreads to the primary position, as well as the downward and horizontal gazes (115).

Usually, surgery is necessary to reduce GO diplopia when both the condition and the motility pattern have been stable for ≥ 6 months (116, 117). Coats et al. (118) explored whether strabismus surgery during active GO aided selected patients; they reported good surgical outcomes in eight patients whose parameters were stable for shorter times than suggested above.

Surgery seeks to create the largest possible binocular single vision fields, particularly in the primary and reading positions (115, 116). In recent decades, success has been graded as excellent, good, acceptable, and poor (119); a tool quantifying residual diplopia and the disease-specific quality-of-life has been developed (the GO-QOL) (120).

The muscles affected by GO are extremely tight. Considering the severe inflammation and thus the enhanced restriction of muscles that are already strongly contracted, recession of tight muscles is strongly recommended (121). Lee et al. (122) reported good surgical outcomes after vertical rectus resection in patients with large angles of deviation (≥ 20 prism diopter [PD]). Only normal-sized muscles were manipulated to prevent inflammation and adverse surgical outcomes. The most controversial issue in this field involves the decision to use (or not use) adjustable sutures. In procedures involving adjustable sutures, overcorrection was evident when recessing the IR muscle (123, 124). However, other studies have not revealed significant differences between fixed and adjustable sutures (125). No randomized controlled trials have compared adjustable and nonadjustable sutures. Kushner (126) reported that semi-adjustable suturing completely abolished muscle slippage. Although Jefferis et al. (127) adjusted recessed SR muscles, this method was only used in patients with complex restrictive disease or small vertical prism fusion ranges. The overcorrection of IR recession via postoperative drift is common (123, 128); it can be explained by impaired contralateral elevation and underestimation of the increased SR tone (129). Suggested approaches to mitigate the risk of consecutive hypertropia include planned surgical dosage reduction; a semi-adjustable hang-back approach toward large recessions; and a long horizontal, intrascleral simple hang-back for small recessions (130). Although bilateral MR recession is frequently used to correct horizontal diplopia, undercorrection may be associated with residual diplopia because the muscles are tight.

Strabismus surgery for GO patients is difficult; the outcomes are unpredictable. Plager (131) found that larger-than-expected recessions were necessary to treat small deviations and smaller-than-expected recessions were required when treating large GO-associated deviations; surgeons must carefully consider the deviations. Generally, the recessions are 3-4 PD/mm for the IR and 3-5 PD/mm for the MR (116, 130). Preoperative forced duction tests in all directions are useful. Nguyen et al. reported that a tailored plan addressed duction restriction; forced duction tests improved surgical success. The unpredictable outcomes of squint surgery for GO patients can mainly be attributed to EOM restriction; preoperative measurement of target muscle tension is critical. After IR recession, an A- or V-pattern deviation may appear if the adduction power is weakened. During reattachment, the recessed muscle should be moved in a nasal direction to reduce the risk of pattern deviation (112).

The success rates vary from 57% to 86% after initial surgery (124, 127, 128), depending on the success criteria used and the involved muscles (132). After orbital decompression surgery, poor prognostic factors include a severe restrictive pattern and a large deviation angle. Relative orbitopathy symmetry at onset

and a shorter time between onset and surgery are factors predictive of good outcomes (133). In a recent study of 448 patients who underwent strabismus surgery, approximately 1 in 4 required reoperations; these mainly included patients in whom multiple muscles were involved during the initial surgery (134).

Vertical rectus muscle recession may exacerbate the retraction of both upper and lower lids. A preferred approach comprises the division of fibrous connections between the SR and upper lid levator complex, and between the IR and the lower lid retractors (112). Several approaches have been used for these purposes, including suturing of the desired point of eyelid retractor apposition to the recessed IR (135), separate suturing for postoperative adjustment of eyelid position (136), and sharp dissection of the fascia of the capsulopalpebral head combined with lysis of the fascial connections between the lower eyelid and the IR (137). Conversely, the recession of a tight IR can alleviate ipsilateral upper lid retraction by elevating the SR tone, consistent with Hering's law.

New surgical techniques have been suggested in recent decades. Dal Canto et al. (138) described a unique approach for intraoperative determination of the position of rectus muscle reattachment. The cited authors allowed the disinserted muscle to rest on the eyeball sclera in the primary position. Such "intraoperative relaxed muscle positioning" considers muscle tightness; it has been associated with a good surgical success rate (88%) (138, 139). Other groups have also reported satisfactory results (140, 141). To reduce IR muscle restriction, tendon elongation uses homologous scleral grafts, polytetrafluoroethylene (Goretex), silicone, bovine pericardium, (142), or fascia lata (143). Jefferis et al. (127) reported favorable outcomes after prioritizing downgaze alignment (rather than primary gaze alignment) to avoid downgaze diplopia.

Postoperative complications after squint surgery include conjunctival injection and scarring, corneal dellen, pyogenic granuloma, muscle slippage and loss, pulled-in-two syndrome, periorbital and orbital cellulitis, scleral perforation, retinal detachment, endophthalmitis, anterior segment ischemia, and recurrent or consecutive postoperative diplopia (144–147). Changes in eyelid position and/or eyelid retraction can also occur, particularly if adjustable sutures are placed. Necrotizing scleritis may develop in patients with immune disorders (148). Because the muscles are extremely tight and the inflammation is pronounced, such complications may be more common if adjustable sutures are placed, compared with routine squint surgery. Such complications may be avoided by gentle manipulation during surgery, meticulous dissection from adjacent tissues including the capsulopalpebral head, and appropriate planning of adjustable suture positions.

Lid surgery

Upper eyelid retraction, known as Dalrymple's sign, is associated with a widened palpebral fissure. The British ophthalmologist John Dalrymple was the first to distinguish lid retraction from exophthalmos, based on the notion that the levator palpebrae superioris muscle can cause upper eyelid retraction (149). Lid retraction, particularly involving the upper eyelid, is the most common sign in GO patients (up to 90%) (150, 151). Because an abnormal lid position can expose the cornea and conjunctiva, ocular surface diseases (e.g., dry eye and exposure keratitis) may develop. Affected patients principally report ocular discomfort and poor cosmesis. Upper eyelid retraction is diagnosed when the lid margin is higher than the normal position of the upper lid (i.e., 1-2 mm below the upper limbus). Lower eyelid retraction is diagnosed if the lower sclera is visible—the normal position is the lower limbus.

Upper eyelid retraction reflects the contraction and fibrosis of levator and Mueller muscles (152, 153). Patients with GD typically exhibit increased sympathetic tone of the Mueller muscle, triggering upper eyelid retraction. Although lower eyelid retraction in GO patients has received less attention than upper eyelid retraction in such patients, Bartley et al. found that 85% of 120 GO patients exhibited lower eyelid retraction at diagnosis (154). Increased adrenergic stimulation of the inferior tarsal muscle, similar to Mueller muscle hyperaction in the upper eyelid, was among the initial theories proposed to explain lower eyelid retraction (155). Anatomically, lower eyelid retraction can be caused by fibrosis of the capsulopalpebral fascia and/or enlargement of the IR muscle (155).

The peak of the normal upper eyelid lies medial to the center of the pupil. However, in GO patients with upper eyelid retraction, the peak of the normal lid contour is lost; the upper lid continues to rise laterally. Thus, a temporal (or lateral) flare is characteristically observed. Additionally, lid lag may be evident when looking down; this constitutes von Graefe's sign. Eyedrops with an adrenergic blocking agent (guanethidine) or a β-adrenergic blocking agent (propranolol) were previously used to treat mild lid retraction (156, 157); however, they are no longer preferred because of adverse effects including vasodilatation, irritation, and ocular discomfort (158–160).

Several reports have shown that lid retraction improves after Botox A injection into the skin or subconjunctiva of the upper lid. This injection method serves as a temporary treatment, both in the acute phase and prior to surgery. However, Botox A injection has been associated with limited transient ptosis and diplopia in GO patients with upper eyelid retraction (161, 162). Furthermore, subconjunctival triamcinolone acetonide (TA) injection can improve upper eyelid retraction in GO patients in the acute and active phases, but its adverse effects include temporary increases in intraocular pressure and ptosis (163–165). Subconjunctival TA injection is commonly administered as follows (163, 166, 167). An ice pack is used to cool the upper eyelid for 1 min to reduce pain and bleeding. Under downgaze, the upper eyelid skin is pulled upward into the supine position. After confirmation that blood reflux is absent, a needle is carefully inserted to a depth of approximately 1 cm. Generally,

0.5 mL (40 mg/mL) of subconjunctival TA is gently injected toward the orbital fat around the levator muscle. The results of several studies have suggested that this approach significantly decreases inflammation of the levator muscle and eyelid fat (163, 166, 167). However, symptom relief was less effective for GO cases with severe retractions. Additionally, intraocular pressure increased after steroid injection into the upper eyelid.

In GO patients, the most common causes of eyelid surgery are corneal and conjunctival exposure on lid retraction and a poor cosmetic appearance. Eyelid retraction surgery remains highly individualized. Its functional goals comprise the treatment of dryness, exposure keratitis, and lagophthalmos by lowering the upper eyelid margin to the normal position. Its esthetic goal comprises ensuring that the heights of the upper eyelid margins are natural and symmetrical. Most oculoplastic surgeons agree that, unless emergency surgery is required to treat medically uncontrollable exposure keratitis, the eyelid position should be stable for 6 to 12 months prior to surgery (168). A surgical decision is made after careful consultation with the patient, considering subjective symptoms and the objective ocular surface condition. Depending on severity, in mild cases, the management of upper eyelid retraction may be confined to conservative treatment with artificial tears (i.e., a nonsurgical method). Several studies showed that orbital decompression surgery could improve eyelid position and reduce proptosis. In patients who underwent consecutive medial and lateral orbital wall decompression, upper and lower lid retraction were improved. The extent of proptosis reduction was significantly associated with the level of lower lid retraction after surgery (169–171). One study investigated the correlation between the extent of enophthalmos and the interpalpebral fissure status of patients with unilateral orbital wall fractures; it revealed that patients with more severe enophthalmos tended to have fewer interpalpebral fissures (172).

Upper eyelid retraction surgery can be performed through a skin or conjunctival approach. An advantage of the skin approach is that anatomical structures inside the eyelids can be directly viewed. However, its disadvantages include a long operation time and extensive dissection. The conjunctival approach is shorter, but it is difficult to distinguish anatomical structures if the surgeon is unfamiliar with the operation.

The treatment of eyelid retraction via disinsertion of the levator and Mueller muscles was described by Henderson in 1965 (173). Since that time, several techniques have been introduced to correct upper eyelid retraction. These techniques involve anterior or posterior Muellerectomy with or without graded levator muscle disinsertion, the use of hang-back sutures, scleral interposition, and full-thickness eyelid transection (blepharotomy) (174–178). Although many studies have focused on the correction of upper eyelid retraction, no method has been strongly recommended. Randomized controlled trials comparing procedures are absent, and no approach is considered superior to others.

Similar to the method used for the upper eyelids, the correction of lower eyelid retraction can be performed through an anterior or posterior approach. Recession or extirpation of the capsulopalpebral fascia with or without spacer placement has been used to correct lower eyelid retraction. The spacer is a supportive material that elevates and maintains the eyelid against the force of gravity. A spacer was first used to correct lower lid retraction by Blair in the 1940s (179). Typical spacers include homologous sclera and tarsus; autologous hard palate mucosa, tarsal conjunctiva, cartilage, and dermis; and bioengineered matrices such as acellular dermis (AlloDerm), a porcine skin xenograft (Enduragen), porous polyethylene (Medpor), and a polyester mesh (Mersilene). All of these spacers are alloplastic materials that lack immunogenicity (155, 180). A few authors have compared grafts (181–183). A retrospective study in 2011 showed that, compared with a dermis-fat graft, AlloDerm was more effective in terms of lower eyelid retraction correction; however, the difference was not statistically significant (183). It is difficult to identify an optimal procedure or spacer because the investigations have not been standardized.

Conventionally, orbital decompression is performed first, followed by lid retraction. However, many studies in recent decades have shown that maximum correction is obtained when upper or lower lid retraction and orbital compression are conducted during a single procedure (184–187). One comparative clinical study investigated the outcomes of upper eyelid retraction surgery performed at or after the time of orbital decompression; transconjunctival Mueller muscle recession performed during deep lateral wall decompression yielded satisfactory results in 67% of 97 cases (187). Another comparative study compared the surgical outcomes of acellular human dermis grafting and lower eyelid retractor recession during orbital decompression; correction of eyelid retraction using the graft during orbital decompression provided excellent results (185).

No definitive treatment has been established for lid retraction in GO patients. Furthermore, it is difficult to predict the outcome and prognosis. Similar to the outcomes of other eyelid surgeries, overcorrection, undercorrection, and lid crease asymmetry may be evident after eyelid retraction. Undercorrection of either the temporal portion of the eyelid or the entire lid is a particularly common postoperative complication of Mueller muscle recession (188). Adequate lysis of the lateral horn of the levator aponeurosis and the Mueller muscle is recommended to avoid uncorrected lateral upper eyelid flare. Recommendations often include the graded levator hinge procedure or graded full-thickness blepharotomy (189–191).

In both the active and inflammatory phases, functional thyroid correction should be medically prioritized. Botox A and TA injections can be administered around the conjunctiva and eyelids in patients who exhibit severe dry eye disease and superficial keratitis caused by lid retraction. Moreover, for patients undergoing orbital decompression, concurrent correction of any lower lid retraction is recommended, using a spacer such as acellular dermal matrix. Importantly, GO patients who require surgery must be continuously monitored to detect anterior segment conditions such as dry eye disease and superficial keratitis.

Conclusions

Rehabilitative surgery is usually included in the treatment of moderate-to-severe ophthalmopathy during the inactive phase; it is intended to reduce proptosis, restore function, and enhance appearance. Typically, the constituent surgical procedures are performed in a fixed sequence, commencing with orbital decompression. Although many approaches to surgical decompression have been optimized, few controlled studies have been conducted regarding their relative efficacies. Therefore, the key objective of surgery and the surgeon's skills are primary concerns when choosing an approach. In diplopia patients, surgical decompression generally precedes strabismus surgery that corrects eye motility abnormalities. Other functional and cosmetic issues are managed later; these issues include facelifting, soft tissue filler injection, and eyelid repair.

Even the use of advanced surgical techniques by the growing number of well-trained surgeons can never fully avoid mild-to-severe complications. There is a need to continue clinical and laboratory investigations of new drugs that reduce long-term orbit deformity, alleviate the requirement for rehabilitative surgery, and improve long-term quality-of-life.

Author contributions

JB, HSC, CK, HK, and SYJ wrote the first draft of the manuscript. JB and SYJ contributed to conception. SYJ reviewed and edited the mansucript. All authors contributed to manuscript revision, read, and approved the submitted version

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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.

Publisher's note

References

1. Abraham-Nordling M, Törring O, Lantz M, Hallengren B, Ohrling H, Lundell G, et al. Incidence of hyperthyroidism in Stockholm, Sweden, 2003-2005. *Eur J Endocrinol* (2008) 158:823–7. doi: 10.1530/eje-07-0877

2. Lantz M, Abraham-Nordling M, Svensson J, Wallin G, Hallengren B. Immigration and the incidence of Graves' thyrotoxicosis, thyrotoxic multinodular goiter and solitary toxic adenoma. *Eur J Endocrinol* (2009) 160:201–6. doi: 10.1530/eje-08-0548

3. Abraham-Nordling M, Byström K, Törring O, Lantz M, Berg G, Calissendorff J, et al. Incidence of hyperthyroidism in Sweden. *Eur J Endocrinol* (2011) 165:899–905. doi: 10.1530/eje-11-0548

4. Smith TJ, Hegedüs L. Graves' disease. *N Engl J Med* (2016) 375:1552–65. doi: 10.1056/NEJMra1510030

5. Zimmermann MB, Boelaert K. Iodine deficiency and thyroid disorders. *Lancet Diabetes Endocrinol* (2015) 3:286–95. doi: 10.1016/s2213-8587(14)70225-6

6. Taylor PN, Albrecht D, Scholz A, Gutierrez-Buey G, Lazarus JH, Dayan CM, et al. Global epidemiology of hyperthyroidism and hypothyroidism. *Nat Rev Endocrinol* (2018) 14:301–16. doi: 10.1038/nrendo.2018.18

7. Bartalena L, Piantanida E, Gallo D, Lai A, Tanda ML. Epidemiology, natural history, risk factors, and prevention of Graves' orbitopathy. *Front Endocrinol (Lausanne)* (2020) 11:615993. doi: 10.3389/fendo.2020.615993

8. Bartley GB. The epidemiologic characteristics and clinical course of ophthalmopathy associated with autoimmune thyroid disease in Olmsted county, Minnesota. *Trans Am Ophthalmol Soc* (1994) 92:477–588.

9. Boulakh L, Nygaard B, Bek T, Faber J, Heegaard S, Toft PB, et al. Nationwide incidence of thyroid eye disease and cumulative incidence of strabismus and surgical interventions in Denmark. *JAMA Ophthalmol* (2022) 140:667–73. doi: 10.1001/jamaophthalmol.2022.1002

10. Garrity JA, Bahn RS. Pathogenesis of graves ophthalmopathy: implications for prediction, prevention, and treatment. *Am J Ophthalmol* (2006) 142:147–53. doi: 10.1016/j.ajo.2006.02.047

11. Kuriyan AE, Phipps RP, Feldon SE. The eye and thyroid disease. *Curr Opin Ophthalmol* (2008) 19:499–506. doi: 10.1097/ICU.0b013e3283131557

12. Bahn RS, Heufelder AE. Pathogenesis of graves' ophthalmopathy. *N Engl J Med* (1993) 329:1468–75. doi: 10.1056/nejm199311113292007

13. Wiersinga WM, Bartalena L. Epidemiology and prevention of graves' ophthalmopathy. *Thyroid* (2002) 12:855–60. doi: 10.1089/105072502761016476

14. Bahn RS. Graves' ophthalmopathy. *N Engl J Med* (2010) 362:726–38. doi: 10.1056/NEJMra0905750

15. Villadolid MC, Yokoyama N, Izumi M, Nishikawa T, Kimura H, Ashizawa K, et al. Untreated graves' disease patients without clinical ophthalmopathy demonstrate a high frequency of extraocular muscle (EOM) enlargement by magnetic resonance. *J Clin Endocrinol Metab* (1995) 80:2830–3. doi: 10.1210/jcem.80.9.7673432

16. Tanda ML, Piantanida E, Liparulo L, Veronesi G, Lai A, Sassi L, et al. Prevalence and natural history of graves' orbitopathy in a large series of patients with newly diagnosed graves' hyperthyroidism seen at a single center. *J Clin Endocrinol Metab* (2013) 98:1443–9. doi: 10.1210/jc.2012-3873

17. Cheng AMS, Wei Y-H, Liao S-L. Strategies in surgical decompression for thyroid eye disease. *Oxid Med Cell Longev* (2020) 2020:3537675. doi: 10.1155/2020/3537675

18. Wong Y, Dickinson J, Perros P, Dayan C, Veeramani P, Morris D, et al. A British ophthalmological surveillance unit (BOSU) study into dysthyroid optic neuropathy in the united kingdom. *Eye* (2018) 32:1555–62. doi: 10.1038/s41433-018-0144-x

19. Sasim IV, Berendschot TT, van Isterdael C, Mourits MP. Planning health care for patients with graves' orbitopathy. *Graefes Arch Clin Exp Ophthalmol* (2008) 246:1315–21. doi: 10.1007/s00417-008-0842-3

20. Bartalena L, Kahaly GJ, Baldeschi L, Dayan CM, Eckstein A, Marcocci C, et al. The 2021 European group on graves' orbitopathy (EUGOGO) clinical practice guidelines for the medical management of graves' orbitopathy. *Eur J Endocrinol* (2021) 185:G43–g67. doi: 10.1530/eje-21-0479

21. Dayan CM, Dayan MR. Dysthyroid optic neuropathy: a clinical diagnosis or a definable entity? *Br J Ophthalmol* (2007) 91:409–10. doi: 10.1136/bjo.2006.110932

22. Neigel JM, Rootman J, Belkin RI, Nugent RA, Drance SM, Beattie CW, et al. Dysthyroid optic neuropathy. the crowded orbital apex syndrome. *Ophthalmology* (1988) 95:1515–21. doi: 10.1016/s0161-6420(88)32978-7

23. McKeag D, Lane C, Lazarus JH, Baldeschi L, Boboridis K, Dickinson AJ, et al. Clinical features of dysthyroid optic neuropathy: A European group on graves' orbitopathy (EUGOGO) survey. *Br J Ophthalmol* (2007) 91:455–8. doi: 10.1136/bjo.2006.094607

24. Verity DH, Rose GE. Acute thyroid eye disease (TED): Principles of medical and surgical management. *Eye (Lond)* (2013) 27:308–19. doi: 10.1038/eye.2012.284

25. Bartley GB. Rundle And his curve. *Arch Ophthalmol* (2011) 129:356–8. doi: 10.1001/archophthalmol.2011.29

26. Wang Y, Sharma A, Padnick-Silver L, Francis-Sedlak M, Holt RJ, Foley C, et al. Physician-perceived impact of thyroid eye disease on patient quality of life in the united states. *Ophthalmol Ther* (2021) 10:75–87. doi: 10.1007/s40123-020-00318-x

27. Kahaly GJ, Petrak F, Hardt J, Pitz S, Egle UT. Psychosocial morbidity of graves' orbitopathy. *Clin Endocrinol (Oxf)* (2005) 63:395–402. doi: 10.1111/j.1365-2265.2005.02352.x

28. Laurberg P, Berman DC, Bülow Pedersen I, Andersen S, Carlé A. Incidence and clinical presentation of moderate to severe Graves' orbitopathy in a Danish population before and after iodine fortification of salt. *J Clin Endocrinol Metab* (2012) 97:2325–32. doi: 10.1210/jc.2012-1275

29. Perros P, Hegedüs L, Bartalena L, Marcocci C, Kahaly GJ, Baldeschi L, et al. Graves' orbitopathy as a rare disease in Europe: A European group on graves' orbitopathy (EUGOGO) position statement. *Orphanet J Rare Dis* (2017) 12:72. doi: 10.1186/s13023-017-0625-1

30. Wiersinga W, Žarković M, Bartalena L, Donati S, Perros P, Okosieme O, et al. Predictive score for the development or progression of Graves' orbitopathy in patients with newly diagnosed graves' hyperthyroidism. *Eur J Endocrinol* (2018) 178:635–43. doi: 10.1530/eje-18-0039

31. Bartalena L, Pinchera A, Marcocci C. Management of Graves' ophthalmopathy: Reality and perspectives. *Endocr Rev* (2000) 21:168–99. doi: 10.1210/edrv.21.2.0393

32. Gillespie EF, Smith TJ, Douglas RS. Thyroid eye disease: Towards an evidence base for treatment in the 21st century. *Curr Neurol Neurosci Rep* (2012) 12:318–24. doi: 10.1007/s11910-012-0256-9

33. Bartalena L, Baldeschi L, Dickinson A, Eckstein A, Kendall-Taylor P, Marcocci C, et al. Consensus statement of the European group on Graves' orbitopathy (EUGOGO) on management of GO. *Eur J Endocrinol* (2008) 158:273–85. doi: 10.1530/eje-07-0666

34. Bartalena L, Baldeschi L, Dickinson AJ, Eckstein A, Kendall-Taylor P, Marcocci C, et al. Consensus statement of the European group on Graves' orbitopathy (EUGOGO) on management of Graves' orbitopathy. *Thyroid* (2008) 18:333–46. doi: 10.1089/thy.2007.0315

35. Smith TJ, Kahaly GJ, Ezra DG, Fleming JC, Dailey RA, Tang RA, et al. Teprotumumab for thyroid-associated ophthalmopathy. *N Engl J Med* (2017) 376:1748–61. doi: 10.1056/NEJMoa1614949

36. Slentz DH, Nelson CC, Smith TJ. Teprotumumab: A novel therapeutic monoclonal antibody for thyroid-associated ophthalmopathy. *Expert Opin Investig Drugs* (2020) 29:645–9. doi: 10.1080/13543784.2020.1772752

37. Shorr N, Seiff SR. The four stages of surgical rehabilitation of the patient with dysthyroid ophthalmopathy. *Ophthalmology* (1986) 93:476–83. doi: 10.1016/s0161-6420(86)33712-6

38. Naik MN, Nair AG, Gupta A, Kamal S. Minimally invasive surgery for thyroid eye disease. *Indian J Ophthalmol* (2015) 63:847–53. doi: 10.4103/0301-4738.171967

39. Pieroni Goncalves AC, Gupta S, Monteiro MLR, Douglas RS. Customized minimally invasive orbital decompression surgery improves lower eyelid retraction and contour in thyroid eye disease. *Ophthalmic Plast Reconstr Surg* (2017) 33:446–51. doi: 10.1097/iop.0000000000000825

40. Barker L, Mackenzie K, Adams GG, Hancox J. Long-term surgical outcomes for vertical deviations in thyroid eye disease. *Strabismus* (2017) 25:67–72. doi: 10.1080/09273972.2017.1318151

41. Mourits MP, Sasim IV. A single technique to correct various degrees of upper lid retraction in patients with Graves' orbitopathy. *Br J Ophthalmol* (1999) 83:81–4. doi: 10.1136/bjo.83.1.81

42. Boboridis KG, Uddin J, Mikropoulos DG, Bunce C, Mangouritsas G, Voudouragkaki IC, et al. Critical appraisal on orbital decompression for thyroid eye disease: A systematic review and literature search. *Adv Ther* (2015) 32:595–611. doi: 10.1007/s12325-015-0228-y

43. Dollinger J. Die druckentlastung der augenhöhle durch entfernung der äusseren orbitalwand bei hochgradigem exophthalmus (Morbus basedowii) und konsekutiver hornhauterkrankung. *Dtsch Med Wochenschr* (1911) 37:1888–90. doi: 10.1055/s-0028-1131009

44. Walsh TE, Ogura JH. Transantral orbital decompression for malignant exophthalmos. *Laryngoscope* (1957) 67:544–68. doi: 10.1288/00005537-195706000-00002

45. Gioacchini FM, Kaleci S, Cassandro E, Scarpa A, Tulli M, Cassandro C, et al. Orbital wall decompression in the management of Graves' orbitopathy: a systematic review with meta-analysis. *Eur Arch Otorhinolaryngol* (2021) 278:4135–45. doi: 10.1007/s00405-021-06698-5

46. Jurek-Matusiak O, Brożek-Mądry E, Jastrzębska H, Krzeski A. Orbital decompression for thyroid eye disease: Surgical treatment outcomes in endocrinological assessment. *Endokrynol Pol* (2021) 72:609–17. doi: 10.5603/EP.a2021.0078

47. Braun TL, Bhadkamkar MA, Jubbal KT, Weber AC, Marx DP. Orbital decompression for thyroid eye disease. *Semin Plast Surg* (2017) 31:40–5. doi: 10.1055/s-0037-1598192

48. Cheng AM, Wei Y-H, Tighe S, Sheha H, Liao S-L. Long-term outcomes of orbital fat decompression in Graves' orbitopathy. *Br J Ophthalmol* (2018) 102:69. doi: 10.1136/bjophthalmol-2016-309888

49. Stark B, Olivari N. Treatment of exophthalmos by orbital fat removal. *Clin Plast Surg* (1993) 20:285–9; discussion 90. doi: 10.1016/S0094-1298(20)31220-7

50. Richter DF, Stoff A, Olivari N. Transpalpebral decompression of endocrine ophthalmopathy by intraorbital fat removal (Olivari technique): Experience and progression after more than 3000 operations over 20 years. *Plast Reconstr Surg* (2007) 120:109–23. doi: 10.1097/01.prs.0000263655.47148.9e

51. Olivari N. Transpalpebral decompression of endocrine ophthalmopathy (Graves' disease) by removal of intraorbital fat: Experience with 147 operations over 5 years. *Plast Reconstr Surg* (1991) 87:627–41.

52. Prat MC, Braunstein AL, Glass LRD, Kazim M. Orbital fat decompression for thyroid eye disease: Retrospective case review and criteria for optimal case selection. *Ophthal Plast Reconstr Surg* (2015) 31:215–8. doi: 10.1097/IOP.0000000000000260

53. Trokel S, Kazim M, Moore S. Orbital fat removal: Decompression for graves orbitopathy. *Ophthalmology* (1993) 100:674–82. doi: 10.1016/S0161-6420(93)31589-7

54. Kazim M, Trokel SL, Acaroglu G, Elliott A. Reversal of dysthyroid optic neuropathy following orbital fat decompression. *Br J Ophthalmol* (2000) 84:600. doi: 10.1136/bjo.84.6.600

55. Garrity JA, Fatourechi V, Bergstralh EJ, Bartley GB, Beatty CW, DeSanto LW, et al. Results of transantral orbital decompression in 428 patients with severe Graves' ophthalmopathy. *Am J Ophthalmol* (1993) 116:533–47. doi: 10.1016/S0002-9394(14)73194-0

56. Michel O, Oberländer N, Neugebauer P, Neugebauer A, Rüßmann W. Follow-up of transnasal orbital decompression in severe Graves' ophthalmopathy. *Ophthalmology* (2001) 108:400–4. doi: 10.1016/S0161-6420(00)00533-9

57. Carter KD, Frueh BR, Hessburg TP, Musch DC. Long-term efficacy of orbital decompression for compressive optic neuropathy of Graves' eye disease. *Ophthalmology* (1991) 98:1435–42. doi: 10.1016/S0161-6420(91)32115-8

58. Kennedy DW, Goodstein ML, Miller NR, Zinreich SJ. Endoscopic transnasal orbital decompression. *Arch Otolaryngology–Head Neck Surg* (1990) 116:275–82. doi: 10.1001/archotol.1990.01870030039006

59. Shorr N, Baylis HI, Goldberg RA, Perry JD. Transcaruncular approach to the medial orbit and orbital apex21 Received July 30, 1999. Accepted April 11, 2000.22The authors have no proprietary, commercial, or financial interest that is related to this manuscript. *Ophthalmology* (2000) 107:1459–63. doi: 10.1016/S0161-6420(00)00241-4

60. Borumandi F, Hammer B, Kamer L, von Arx G. How predictable is exophthalmos reduction in Graves' orbitopathy? A review of the literature. *Br J Ophthalmol* (2011) 95:1625. doi: 10.1136/bjo.2010.181313

61. Mourits MP, Bijl H, Altea MA, Baldeschi L, Boboridis K, Currò N, et al. Outcome of orbital decompression for disfiguring proptosis in patients with Graves' orbitopathy using various surgical procedures. *Br J Ophthalmol* (2009) 93:1518. doi: 10.1136/bjo.2008.149302

62. Lima WT, Perches M, Valera FC, Demarco RC. Orbital endoscopic decompression in graves ophthalmopathy. *Braz J Otorhinolaryngol* (2006) 72:283–7. doi: 10.1016/s1808-8694(15)30069-0

63. Kronlein RJBKC. Zur pathologie und behandlung der dermoidcysten der orbita. *Beitr Klin Chir* (1888) 4:149.

64. Jefferis JM, Jones RK, Currie ZI, Tan JH, Salvi SM. Orbital decompression for thyroid eye disease: Methods, outcomes, and complications. *Eye* (2018) 32:626–36. doi: 10.1038/eye.2017.260

65. Chang EL, Piva AP. Temporal fossa orbital decompression for treatment of disfiguring thyroid-related orbitopathy. *Ophthalmology* (2008) 115:1613–9. doi: 10.1016/j.ophtha.2008.02.024

66. Korinth MC, Ince A, Banghard W, Gilsbach JM. Clinical articles follow-up of extended pterional orbital decompression in severe Graves' ophthalmopathy. *Acta Neurochir (Wien)* (2002) 144:113–20. doi: 10.1007/s007010200013

67. Cruz AAV, Equiterio BSN, Cunha BSA, Caetano FB, Souza RL. Deep lateral orbital decompression for graves orbitopathy: A systematic review. *Int Ophthalmol* (2021) 41:1929–47. doi: 10.1007/s10792-021-01722-3

68. Kim KW, Byun JS, Lee JK. Surgical effects of various orbital decompression methods in thyroid-associated orbitopathy: Computed tomography-based comparative analysis. *J Cranio-Maxillofacial Surg* (2014) 42:1286–91. doi: 10.1016/j.jcms.2014.03.011

69. Baldeschi L, MacAndie K, Hintschich C, Wakelkamp IMMJ, Prummel MF, Wiersinga WM. The removal of the deep lateral wall in orbital decompression: Its contribution to exophthalmos reduction and influence on consecutive diplopia. *Am J Ophthalmol* (2005) 140:642.e1–.e8. doi: 10.1016/j.ajo.2005.04.023

70. Nguyen J, Fay A, Yadav P, MacIntosh PW, Metson R. Stereotactic microdebrider in deep lateral orbital decompression for patients with thyroid eye disease. *Ophthal Plast Reconstr Surg* (2014) 30:262–6. doi: 10.1097/IOP.0000000000000132

71. Ben Simon GJ, Syed AM, Lee S, Wang DY, Schwarcz RM, McCann JD, et al. Strabismus after deep lateral wall orbital decompression in thyroid-related orbitopathy patients using automated Hess screen. *Ophthalmology* (2006) 113:1050–5. doi: 10.1016/j.ophtha.2006.02.015

72. Siah WF, Patel BCK, Malhotra R. Surgical management of temple-related problems following lateral wall rim-sparing orbital decompression for thyroid-related orbitopathy. *Br J Ophthalmol* (2016) 100:1144. doi: 10.1136/bjophthalmol-2015-307600

73. Sellari-Franceschini S, Dallan I, Bajraktari A, Fiacchini G, Nardi M, Rocchi R, et al. Surgical complications in orbital decompression for Graves' orbitopathy. *Acta Otorhinolaryngol Ital* (2016) 36:265. doi: 10.14639/0392-100X-1082

74. Paridaens D, Lie A, Grootendorst RJ, van den Bosch WA. Efficacy and side effects of 'swinging eyelid' orbital decompression in graves' orbitopathy: A proposal for standardized evaluation of diplopia. *Eye* (2006) 20:154–62. doi: 10.1038/sj.eye.6701827

75. Stähr K, Daser A, Oeverhaus M, Hussain T, Lang S, Eckstein A, et al. Proposing a surgical algorithm for graduated orbital decompression in patients with graves' orbitopathy. *Eur Arch Otorhinolaryngol* (2022) 279:2401–7. doi: 10.1007/s00405-021-07003-0

76. Leite CA, Pereira TS, Chiang J, Moritz RB, Gonçalves ACP, Monteiro MLR. Ocular motility changes after inferomedial wall and balanced medial plus lateral wall orbital decompression in Graves' orbitopathy: A randomized prospective comparative study. *Clinics (Sao Paulo)* (2021) 76:e2592. doi: 10.6061/clinics/2021/e2592

77. Boboridis KG, Bunce C. Surgical orbital decompression for thyroid eye disease. *Cochrane Database Syst Rev* (2011). doi: 10.1002/14651858.CD007630.pub2

78. Goldberg RA, Perry JD, Hortaleza V, Tong JT. Strabismus after balanced medial plus lateral wall versus lateral wall only orbital decompression for dysthyroid orbitopathy. *Ophthal Plast Reconstr Surg* (2000) 16:271–7.

79. Ünal M, leri F, Konuk O, Hasanreisoglu B. Balanced orbital decompression combined with fat removal in graves ophthalmopathy: Do we really need to remove the third wall? *Ophthal Plast Reconstr Surg* (2003) 19:112–8. doi: 10.1097/01.IOP.0000056145.71641.F5.

80. Baldeschi L. Small versus coronal incision orbital decompression in Graves' orbitopathy. *Orbit* (2009) 28:231–6. doi: 10.1080/01676830903104579

81. Rocchi R, Lenzi R, Marinò M, Latrofa F, Nardi M, Piaggi P, et al. Rehabilitative orbital decompression for graves' orbitopathy: Risk factors influencing the new onset of diplopia in primary gaze, outcome, and patients' satisfaction. *Thyroid* (2012) 22:1170–5. doi: 10.1089/thy.2012.0272

82. Mainville NP, Jordan DR. Effect of orbital decompression on diplopia in thyroid-related orbitopathy. *Ophthal Plast Reconstr Surg* (2014) 30:137–40. doi: 10.1097/IOP.0000000000000029

83. Fichter N, Guthoff R, Schittkowski M. Orbital decompression in thyroid eye disease. *Int Scholarly Res Notices* (2012) 2012). doi: 10.5402/2012/739236

84. Ashutosh K, Michael K, Mark M, Stephen T, Lanny GC. "Balanced" orbital decompression for severe graves' orbitopathy: Technique with treatment algorithm. *Otolaryngology–Head Neck Surg* (2003) 128:228–35. doi: 10.1067/mhn.2003.61

85. Cansız H, Yılmaz S, Karaman E, Öğreden Ş, Acıoğlu E, Şekercioğlu N, et al. Three-wall orbital decompression superiority to 2-wall orbital decompression in thyroid-associated ophthalmopathy. *J Oral Maxillofac Surg* (2006) 64:763–9. doi: 10.1016/j.joms.2006.01.024

86. Takahashi Y, Kakizaki H. Horizontal eye position in thyroid eye disease: A retrospective comparison with normal individuals and changes after orbital decompression surgery. *PLoS One* (2014) 9:e114220. doi: 10.1371/journal.pone.0114220

87. Heisel CJ, Tuohy MM, Riddering AL, Sha C, Kahana A. Stereotactic navigation improves outcomes of orbital decompression surgery for thyroid associated orbitopathy. *Ophthalmic Plast Reconstr Surg* (2020) 36:553–6. doi: 10.1097/iop.0000000000001630

88. Prevost A, Dekeister C, Caron P, Imbert P, Cavallier Z, Lauwers F, et al. Outcomes of orbital decompression using surgical navigation in thyroid-associated ophthalmopathy. *Int J Oral Maxillofac Surg* (2020) 49:1279–85. doi: 10.1016/j.ijom.2020.02.008

89. Leong SC, Karkos PD, MacEwen CJ, White PS. A systematic review of outcomes following surgical decompression for dysthyroid orbitopathy. *Laryngoscope* (2009) 119:1106–15. doi: 10.1002/lary.20213

90. Vaidya A, Kakizaki H, Takahashi Y. Changes in field of binocular single vision and ocular deviation angle after balanced orbital decompression in thyroid eye disease. *Ophthalmic Plast Reconstr Surg* (2021) 37:154–60. doi: 10.1097/iop.0000000000001712

91. Cho RI, Choe CH, Elner VM. Ultrasonic bone removal versus high-speed burring for lateral orbital decompression: Comparison of surgical outcomes for the treatment of thyroid eye disease. *Ophthal Plast Reconstr Surg* (2010) 26:83–7. doi: 10.1097/IOP.0b013e3181b8e614

92. Mehta P, Durrani OM. Outcome of deep lateral wall rim-sparing orbital decompression in thyroid-associated orbitopathy: A new technique and results of a case series. *Orbit* (2011) 30:265–8. doi: 10.3109/01676830.2011.603456

93. Ben Simon GJ, Wang L, McCann JD, Goldberg RA. Primary-gaze diplopia in patients with thyroid-related orbitopathy undergoing deep lateral orbital decompression with intraconal fat debulking: A retrospective analysis of treatment outcome. *Thyroid* (2004) 14:379–83. doi: 10.1089/105072504774193221

94. Chang EL, Bernardino CR, Rubin PAD. Transcaruncular orbital decompression for management of compressive optic neuropathy in thyroid-related orbitopathy. *Plast Reconstr Surg* (2003) 112:739–47. doi: 10.1097/01.PRS.0000069708.70121.67

95. Liao S-L, Lin LL-K, Shih M-J, Chang T-C. Transforniceal lateral deep bone decompression–a modified technique to prevent postoperative diplopia in patients with disfiguring exophthalmos due to dysthyroid orbitopathy. *J Formos Med Assoc* (2006) 105:611–6. doi: 10.1016/S0929-6646(09)60159-5

96. Nair AA, Ediriwickrema LS, Dolman PJ, Law G, Harrison AR, Mokhtarzadeh A, et al. Predictive modeling of new-onset postoperative diplopia following orbital decompression for thyroid eye disease. *Ophthalmic Plast Reconstr Surg* (2022) 38:551–7. doi: 10.1097/iop.0000000000002196

97. Nunery WR, Nunery CW, Martin RT, Truong TV, Osborn DR. The risk of diplopia following orbital floor and medial wall decompression in subtypes of ophthalmic graves' disease. *Ophthal Plast Reconstr Surg* (1997) 13:153–60.

98. Leone CR Jr., Piest KL, Newman RJ. Medial and lateral wall decompression for thyroid ophthalmopathy. *Am J Ophthalmol* (1989) 108:160–6. doi: 10.1016/0002-9394(89)90011-1

99. McNab AA. Orbital decompression for thyroid orbitopathy. *Aust N Z J Ophthalmol* (1997) 25:55–61. doi: 10.1111/j.1442-9071.1997.tb01276.x

100. Paridaens DA, Verhoeff K, Bouwens D, van den Bosch WA. Transconjunctival orbital decompression in Graves' ophthalmopathy: lateral wall approach ab interno. *Br J Ophthalmol* (2000) 84:775. doi: 10.1136/bjo.84.7.775

101. Paridaens D, Hans K, van Buitenen S, Mourits MP. The incidence of diplopia following coronal and translid orbital decompression in graves' orbitopathy. *Eye* (1998) 12:800–5. doi: 10.1038/eye.1998.207

102. Cruz AA, Leme VR. Orbital decompression: A comparison between transfornix/transcaruncular inferomedial and coronal inferomedial plus lateral approaches. *Ophthalmic Plast Reconstr Surg* (2003) 19:440–5; discussion 5. doi: 10.1097/01.Iop.0000092796.43025.B1

103. Bengoa-González Á, Galindo-Ferreiro A, Mencía-Gutiérrez E, Sánchez-Tocino H, Martín-Clavijo A, Lago-Llinás M-D. Deep lateral wall partial rim-sparing orbital decompression with ultrasonic bone removal for treatment of thyroid-related orbitopathy. *J Ophthalmol* (2019) 2019:9478512. doi: 10.1155/2019/9478512

104. Fayers T, Barker LE, Verity DH, Rose GE. Oscillopsia after lateral wall orbital decompression. *Ophthalmology* (2013) 120:1920–3. doi: 10.1016/j.ophtha.2013.01.063

105. Alper MG. Pioneers in the history of orbital decompression for Graves' ophthalmopathy. R.U. Kroenlein (1847-1910), O. Hirsch (1877-1965) and H.C. Naffziger (1884-1961). *Doc Ophthalmol* (1995) 89:163–71. doi: 10.1007/bf01203409

106. Williams JS, Sahu PD. Surgical management of the orbit in thyroid eye disease: Lateral orbital decompression. *Curr Opin Otolaryngol Head Neck Surg* (2021) 29:289–93. doi: 10.1097/moo.0000000000000728

107. Leong SC, White PS. Outcomes following surgical decompression for dysthyroid orbitopathy (Graves' disease). *Curr Opin Otolaryngol Head Neck Surg* (2010) 18:37–43. doi: 10.1097/MOO.0b013e328335017c

108. Kansakar P, Sundar G. Vision loss associated with orbital surgery – a major review. *Orbit* (2020) 39:197–208. doi: 10.1080/01676830.2019.1658790

109. Guo J, Li X, Ma R, Gan L, Qian J. The changes of retinal nerve fibre layer and ganglion cell layer with different severity of thyroid eye disease. *Eye (Lond)* (2022) 36:129–34. doi: 10.1038/s41433-021-01453-w

110. Sellari-Franceschini S, Muscatello L, Seccia V, Lenzi R, Santoro A, Nardi M, et al. Reasons for revision surgery after orbital decompression for Graves' orbitopathy. *Clin Ophthalmol* (2008) 2:283–90. doi: 10.2147/opth.s2416

111. Wu CY, Niziol LM, Musch DC, Kahana A. Thyroid-related orbital decompression surgery: A multivariate analysis of risk factors and outcomes. *Ophthal Plast Reconstr Surg* (2017) 33:189. doi: 10.1097/IOP.0000000000000699

112. Harrad R. Management of strabismus in thyroid eye disease. *Eye (Lond)* (2015) 29:234–7. doi: 10.1038/eye.2014.282

113. Dyer JA. The oculorotary muscles in Graves' disease. *Trans Am Ophthalmol Soc* (1976) 74:425–56.

114. Ben Simon GJ, Syed HM, Douglas R, McCann JD, Goldberg RA. Extraocular muscle enlargement with tendon involvement in thyroid-associated orbitopathy. *Am J Ophthalmol* (2004) 137:1145–7. doi: 10.1016/j.ajo.2004.01.033

115. Jellema HM, Braaksma-Besselink Y, Limpens J, von Arx G, Wiersinga WM, Mourits MP. Proposal of success criteria for strabismus surgery in patients with Graves' orbitopathy based on a systematic literature review. *Acta Ophthalmol* (2015) 93:601–9. doi: 10.1111/aos.12717

116. Schotthoefer EO, Wallace DK. Strabismus associated with thyroid eye disease. *Curr Opin Ophthalmol* (2007) 18:361–5. doi: 10.1097/ICU.0b013e32827038f2

117. Lyons CJ, Rootman J. Strabismus in graves' orbitopathy. *Pediatr Endocrinol Rev* (2010) 7 Suppl 2:227–9.

118. Coats DK, Paysse EA, Plager DA, Wallace DK. Early strabismus surgery for thyroid ophthalmopathy. *Ophthalmology* (1999) 106:324–9. doi: 10.1016/S0161-6420(99)90071-4

119. Pitchon EM, Klainguti G. [Surgical treatment of diplopia in Graves' orbitopathy]. *Klin Monbl Augenheilkd* (2007) 224:331–3. doi: 10.1055/s-2007-962903

120. Terwee CB, Gerding MN, Dekker FW, Prummel MF, Wiersinga WM. Development of a disease specific quality of life questionnaire for patients with graves' ophthalmopathy: The GO-QOL. *Br J Ophthalmol* (1998) 82:773–9. doi: 10.1136/bjo.82.7.773

121. Kraus DJ, Bullock JD. Treatment of thyroid ocular myopathy with adjustable and nonadjustable suture strabismus surgery. *Trans Am Ophthalmol Soc* (1993) 91:67–79; discussion -84.

122. Lee JY, Park KA, Woo KI, Kim YD, Oh SY. Surgical outcomes of unilateral recession-resection for vertical strabismus in patients with thyroid eye disease. *J AAPOS* (2017) 21:19–22. doi: 10.1016/j.jaapos.2016.11.019

123. Sprunger DT, Helveston EM. Progressive overcorrection after inferior rectus recession. *J Pediatr Ophthalmol Strabismus* (1993) 30:145–8. doi: 10.3928/0191-3913-19930501-04

124. Scott WE, Thalacker JA. Diagnosis and treatment of thyroid myopathy. *Ophthalmology* (1981) 88:493–8. doi: 10.1016/s0161-6420(81)34988-4

125. Peragallo JH, Velez FG, Demer JL, Pineles SL. Postoperative drift in patients with thyroid ophthalmopathy undergoing unilateral inferior rectus muscle recession. *Strabismus* (2013) 21:23–8. doi: 10.3109/09273972.2012.762533

126. Kushner BJ. An evaluation of the semiadjustable suture strabismus surgical procedure. *J AAPOS* (2004) 8:481–7. doi: 10.1016/j.jaapos.2004.07.005

127. Jefferis JM, Raoof N, Burke JP. Prioritising downgaze alignment in the management of vertical strabismus for thyroid eye disease: Principles and outcomes. *Eye (Lond)* (2020) 34:906–14. doi: 10.1038/s41433-019-0574-0

128. Wright KW. Late overcorrection after inferior rectus recession. *Ophthalmology* (1996) 103:1503–7. doi: 10.1016/s0161-6420(96)30476-4

129. De Hoog J, Stravers S, Kalmann R. Recession of the inferior rectus muscle in graves' orbitopathy. *Eye (Lond)* (2010) 24:1011–7. doi: 10.1038/eye.2009.267

130. Honglertnapakul W, Cavuoto KM, McKeown CA, Capo H. Surgical treatment of strabismus in thyroid eye disease: Characteristics, dose-response, and outcomes. *J AAPOS* (2020) 24:72.e1–e7. doi: 10.1016/j.jaapos.2019.12.014

131. Plager DA ed. *Strabismus surgery: Basic and advanced strategies*. New York, NY: Oxford University Press (2004).

132. Cestari DM, Freire MV, Chun BY. Vertical rectus muscle recession versus combined vertical and horizontal rectus muscle recession in patients with thyroid eye disease and hypotropia. *J AAPOS* (2018) 22:257–61. doi: 10.1016/j.jaapos.2018.04.007

133. Nassar MM, Dickinson AJ, Neoh C, Powell C, Buck D, Galal E, et al. Parameters predicting outcomes of strabismus surgery in the management of graves' ophthalmopathy. *J AAPOS* (2009) 13:236–40. doi: 10.1016/j.jaapos.2008.11.007

134. Hwang B, Heo H, Lambert SR. Risk factors for reoperation after strabismus surgery among patients with thyroid eye disease. *Am J Ophthalmol* (2022) 238:10–5. doi: 10.1016/j.ajo.2021.11.022

135. Kushner BJ. A surgical procedure to minimize lower-eyelid retraction with inferior rectus recession. *Arch Ophthalmol* (1992) 110:1011–4. doi: 10.1001/archopht.1992.01080190117039

136. Pacheco EM, Guyton DL, Repka MX. Changes in eyelid position accompanying vertical rectus muscle surgery and prevention of lower lid retraction with adjustable surgery. *J Pediatr Ophthalmol Strabismus* (1992) 29:265–72. doi: 10.3928/0191-3913-19920901-03

137. Liao SL, Shih MJ, Lin LL. A procedure to minimize lower lid retraction during large inferior rectus recession in graves ophthalmopathy. *Am J Ophthalmol* (2006) 141:340–5. doi: 10.1016/j.ajo.2005.10.009

138. Dal Canto AJ, Crowe S, Perry JD, Traboulsi EI. Intraoperative relaxed muscle positioning technique for strabismus repair in thyroid eye disease. *Ophthalmology* (2006) 113:2324–30. doi: 10.1016/j.ophtha.2006.04.036

139. Lekskul A, Tangtammaruk P, Wuthisiri W. The outcome of one-to-Four muscle surgery by intraoperative relaxed muscle positioning with adjustable suture technique in thyroid eye disease. *Clin Ophthalmol* (2021) 15:3833–9. doi: 10.2147/OPTH.S333377

140. Nicholson BP, De Alba M, Perry JD, Traboulsi EI. Efficacy of the intraoperative relaxed muscle positioning technique in thyroid eye disease and analysis of cases requiring reoperation. *J AAPOS* (2011) 15:321–5. doi: 10.1016/j.jaapos.2011.03.014

141. Sarici AM, Mergen B, Oguz V, Dogan C. Intraoperative relaxed muscle positioning technique results in a tertiary center for thyroid orbitopathy related strabismus. *BMC Ophthalmol* (2018) 18:305. doi: 10.1186/s12886-018-0974-0

142. Hedergott A, Pink-Theofylaktopoulos U, Neugebauer A, Fricke J. Tendon elongation with bovine pericardium in strabismus surgery-indications beyond graves' orbitopathy. *Graefes Arch Clin Exp Ophthalmol* (2021) 259:145–55. doi: 10.1007/s00417-020-04939-7

143. Prinz J, Hartmann K, Migliorini F, Hamesch K, Walter P, Fuest M, et al. Elongation of the inferior rectus tendon with fascia lata graft for large vertical squint angles in patients with Graves' orbitopathy. *Graefes Arch Clin Exp Ophthalmol* (2022) 260:3365–73. doi: 10.1007/s00417-022-05696-5

144. Bailey MD, Sigireddi RR, Kim EJ, Yen KG. Challenges of managing strabismus in thyroid eye disease. *Int Ophthalmol Clin* (2021) 61:107–25. doi: 10.1097/iio.0000000000000347

145. Lueder GT, Scott WE, Kutschke PJ, Keech RV. Long-term results of adjustable suture surgery for strabismus secondary to thyroid ophthalmopathy. *Ophthalmology* (1992) 99:993–7. doi: 10.1016/s0161-6420(92)31866-4

146. Xu L, Glass LR, Kazim M. Reactivation of thyroid eye disease following extraocular muscle surgery. *Ophthalmic Plast Reconstr Surg* (2014) 30:e5–6. doi: 10.1097/IOP.0b013e3182873cfe

147. Campbell A, Whittaker TJ, Sokol JA. Re: "Reactivation of thyroid eye disease following extraocular muscle surgery". *Ophthalmic Plast Reconstr Surg* (2014) 30:353. doi: 10.1097/iop.0000000000000197

148. Huang CY, Lin HC, Yang ML. Necrotizing scleritis after strabismus surgery in thyroid eye disease. *J aapos* (2013) 17:535–6. doi: 10.1016/j.jaapos.2013.04.010

149. James RR. BRITISH MASTERS OF OPHTHALMOLOGY SERIES: 17.-JOHN DALRYMPLE, F.R.S., 1803-1852. *Br J Ophthalmol* (1926) 10:nil2–247. doi: 10.1136/bjo.10.5.nil2

150. Phelps PO, Williams K. Thyroid eye disease for the primary care physician. *Dis Mon* (2014) 60:292–8. doi: 10.1016/j.disamonth.2014.03.010

151. Bartley GB, Gorman CA. Diagnostic criteria for Graves' ophthalmopathy. *Am J Ophthalmol* (1995) 119:792–5. doi: 10.1016/s0002-9394(14)72787-4

152. Cockerham KP, Hidayat AA, Brown HG, Cockerham GC, Graner SR. Clinicopathologic evaluation of the Mueller muscle in thyroid-associated orbitopathy. *Ophthalmic Plast Reconstr Surg* (2002) 18:11–7. doi: 10.1097/00002341-200201000-00003

153. Grove ASJr. Upper eyelid retraction and Graves' disease. *Ophthalmology* (1981) 88:499–506. doi: 10.1016/s0161-6420(81)34991-4

154. Bartley GB, Fatourechi V, Kadrmas EF, Jacobsen SJ, Ilstrup DM, Garrity JA, et al. Clinical features of Graves' ophthalmopathy in an incidence cohort. *Am J Ophthalmol* (1996) 121:284–90. doi: 10.1016/s0002-9394(14)70276-4

155. Ribeiro SF, Shekhovtsova M, Duarte AF, Velasco Cruz AA. Graves lower eyelid retraction. *Ophthalmic Plast Reconstr Surg* (2016) 32:161–9. doi: 10.1097/iop.0000000000000613

156. Cartlidge NE, Crombie AL, Anderson J, Hall R. Critical study of 5 per cent guanethidine in ocular manifestations of Graves's disease. *Br Med J* (1969) 4:645–7. doi: 10.1136/bmj.4.5684.645

157. Gay AJ, Wolkstein MA. Topical guanethidine therapy for endocrine lid retraction. *Arch Ophthalmol* (1966) 76:364–7. doi: 10.1001/archopht.1966.03850010366012

158. Cant JS, Lewis DR. Unwanted pharmacological effects of local guanethidine in the treatment of dysthyroid upper lid retraction. *Br J Ophthalmol* (1969) 53:239–45. doi: 10.1136/bjo.53.4.239

159. Buffam FV, Rootman J. Lid retraction–its diagnosis and treatment. *Int Ophthalmol Clin* (1978) 18:75–86.

160. Doxanas MT, Dryden RM. The use of sclera in the treatment of dysthyroid eyelid retraction. *Ophthalmology* (1981) 88:887–94. doi: 10.1016/s0161-6420(81)80002-4

161. Shih MJ, Liao SL, Lu HY. A single transcutaneous injection with botox for dysthyroid lid retraction. *Eye (Lond)* (2004) 18:466–9. doi: 10.1038/sj.eye.6700690

162. Uddin JM, Davies PD. Treatment of upper eyelid retraction associated with thyroid eye disease with subconjunctival botulinum toxin injection. *Ophthalmology* (2002) 109:1183–7. doi: 10.1016/s0161-6420(02)01041-2

163. Chee E, Chee SP. Subconjunctival injection of triamcinolone in the treatment of lid retraction of patients with thyroid eye disease: A case series. *Eye (Lond)* (2008) 22:311–5. doi: 10.1038/sj.eye.6702933

164. Young SM, Kim YD, Lang SS, Woo KI. Transconjunctival triamcinolone injection for upper lid retraction in thyroid eye disease-a new injection method. *Ophthalmic Plast Reconstr Surg* (2018) 34:587–93. doi: 10.1097/iop.0000000000001120

165. Lee JM, Lee H, Park M, Baek S. Subconjunctival injection of triamcinolone for the treatment of upper lid retraction associated with thyroid eye disease. *J Craniofac Surg* (2012) 23:1755–8. doi: 10.1097/SCS.0b013e3182646043

166. Kozaki A, Nakamura H, Inoue T. Clinical efficacy of transcutaneous triamcinolone acetonide injection for upper eyelid retraction and swelling in patients with thyroid eye disease. *Int Med Case Rep J* (2018) 11:325–31. doi: 10.2147/imcrj.S177671

167. Lee SJ, Rim TH, Jang SY, Kim CY, Shin DY, Lee EJ, et al. Treatment of upper eyelid retraction related to thyroid-associated ophthalmopathy using subconjunctival triamcinolone injections. *Graefes Arch Clin Exp Ophthalmol* (2013) 251:261–70. doi: 10.1007/s00417-012-2153-y

168. Ceisler EJ, Bilyk JR, Rubin PA, Burks WR, Shore JW. Results of müllerotomy and levator aponeurosis transposition for the correction of upper eyelid retraction in graves disease. *Ophthalmology* (1995) 102:483–92. doi: 10.1016/s0161-6420(95)30996-7

169. Cho RI, Elner VM, Nelson CC, Frueh BR. The effect of orbital decompression surgery on lid retraction in thyroid eye disease. *Ophthalmic Plast Reconstr Surg* (2011) 27:436–8. doi: 10.1097/IOP.0b013e3182232465

170. Cruz AAV, Equitério B, Diniz SB, Garcia DM, Rootman DB, Goldberg RA, et al. Upper eyelid contour changes after orbital decompression in graves orbitopathy. *Ophthalmic Plast Reconstr Surg* (2022) 38:289–93. doi: 10.1097/iop.0000000000002093

171. Kim SH, Kang SM. Changes in eyelid parameters after orbital decompression according to the surgical approach in thyroid eye disease. *Korean J Ophthalmol* (2021) 35:421–8. doi: 10.3341/kjo.2021.0035

172. Lee ES, Han JW, Choi HS, Jang JW, Kim SJ, Jang SY. Differences in interpalpebral fissure measurement in patients with unilateral enophthalmos resulting from orbital wall fractures. *J Craniomaxillofac Surg* (2017) 45:690–3. doi: 10.1016/j.jcms.2017.02.017

173. Henderson JW. A surgical procedure for retraction of eyelids in endocrine exophthalmos (a moving picture). *Trans Am Ophthalmol Soc* (1965) 63:70–4.

174. McNab AA, Galbraith JE, Friebel J, Caesar R. Pre-whitnall levator recession with hang-back sutures in graves orbitopathy. *Ophthalmic Plast Reconstr Surg* (2004) 20:301–7. doi: 10.1097/01.iop.0000129529.36577.5b

175. Elner VM, Hassan AS, Frueh BR. Graded full-thickness anterior blepharotomy for upper eyelid retraction. *Arch Ophthalmol* (2004) 122:55–60. doi: 10.1001/archopht.122.1.55

176. Ben Simon GJ, Mansury AM, Schwarcz RM, Modjtahedi S, McCann JD, Goldberg RA. Transconjunctival müller muscle recession with levator disinsertion for correction of eyelid retraction associated with thyroid-related orbitopathy. *Am J Ophthalmol* (2005) 140:94–9. doi: 10.1016/j.ajo.2005.02.034

177. Hintschich C, Haritoglou C. Full thickness eyelid transsection (blepharotomy) for upper eyelid lengthening in lid retraction associated with graves' disease. *Br J Ophthalmol* (2005) 89:413–6. doi: 10.1136/bjo.2004.052852

178. Pinas D, OBDK R, Wubbels RJ, van den Bosch WA, Paridaens D. Results of surgical correction of upper eyelid retraction in graves' orbitopathy. *Acta Ophthalmol* (2021) 99:e608–e13. doi: 10.1111/aos.14622

179. Blair V, Byars LJSG, Obst. L. Paralysis of the lower lid and scleral scars and grafts. *Surg Gynec & Obst* (1940) 70:1.

180. Park E, Lewis K, Alghoul MS. Comparison of efficacy and complications among various spacer grafts in the treatment of lower eyelid retraction: A systematic review. *Aesthet Surg J* (2017) 37:743–54. doi: 10.1093/asj/sjx003

181. Li TG, Shorr N, Goldberg RA. Comparison of the efficacy of hard palate grafts with acellular human dermis grafts in lower eyelid surgery. *Plastic and Reconstructive Surgery* (2005) 116:873–8. doi: 10.1097/01.prs.0000177694.39466.b2

182. Oestreicher JH, Pang NK, Liao WJOP, Surgery R. Treatment of lower eyelid retraction by retractor release and posterior lamellar grafting: An analysis of 659 eyelids in 400 patients. *Ophthalmic Plastic and Reconstructive Surgery* (2008) 24:207–12. doi: 10.1097/IOP.0b013e3181706840

183. Chang HS, Lee D, Taban M, Douglas RS, Goldberg RA. "En-glove" lysis of lower eyelid retractors with AlloDerm and dermis-fat grafts in lower eyelid retraction surgery. *Ophthalmic Plastic and Reconstructive Surgery* (2011) 27:137–41. doi: 10.1097/IOP.0b013e3181c53d38

184. Norris JH, Ross JJ, O'Reilly P, Malhotra R. A review of combined orbital decompression and lower eyelid recession surgery for lower eyelid retraction in thyroid orbitopathy. *Br J Ophthalmol* (2011) 95:1664–9. doi: 10.1136/bjophthalmol-2011-300698

185. Kim KY, Woo YJ, Jang SY, Lee EJ, Yoon JS. Correction of lower eyelid retraction using acellular human dermis during orbital decompression. *Ophthalmic Plast Reconstr Surg* (2017) 33:168–72. doi: 10.1097/iop.0000000000000683

186. Taban MR. Combined orbital decompression and lower eyelid retraction surgery. *J Curr Ophthalmol* (2018) 30:169–73. doi: 10.1016/j.joco.2017.12.003

187. Ben Simon GJ, Mansury AM, Schwarcz RM, Lee S, McCann JD, Goldberg RA. Simultaneous orbital decompression and correction of upper eyelid retraction versus staged procedures in thyroid-related orbitopathy. *Ophthalmology* (2005) 112:923–32. doi: 10.1016/j.ophtha.2004.12.028

188. Olver JM, Fells P. 'Henderson's' relief of eyelid retraction revisited. *Eye (Lond)* (1995) 9(Pt 4):467–71. doi: 10.1038/eye.1995.108

189. Elner VM, Hassan AS, Frueh BR. Graded full-thickness anterior blepharotomy for upper eyelid retraction. *Trans Am Ophthalmol Soc* (2003) 101:67–73; discussion -5.

190. Schaefer DP. The graded levator hinge procedure for the correction of upper eyelid retraction (an American ophthalmological society thesis). *Trans Am Ophthalmol Soc* (2007) 105:481–512.

191. Lee J, Lee H, Park M, Baek S. Modified full thickness graded blepharotomy for upper eyelid retraction associated with thyroid eye disease in East asians. *Ann Plast Surg* (2016) 77:592–6. doi: 10.1097/sap.0000000000000656

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High IgG4 serum concentration is associated with active Graves orbitopathy

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Background: The aim of the study was to evaluate the differences in clinical profile, laboratory parameters, and ophthalmological signs, and symptoms between patients with high IgG4 Graves orbitopathy and patients with normal IgG4 Graves orbitopathy.

Methods: This was a prospective observational study. We recruited adult patients with Graves Orbitopathy(GO) referred to our clinic for further diagnostics and treatment. Eventually, 60 patients with GO were enrolled in the study. All patients underwent ophthalmological assessment, magnetic resonance imaging (MRI) of the orbits, and laboratory tests, including IgG4 serum concentration measurement. High IgG4 GO was diagnosed if the IgG4 concentration exceeded 135 mg/dl. We used both the clinical activity score (CAS) and magnetic resonance imaging (MRI) to assess the activity of GO. Eventually, active GO was defined according to MRI results.

Results: Among 60 GO patients, 15 (25%) patients had elevated IgG4 levels. Patients in the high IgG4 group had a higher prevalence of active GO by MRI than patients with normal IgG4 (100% vs. 64.44%, P=0.006). They also had a higher eosinophile count in peripheral blood, a lower bilirubin level, a more frequent lower eyelid retraction, and a lower prevalence of glaucoma. There were no statistically significant differences between the groups in CAS. Patients with active GO, had higher median IgG4 level [89.95 (55.48; 171.1) vs 43.45 (32.48; 49.68) mg/dl, P<0.001]. The receiver operating characteristic (ROC) analysis for IgG4 as a marker of active GO revealed the following results: AUC 0.848 for the cut-off value of 54.2 mg/dl, sensitivity 79.5%, specificity 87.5%, positive predictive value 94.6%, negative predictive value 59.1%.

Conclusions: We demonstrated that IgG4 is a marker of GO activity. Certain differences in the clinical profile of patients with high IgG4 GO, and normal IgG4 GO were observed. More data is needed to establish whether patients with high

IgG4 GO are GO patients with particularly active disease or actually represent a distinct clinical entity related to IgG4-Related Disease.

KEYWORDS

IgG4, Graves disease, Graves orbitopathy, ophtalmopathy, IgG4-related disease, thyroid eye disease (TED)

Introduction

Human immunoglobulin G4 (IgG4) usually constitutes less than five percent of the total amount of IgG in the serum. This makes it the least abundant IgG subclass but certainly not the least important (1). It has unusual biological features that distinguish it from other antibodies, such as inhibition of the formation of immune complexes, lack of antibody-dependent cell-mediated cytotoxicity, and the capability of undergoing Fab-arm exchange (2). Its role in the inflammatory process can be protective (e.g., immune tolerance-inducing), directly pathogenic, or it could be a marker of an atypical inflammatory response (3). IgG4 has been the focal point of many research projects in recent years due to its unique characteristics. High serum concentrations of IgG4 were firstly described in a group of patients with sclerosing autoimmune pancreatitis by Hamano et al. (4). This further led to the discovery of IgG4-related disease (IgG4-RD), which is a chronic disorder characterized by fibrosis and inflammation. Typical features of IgG4-RD are increased plasma level of IgG4, tissue infiltration with IgG4-positive plasma cells, obliterative phlebitis, storiform fibrosis, and a very good response to glucocorticoid treatment (5–7). The disease affects predominately white males in their middle age or older. However, interestingly, patients with the disease limited to the head and neck region were more commonly females, especially of Asian origin (7–9).

The course of IgG4-RD can be heterogeneous and depends on the affected area. It usually affects the pancreas, salivary and lacrimal glands, lungs, biliary tract, retroperitoneum, kidneys, liver, or even aorta[3,6]. Typical manifestations are pancreatitis, chronic sclerosing sialadenitis, dacryoadenitis, thyroiditis, mediastinal or retroperitoneal fibrosis, periaortitis, cholangitis, inflammatory pseudotumor, and Mikulicz disease (7, 10).

The role of IgG4 has also been evaluated in the thyroid disease. Based on current research, the fibrosing variant of Hashimoto's thyroiditis and Riedel's thyroiditis show the biggest histological and clinical resemblance to IgG4-RD. They are acknowledged by many as disorders of the IgG4-RD spectrum. However, high levels of IgG4 have also been noticed in some patients with Graves disease (GD), especially in a subgroup of patients with Graves orbitopathy (GO) (11). Graves orbitopathy is the most common extrathyroidal manifestation of Graves disease (GD). Despite ongoing research and development of new treatment methods, managing GO still poses several diagnostic and therapeutic challenges (12, 13). Thus, the development of new diagnostic tools is crucial.

So far, the role of IgG4 in GD and orbitopathy has been assessed to a limited extent. According to a recent review, the average prevalence of elevated IgG4 levels in GD patients is around 10% (5.4% in patients without GO and 17.6% in patients with orbitopathy). While some studies linked elevated IgG4 levels with the occurrence of GO and its activity, better response to thiamazole, or increased thyroid antibody levels, other studies failed to find such associations (14, 15). The vast majority of studies were carried out on the Asian population, while data from other regions are scarce. Moreover, several study groups included only a limited number of patients with GO in their investigation.

In our study, we aimed to evaluate whether IgG4 can be used as a marker of GO activity in clinical practice and assess the differences in clinical profile, laboratory parameters, and ophthalmological signs and symptoms between patients with GO and high IgG4 serum concentration and patients with GO and normal IgG4 serum concentration.

Materials and methods

Study design and patients' enrollment

This was a prospective observational study. It was conducted at the Department of Endocrinology, Metabolism, and Internal Medicine of the Poznan University of Medical Sciences (tertiary referral hospital). We recruited all adult patients (>= 18 years old) diagnosed with Graves orbitopathy, who were referred to our department for diagnostics and treatment of the disease. Exclusion criteria were: 1) systemic immunosuppressive or immunomodulatory treatment at the time of admission or in the previous 6 months; 2) Chronic kidney disease stages 4 and 5; 3) Liver failure; 4) Active neoplastic disease or suspicion of malignant disease; 5) Active acute or chronic infections; 6) Any immunodeficiency disorder 7) pregnancy.

Eventually, 60 patients with GO were enrolled in the study, of whom 25 underwent previous thyroidectomy, 28 were treated with radioiodine in the past (5 underwent both thyroidectomy and radioiodine therapy), and 6 were still on antithyroid medication. All patients were screened for human immunodeficiency virus, hepatitis B, and hepatitis C. Patients who were carriers of those viruses were excluded from the study.

A detailed history of treatment and comorbidities, including smoking status, was obtained from each patient.

Ophthalmologic examination

An extensive ophthalmologic examination was performed in each patient by an experienced ophthalmologist who was blinded to IgG4 results throughout the study. Hertl's exophthalmometer was used for precise exophthalmos measurements. Patients were evaluated according to the Clinical Activity Score (CAS), based on the following symptoms 1) Periorbital or retroorbital pain or pressure; 2) Pain with lateral, downward, or upward movement, and following signs 1) Swelling of the eyelids; 2) Redness of the eyelids; 3) Conjunctival injection; 4) Chemosis; 5) Inflammation of the caruncle or plica. Intraocular pressure (IOP) values were obtained in each patient with Goldmann applanation tonometry. IOP values over 21 mm Hg were considered diagnostic for glaucoma. However, it is worth noting that some patients have been diagnosed with glaucoma before entering the study and at the time of admission had IOP <21 on IOP lowering medication. Patient's best corrected visual acuity was measured and defined according to the WHO definitions of vision impairment: mild – visual acuity worse than 6/12 to 6/18; moderate – visual acuity between 6/18 and 6/60; severe – visual acuity between 6/60 and 3/60, blindness – visual acuity worse than 3/60. Extraocular muscle involvement was defined as restriction in eyeball motility resulting in double vision in either primary or extreme gaze positions. Optic nerve involvement was defined as pallor or choking of the optic disc with preserved or diminished visual acuity; Corneal involvement was defined as the presence of stippling, ulceration, clouding, or perforation of the cornea.

Laboratory assessment

Fasting (overnight) venous blood samples were taken from each patient. Detailed laboratory analysis was conducted, including thyroid-related hormones [thyroid-stimulating hormone (TSH), free triiodothyronine (fT3), free thyroxine (fT4)), thyroid autoantibody profile (anti-TSH receptor antibodies(TRAb), anti-thyroid peroxidase antibodies (TPOAb), anti-thyroglobulin antibodies (TgAb)], renal function (creatinine), liver function (ALT, AST, bilirubin), electrolytes (total calcium, sodium, potassium), metabolic profile (total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides) and inflammatory process markers (C-reactive protein) and complete blood count with differential (CBC-D).

The CBC-D was measured by the flow cytometry based hematology analyzer Sysmex-XN 1000 (Sysmex Europe GmbH) TRAb levels were evaluated by the radioimmunological method with a commercially available radioimmunoassay kit (Brahms GmbH). The rest of the parameters mentioned above were assessed with the use of the COBAS 8000 analyzer (Roche).

Finally, IgG4 serum concentration was measured by an immune–enzymatic assay using commercially available ELISA kits (Sunredbio, Shanghai). Based on IgG4 levels, we divided patients into two groups – GO with high IgG4 and GO with normal IgG4 serum concentration. We applied the widely recognized cut-off value diagnostic for IgG4-RD (135 mg/dl), which was also used by the majority of previous studies on the role of IgG4 in GD.

Imaging tests

Each patient underwent thyroid ultrasound. The volume of each thyroid lobe was calculated with the use of the following formula: 0.52 x length x width x depth. The cumulative volume of the thyroid gland was obtained after adding together volumes of the right and left lobe. For differential diagnosis and to assess the activity of GO, we performed a magnetic resonance imaging (MRI) of the orbits in each patient. MRI was performed by Magnetom Skyra 3T scanner (Siemens Healthcare Gmbh). Patients with signs of active inflammatory process in dedicated sequence of the MRI of the orbits were placed in the active GO group, while patients without signs of active inflammation were placed in the inactive GO group. Active disease was diagnosed if the MRI revealed swollen extraocular muscles with increased signal intensity in the STIR (short tau inversion recovery) or T2-weighted sequences. If the imaging test did not show any abnormalities or just swelling of the extraocular muscles without increased signal intensity then inactive GO was diagnosed.

Ethics

Every patient signed a written informed consent to participate in the study. The project was conducted in accordance with the declaration of Helsinki (16). The study was reviewed and approved by the Bioethics Committee at the Poznan University of Medical Sciences (Decision number: 774/20)

Statistical analysis

The statistical analyses were performed using PQ Stat v.1.8.4. The Shapiro-Wilk test was used to check for normality. We assessed the equality of variances with Levene's test. We used the unpaired student's T-test to compare continuous, normally distributed data with homogenous variances. The Mann-Whitney U test was used to compare nonparametric data. The comparison of qualitative variables was carried out with the use of Fisher's exact test. Pearson's test was used for the correlation analysis of parametric data, while the Spearman test was used for the correlation analysis of nonparametric data. Data are presented as mean ± Standard Error (SE) or median (first Quartile; third Quartile). The P level <0.05 was considered significant. All tests were two-tailed. The ROC (receiver operating characteristic) curves were built. AUC was calculated with the DeLong method. The P level <0.05 was considered significant. All tests were two-tailed.

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Results

A total number of 60 patients were enrolled in the study. We divided patients into the high IgG4 group (IgG4 serum concentration >135 mg/dl) and normal IgG4 group (IgG4 serum concentration <135 mg/dl). 15 (25%) patients were placed in the high IgG4 group and 45 (75%) in the normal IgG4 group. Patients did not differ significantly in age, gender, or smoking status. There were also no statistically significant differences between those two groups in the number of patients treated with levothyroxine or antithyroid medications. The groups also did not differ in the number of patients who previously were treated with thyroidectomy radioiodine or received intravenous glucocorticoid pulse therapy in the past (>6 months ago). The thyroid volume was comparable among those two groups (a separate analysis was done for patients who received radioiodine in the past). There was no statistically significant difference in IgG4 serum concentrations between patients previously treated with methylprednisolone pulse therapy compared to patients who have never been treated (98.65 (48.53; 156.4) vs. 60.3 (47.43; 119.83) mg/dl, P=0.275). A detailed summary of patient's ultrasound results, history and demographic data are presented in Table 1.

Patients in the high IgG4 group had a higher prevalence of active GO than patients in the normal IgG4 group (100% vs. 64.44%, P=0.006). Patients in the elevated IgG4 group had also a higher eosinophile count (240 (190–320) vs 130 (70–250) cells/µl, P=0.041) and a lower total bilirubin level [0.49 (0.4; 0.59) vs 0,67 (0.51; 0.59) mg/dl, P=0.019]. Other biochemical parameters, including complete blood count, TRAb, TPOAb, TgAb, TSH, fT3, fT4, ALT, AST, creatinine, electrolytes, and lipid profile parameters, did not differ significantly. A full comparison of biochemical parameters is presented in Table 2.

We performed a detailed ophthalmologic examination to check for differences in ocular signs and symptoms between the high IgG4 and normal IgG4 groups. Patients in the high IgG4 group had more frequently lower eyelid retraction (93.33% vs. 62.22%, P=0.025). They suffered less often from glaucoma (51.11% vs. 20%, P=0.041). We also observed that patients with elevated IgG4 levels tended to manifest conjunctival injection more frequently (60% vs. 28.89%), but the result failed to achieve statistical significance (P=0.060). There were no statistically significant differences between the groups in CAS (and its components), intraocular pressure (IOP), visual acuity, proptosis, soft tissue involvement, extraocular muscle involvement, optic nerve involvement, GO signs (Dalrymple's, Kocher's, Rosenbach's, Von Graefe's, Möbius). Findings from the extensive ophthalmological examination are summarized in Table 3.

We divided patients into groups based on the activity of the disease. Patients with active disease had a higher IgG4 level (89.95 (55.48; 171.1) vs 43.45 (32.48; 49.68) mg/dl, P<0.001) – Figure 1. They had also higher TRAb titers (13.79 (15; 20.7) vs 0,8 (0.54; 2.4) µU/ml, P=0.012. No differences in TSH, fT3, fT4, TPOAb, and TgAb were observed (Table 4). Patients in the active group also tended to have lower bilirubin levels than patients in the inactive group, but this result was not statistically significant (P=0.056). We did not find any correlations between IgG4 and thyroid volume, CAS, TSH, fT3, fT4, TPOAb, TGAb, TRAblevels, and other laboratory parameters.

We performed a receiver operating characteristic (ROC) analysis to evaluate the potential of IgG as a diagnostic marker of GO activity (Figure 2). The cut-off for the maximum potential effectiveness of IgG4 as a biomarker (The Youden index) was ≥ 54.2 mg/dl. The AUC was 0.848 (P<0.001). For the aforementioned cut-off value sensitivity was 79.5%, specificity 87.5%, positive predictive value (PPV) 94.6%, negative predictive value (NPV) 59.1%.

TABLE 1 Summary of patient history and demographic data.

	Normal IgG4 group (n=45)	High IgG4 group (n=15)	P value
Age (years)	53.93 ± 16.71	54.27 ± 14.29	0.946
Time since Graves orbitopathy onset (months)	18 [11; 36]	12 [5; 36]	0.328
Gender [n of males(%)]	10 (22.22%)	4 (26.67%)	0.734
Prior thyroidectomy	21 (46.67%)	4 (26.67%)	0.232
Prior radioiodine therapy	20 (44.44%)	8 (53.33%)	0.567
Prior intravenous glucocorticoid pulse therapy >6 months ago	10 (23.91%)	4 (28.57%)	0.733
No thyroidectomy or radioiodine	8 (17.78%)	4 (26.67%)	0.472
Levothyroxine therapy	39 (86.67%)	11 (73.33%)	0.250
Antithyroid treatment	3 (6.67%)	3 (20%)	0.159
Active smoker	22 (48.89%)	5 (33.33%)	0.375
Past smoker	4 (8.89%)	0 (0%)	0.564
Thyroid volume in patients after radioiodine treatment (cm^3)	3.38 ± 0.77	2.10 ± 0.72	0.325
Thyroid volume in patients with an intact thyroid gland (cm^3)	27.20 ± 7.33	21.69 ± 9.25	0.656

Continuous variables with a normal distribution are shown as mean ± SE, nonparametric variables are shown as median [lower quartile, upper quartile], nominal variables are snown as N (%).

TABLE 2 Comparison of laboratory parameters between the high IgG4 group and normal IgG4 group.

Parameter	Normal IgG4 group (n=45)	High IgG4 group (n=15)	P value
TSH (µU/ml)	1.4 [0.58; 3.75]	0.97 [0.35; 1.89]	0.338
fT3 (pmol/l)	4.19 [3.57; 4.67]	4.61 [3.85; 5.38]	0.156
fT4 (pmol/l)	18.6 [16; 20.4]	19.1 [13.85; 21]	0.880
TRAb (IU/I)	3.81 [1.73; 19.11]	9.66 [3.76; 12.49]	0.920
TPOAb (IU/ml)	82 [12.5; 205]	34 [15.75; 104]	0.363
TgAb (IU/ml)	15.5 [13; 147]	17 [13.5; 849]	0.600
Creatinine (mg/dl)	0.77 [0.65; 0.88]	0.72 [0.69; 0.81]	0.814
Total calcium (mg/dl)	9.71 [9.39; 9.94]	9.74 [9.43; 10.11]	0.592
Sodium (mmol/l)	141 [139; 142]	141 [138.5; 142.75]	0.739
Potassium (mmol/l)	4.36 [4.24; 4.71]	4.44 [4.3; 4.75]	0.563
Bilirubin (mg/dl)	0.67 [0.51; 0.79]	0.49 [0.4; 0.59]	**0.019**
AST (U/I)	19 [16; 24]	21 [17; 26.5]	0.316
ALT (U/I)	16 [13; 24]	18 [15.5; 25]	0.392
Glucose (mg/dl)	95 [90.75; 109.5]	98 [93; 104.5]	0.864
Total Cholesterol (mg/dl)	204.27 ± 66.14	205.93 ± 44.12	0.952
HDL (mg/dl)	61 [52; 69]	58 [52; 66.5]	0.632
LDL (mg/dl)	131.65 ± 53.5	134.31 ± 37.92	0.869
Triglycerides (mg/dl)	123,5 [93.25; 152.5]	113 [93; 130]	0.660
WBC (x10^3/µl)	6.37 [5.19; 7.41]	5.87 [5.13; 7.71]	0.951
Neutrophiles (x10^3/µl)	3.13 [2.54; 3.92]	3.32 [2.86; 3.85]	0.814
Lymphocytes (x10^3/µl)	2.11 ± 0.72	2.28 ± 0.69	0.568
Monocythes (x10^3/µl)	0.53 [0.4; 0.58]	0.42 [0.33; 0.51]	0.236
Eosinophiles (x10^3/µl)	0.13 [0.07; 0.25]	0.24 [0.19; 0.32]	**0.041**
RBC (x10^6/µl)	4.53 ± 0.4	4.68 ± 0.41	0.210
Hemoglobin (g/dl)	13.89 ± 1.48	14.19 ± 1.24	0.487
Platelets (x10^3/µl)	251.95 ± 66.42	248.53 ± 61.75	0.862
CRP (mg/l)	1.5 [0.7; 2.6]	1.8 [0.65; 3.75]	0.691
IgG4 (mg/dl)	51.9 [39.5; 82.9]	236.3 [172.3; 308.75]	**<0.001**

Statistically significant P values (<0.05) were displayed in bold.

Sensitivity and specificity at different IgG4 serum concentrations are plotted in Figure 3.

Discussion

Sixty patients with GO were enrolled in our study. 15 (25%) of our patients had IgG4 serum concentration elevated over 135 mg/dl, which is more prevalent than the reported average of IgG4 elevation in GO (17.6%) (14). Some authors, however, found high IgG4 levels in even 37.5% of GD patients (17). The mean IgG4 serum levels in both the high IgG4 group and normal IgG4 group were also similar to values reported by most previous authors (14).

In our study, 15 (100%) of the patients with high IgG4 levels had active GO compared to only 29 of 45 (64.44%) in the normal IgG4 group. Other studies have also reported a higher prevalence of active GO in elevated IgG4 patients (18, 19). Some studies have also found higher CAS in patients with elevated IgG4 titers (17, 19), while others failed to demonstrate any significant association between CAS and IgG4 levels (20–22).

However, our study is the only one where GO activity was assessed with the combined use of MRI with CAS. Other studies used only CAS to divide patients into active and inactive GO groups. Even though CAS is undoubtedly a great diagnostic tool, it has to be interpreted cautiously. Some papers report that its sensitivity can be as low as 55% and the PPV is 65% (23). Other

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TABLE 3 Comparison of findings from ophthalmological examination in the normal and high IgG4 groups.

	Normal IgG4 group (n=45)	High IgG4 group (n=15)	P value
Active phase of orbitopathy	29 (64.44%)	15 (100%)	**0.006**
IOP in the right eye (mm Hg)	18.91 ± 3.32	18.2 ± 2.65	0.460
IOP in left eye (mm Hg)	18.47 ± 2.83	18.07 ± 4.16	0.690
Protrusion of the right eye (mm)	19.86 ± 4.23	20.43 ± 4.47	0.668
Protrusion of the left eye (mm)	19.57 ± 4.03	21.71 ± 3.81	0.087
Protrusion of the eye with greater proptosis (mm)	20.58 ± 3.98	21.93 ± 3.73	0.269
Lower eyelid retraction	28 (62.22%)	14 (93.33%)	**0.025**
Upper eyelid retraction	27 (60%)	9 (60%)	1
Soft tissue involvement	33 (73.33%)	14 (93.33%)	0.153
Proptosis	29 (64.44%)	9 (60%)	0.766
Extraocular muscle involvement	21 (46.67%)	7 (46.67%)	1
Corneal involvement	10 (22.22%)	2 (13.33%)	0.712
Optic nerve involvement	9 (20%)	1 (6.67%)	0.426
Glaucoma	23 (51.11%)	3 (20%)	**0.041**
Dalrymple's sign	28 (62.22%)	12 (80%)	0.343
Kocher's sign	12 (26.67%)	4 (26.67%)	1
Rosenbach's sign	24 (53.33%)	7 (46.67%)	0.769
Von Graefe's sign	17 (37.78%)	8 (53.33%)	0.369
Möbius sign	26 (57.78%)	5 (33.33%)	0.139
Pain or pressure in a periorbital or retroorbital distribution	13 (28.89%)	3 (20%)	0.738
Pain with upward, downward, or lateral eye movement	17 (37.78%)	3 (20%)	0.343
Redness of the eyelids	10 (22.22%)	3 (20%)	1
Conjunctival injection	13 (28.89%)	9 (60%)	0.06
Chemosis	10 (22.22%)	4 (26.67%)	0.734
Inflammation of the caruncle or plica	8 (17.78%)	5 (33.33%)	0.279
Swelling of the eyelids	25 (55.56%)	10 (66.67%)	0.552
CAS >=3	15 (33.33%)	7 (46.67%)	0.372
Mild or no vision impairment	41 (91.11%)	14 (93.33%)	1
Moderate to severe vision impairment or blindness	4 (8.89%)	1 (6.67%)	1

IOP, Intraocular pressure; CAS, Clinical Activity Score. Continuous variables with a normal distribution are shown as mean ± SE, nonparametric variables are shown as median [lower quartile, upper quartile], nominal variables are snown as N(%). Best corrected visual acuity was defined according to WHO definitions of vision impairment(blindness, moderate, severe, mild or no vision impairment).
Statistically significant P values (<0.05) were displayed in bold.

researchers have compared the diagnostic utility of both CAS and MRI and found that MRI offers better sensitivity, specificity, PPV and NPV (24, 25).

Interestingly, in our study 8 out of 15 patients in the high IgG4 group had a CAS score of <3, but all of them had signs of active disease on MRI of the orbits. To a certain extent this could be explained by a small number of cases with severe or sight threating threating GO.

However, this also shows that we cannot rely solely on CAS in diagnosing active GO. There is a significant group of patients who present with troublesome symptoms (e.g., diplopia), which could still be treated with immunosuppressive/immunomodulatory drugs. If we relied solely on the CAS score, they might be falsely pronounced "inactive" and thus do not receive proper treatment. Based on this observation, we hypothesize that IgG4 might be a very sensitive marker of the inflammatory process, which is also elevated in patients, who do not show typical signs of active orbitopathy like inflammation of the conjunctiva, plica, eyelids, or chemosis.,but have active disease in the extraocular muscles and periorbital soft tissue. IgG4 serum concentration measurement would help to avoid false negative ("inactive") diagnoses in patients with active disease and low CAS scores, especially in situations when access to MRI is

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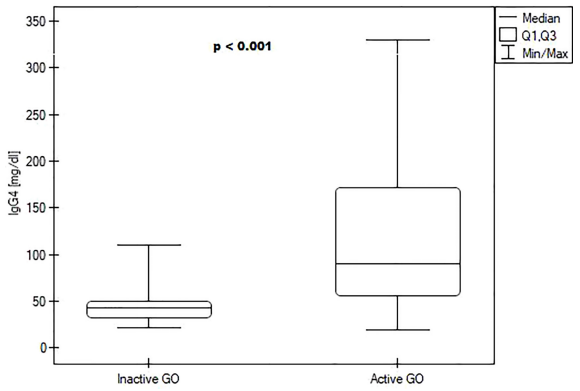

FIGURE 1
Boxplots comparing median IgG4 levels between the inactive Graves orbitopathy group and active Graves orbitopathy group.

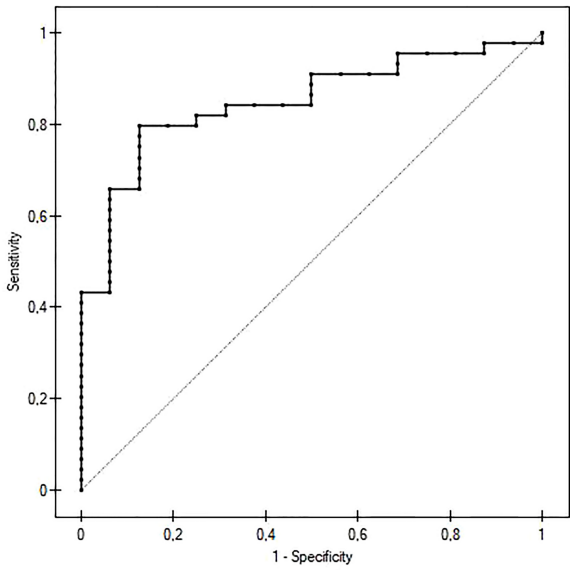

FIGURE 2
ROC curve of IgG4 serum concentration predicting active Graves orbitopathy. The cut-off value was 54,2 mg/dl. The AUC was 0,848 (P<0.001), sensitivity 79,5%, specificity 87,5%, positive predictive value 94,6%, negative predictive value 59,1%.

limited, the patient has contraindications to MRI, or the results of imaging studies are ambiguous.

Various serum markers in GO have been studied recently, including Th2-derived chemokines (e.g., CCL2 or IL-29) (26, 27). Our ROC analysis confirms that IgG4 is a potential serum biomarker of active GO. It has a decent sensitivity and specificity with a very high PPV of 94.6% at the cut-off value of 54.2 mg/dl. This makes it a potentially very useful diagnostic test that could be used as a "rule in" test for active GO. test for active GO.

Some researchers described that patients with high IgG4 GD had high TRAb levels, which positively correlated with IgG4 serum concentration (18, 22). Others found increased TPOAb (19, 28) or TGAb levels (28). However, the majority of studies, including ours, did not find any statistically significant differences in TPOAb, TGAb (18, 20, 29), or TRAb (19, 20, 28, 29) between high IgG4 GD and normal IgG4 GD. Based on our study and the current body of evidence we would lean, towards the opinion that IgG4 is rather an independent marker of ongoing inflammation, without a particularly strong association with thyroid antibodies.

We did not find any associations between CAS and IgG4 levels, which is in concordance with results reported in other papers (20, 22). However, other research groups describe higher CAS levels in patients with high IgG4 GO (17, 19), and observed that IgG4 levels were ascending in order of CAS (18). The relationship between IgG4 levels and CAS remains equivocal; as demonstrated by Li et al, it seems to be significant in patients with a shorter duration of GO (19), and insignificant in patients with a longstanding disease, which comprised the majority of our group.

Patients with GD and elevated IgG4 levels were found to have lower echogenicity of the thyroid on ultrasound examination (20, 29). Unfortunately, the vast majority of our patient at the time of admission was already after thyroidectomy or radioiodine treatment. Thus, we were only able to compare thyroid volumes and could not perform a more detailed analysis of the ultrasound images.

A recent study by Li et al. reported that IgG4 levels decreased after intravenous methylprednisolone treatment and that patients

TABLE 4 Comparison of chosen biochemical parameters between inactive GO and active GO groups.

Parameter	Inactive GO (n=16)	Active GO (n=44)	P value
IgG4 (mg/dl)	43.45 [32.48; 49.68]	89.95 [55.48; 171.1]	**<0.001**
TSH (µU/ml)	0.8 [0.54; 2.4]	1.35 [0.45; 3.6]	0.686
fT3 (pmol/l)	4.3 [3.95; 4.83]	4.17 [3.51; 4.85]	0.532
fT4 (pmol/l)	17.92 [16; 20.25]	18.7 [15; 20.7]	0.747
TRAb (IU/I)	2.07 [0.96; 3,9]	9.66 [2.47; 20.87]	**0.012**
TPOAb (IU/ml)	42 [12; 172]	66 [16; 238.5]	0.625
TgAb (IU/ml)	15 [13.5; 22]	31 [13; 643.5]	0.260
Bilirubin (mg/dl)	0.74 ± 0.25	0.60 ± 0.22	0.056

TSH, thyroid stimulating hormone; fT3, free triiodothyronine; fT4, free thyroxine; TRAb, anti-TSH receptor antibodies; TPOAb, anti-thyroid peroxidase antibodies; TgAb, anti-thyroglobulin antibodies; IgG4m Immunoglobulin 4. Continuous variables with a normal distribution are shown as mean ± SE, nonparametric variables are shown as median [lower quartile, upper quartile], nominal variables are snown as N(%).
Statistically significant P values (<0.05) were displayed in bold.

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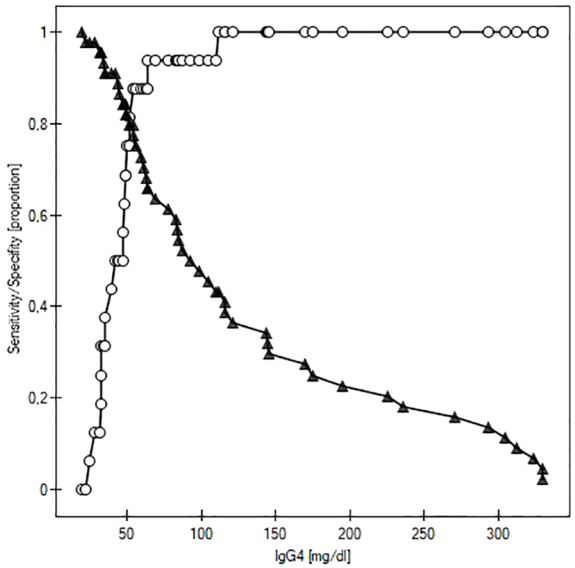

FIGURE 3
Curves of sensitivity (white circles) and specificity (black triangles) of IgG4 as a predictor of active Graves orbitopathy.

with high IgG4 levels had better treatment outcomes. Our study was not longitudinal in design, and thus we could not check for post-treatment results. However, patients enrolled in our study, who were previously treated with methylprednisolone pulse therapy (>6 months ago) did not differ in IgG4 levels from treatment naïve patients.

Previous studies did not find any differences in ocular signs or symptoms other than CAS between patients with elevated IgG4 and normal IgG4 levels (19, 22). However, they did not report such a detailed ophthalmological examination as we did. Still, the only few significant differences we were able to find were a higher prevalence of lower eyelid retraction and a lower prevalence of glaucoma. There are no pathognomonic clinical features, which would differentiate GO from IgG4-RD, however eyelid retraction is associated rather with GO than IgG4-RD (30). We found a significantly higher eosinophil count in peripheral blood in high IgG4 GO patients compared to normal IgG4 GO. This finding is in concordance with the observations of Torimoto et al. (29) Interestingly, peripheral blood eosinophilia has also been reported in about 40% of patients with IgG4-RD (31, 32), however this similarity is insufficient to imply a direct correlation between those two diseases. Increased eosinophil count is also observed in patients with atopic conditions (33, 34)., but the prevalence of patients with atopic conditions in our cohort was small (4 in the normal IgG4 group, 0 in the high IgG4 group). This might be due to the exclusion criteria which were used in the study (we excluded patients with symptoms of infection, which overlap with those of exacerbated asthma or rhinitis, or patients during immunomodulatory treatment).

An interesting novel finding from our study is that patients in the elevated IgG4 group had lower bilirubin levels than GO patients with normal IgG4 values. Previous studies did not check for bilirubin levels. Historically, only high bilirubin serum concentrations were considered disturbing findings. However, more recently, low serum bilirubin levels have been reported as a risk factor for adverse outcomes like stroke or coronary artery disease, diabetes, cerebral deep white matter lesions, and many others (35–37). Bilirubin has antioxidative and anti-inflammatory properties. Preclinical studies on animal models showed that bilirubin could increase anti-inflammatory cytokine levels, suppress inflammatory cell recruitment and reduce the secretion of pro-inflammatory cytokines (38–40). Some studies suggest that bilirubin can be a protective factor for autoimmune diseases e.g., ulcerative colitis (41). Our results suggest that low bilirubin serum concentration might be associated with high IgG4 GO. Our study did not show that low bilirubin levels are associated with activity or severity of GO. Our results regarding bilirubin have to be interpreted with big caution as we have performed analyses of multiple parameters and thus the risk of a type I error is substantial. Applying a Bonferonni correction would render this result statistically insignificant. Further studies on this topic on larger groups with greater statistical power are warranted.

Our study has several limitations. Firstly, it was a single-center study. Secondly, most of the patients referred to our hospital had a history of the longstanding disease, and most of them had active GO, while patients with inactive GO were underrepresented. In addition, the majority of our patients were already after thyroidectomy or radioiodine treatment, and we had no histopathological data either from thyroid specimens or from orbital biopsies. We also did not assess total IgG serum concentration, however previous studies have shown that total IgG does not offer an adequate estimation of IgG4 levels.

Conclusions

This study shows that patients with active GO have higher IgG4 serum concentrations than patients with inactive GO. Moreover, patients with high IgG4 GO have more frequently active GO, higher eosinophil count in peripheral blood, and lower bilirubin levels. We demonstrate that IgG4 serum concentrations can be used as a useful diagnostic tool to detect patients with active GO. Apart from disease activity, frequent lower eyelid retraction, and a decreased prevalence of glaucoma, we did not find many differences in clinical features between high IgG4 GO, and normal IgG4 GO. Thus, the debate if patients with high IgG4 GO are GO patients with particularly active disease or actually represent a distinct clinical entity related to IgG4-RD will probably continue until more studies, especially with histopathological examinations of thyroid specimens or orbital biopsies, emerge.

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 human participants were reviewed and approved by Bioethics Committee at the Poznan University of Medical Sciences. The patients/participants provided their written informed consent to participate in this study.

Author contributions

MO, ES-P, and MR contributed to the conception and design of the study. MO, AO-K, and PA organized the database. MO performed the statistical analysis. MO wrote the first draft of the manuscript. AO-K and PA contributed to the first draft of the introduction section. All authors contributed to manuscript revision, read, and approved the submitted version.

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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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References

1. Aalberse RC, Stapel SO, Schuurman J, Rispens T. Immunoglobulin G4: An odd antibody. *Clin Exp Allergy J Br Soc Allergy Clin Immunol* (2009) 39:469–77. doi: 10.1111/j.1365-2222.2009.03207.x

2. Davies AM, Sutton BJ. Human IgG4: A structural perspective. *Immunol Rev* (2015) 268:139–59. doi: 10.1111/imr.12349

3. Trampert DC, Hubers LM, van de Graaf SFJ, Beuers U. On the role of IgG4 in inflammatory conditions: Lessons for IgG4-related disease. *Biochim Biophys Acta BBA - Mol Basis Dis* (2018) 1864:1401–9. doi: 10.1016/j.bbadis.2017.07.038

4. Hamano H, Kawa S, Horiuchi A, Unno H, Furuya N, Akamatsu T, et al. High serum IgG4 concentrations in patients with sclerosing pancreatitis. *N Engl J Med* (2001) 344:732–8. doi: 10.1056/NEJM200103083441005

5. Umehara H, Okazaki K, Masaki Y, Kawano M, Yamamoto M, Saeki T, et al. A novel clinical entity, IgG4-related disease (IgG4RD): General concept and details. *Mod Rheumatol* (2012) 22:1–14. doi: 10.1007/s10165-011-0508-6

6. Liu J, Yin W, Westerberg LS, Lee P, Gong Q, Chen Y, et al. Immune dysregulation in IgG4-related disease. *Front Immunol* (2021) 12. doi: 10.3389/fimmu.2021.738540

7. Legatowicz-Koprowska M. IgG4-related disease: Why is it so important? *Cent Eur J Immunol* (2018) 43:204–8. doi: 10.5114/ceji.2018.77391

8. Lanzillotta M, Mancuso G, Della-Torre E. Advances in the diagnosis and management of IgG4 related disease. *BMJ* (2020) m1067. doi: 10.1136/bmj.m1067

9. Lanzillotta M, Campochiaro C, Mancuso G, Ramirez GA, Capurso G, Falconi M, et al. Clinical phenotypes of IgG4-related disease reflect different prognostic outcomes. *Rheumatol Oxf Engl* (2020) 59:2435–42. doi: 10.1093/rheumatology/keaa221

10. Al-Khalili OM, Erickson AR. IgG-4 related disease: An introduction. *Mo Med* (2018) 115:253–6.

11. Dutta D, Ahuja A, Selvan C. Immunoglobulin G4 related thyroid disorders: Diagnostic challenges and clinical outcomes. *Endokrynol Pol* (2016) 67:520–4. doi: 10.5603/EP.2016.0061

12. Nowak M, Marek B, Kos-Kudła B, Siemińska L, Londzin-Olesik M, Głogowska-Szelag J, et al. Optimization of the treatment of moderate to severe and active thyroid orbitopathy considering the recommendations of the European group on graves' orbitopathy (EUGOGO) [Optymalizacja leczenia umiarkowanej do ciężkiej i aktywnej orbitopatii tarczycowej z uwzględnieniem zaleceń European group on graves' orbitopathy (EUGOGO)]. *Endokrynol Pol* (2022) 73:756–77. doi: 10.5603/EP.a2022.0040

13. Bartalena L, Kahaly GJ, Baldeschi L, Dayan CM, Eckstein A, Marcocci C, et al. The 2021 European group on graves' orbitopathy (EUGOGO) clinical practice guidelines for the medical management of graves' orbitopathy. *Eur J Endocrinol* (2021) 185:G43–67. doi: 10.1530/EJE-21-0479. EUGOGO †.

14. Olejarz M, Szczepanek-Parulska E, Dadej D, Sawicka-Gutaj N, Domin R, Ruchała M. IgG4 as a biomarker in graves' orbitopathy. *Mediators Inflammation* (2021) 2021:5590471. doi: 10.1155/2021/5590471

15. Rotondi M, Carbone A, Coperchini F, Fonte R, Chiovato L. DIAGNOSIS OF ENDOCRINE DISEASE: IgG4-related thyroid autoimmune disease. *Eur J Endocrinol* (2019) 180:R175–83. doi: 10.1530/EJE-18-1024

16. Sawicka-Gutaj N, Gruszczyński D, Guzik P, Mostowska A, Walkowiak J. Publication ethics of human studies in the light of the declaration of Helsinki – a mini-review. *J Med Sci* (2022) 91:e700–0. doi: 10.20883/medical.e700

17. Bozkirli E, Bakiner OS, Ersozlu Bozkirli ED, Eksi Haydardedeoglu F, Sizmaz S, Torun AI, et al. Serum immunoglobulin G4 levels are elevated in patients with graves' ophthalmopathy. *Clin Endocrinol (Oxf)* (2015) 83:962–7. doi: 10.1111/cen.12671

18. Yu SH, Kang JG, Kim CS, Ihm S-H, Choi MG, Yoo HJ, et al. Clinical implications of immunoglobulin G4 to graves' ophthalmopathy. *Thyroid* (2017) 27:1185–93. doi: 10.1089/thy.2017.0126

19. Li Y, Luo B, Zhang J, Zhou X, Shao S, Xu W, et al. Clinical relevance of serum immunoglobulin G4 in glucocorticoid therapy of graves' ophthalmopathy. *Clin Endocrinol (Oxf)* (2021) 95:657–67. doi: 10.1111/cen.14493

20. Takeshima K, Inaba H, Furukawa Y, Nishi M, Yamaoka H, Miyamoto W, et al. Elevated serum immunoglobulin G4 levels in patients with graves' disease and their clinical implications. *Thyroid Off J Am Thyroid Assoc* (2014) 24:736–43. doi: 10.1089/thy.2013.0448

21. Sy A, Silkiss RZ. Serum total IgG and IgG4 levels in thyroid eye disease. *Int Med Case Rep J* (2016) 9:325–8. doi: 10.2147/IMCRJ.S116331

22. Luo B, Yuan X, Wang W, Zhang J, Liu R, Hu W, et al. Ocular manifestations and clinical implications of serum immunoglobulin G4 levels in graves' ophthalmopathy patients. *Ocul Immunol Inflammation* (2020) 30(3):1–8. doi: 10.1080/09273948.2020.1826537

23. Mourits MP, Prummel MF, Wiersinga WM, Koornneef L. Clinical activity score as a guide in the management of patients with graves' ophthalmopathy. *Clin Endocrinol (Oxf)* (1997) 47:9–14. doi: 10.1046/j.1365-2265.1997.2331047.x

24. Szumowski P, Abdelrazek S, Żukowski Ł, Mojsak M, Sykała M, Siewko K, et al. Efficacy of 99mTc-DTPA SPECT/CT in diagnosing orbitopathy in graves' disease. *BMC Endocr Disord* (2019) 19:10. doi: 10.1186/s12902-019-0340-0

25. Tachibana S, Murakami T, Noguchi H, Noguchi Y, Nakashima A, Ohyabu Y, et al. Orbital magnetic resonance imaging combined with clinical activity score can improve the sensitivity of detection of disease activity and prediction of response to immunosuppressive therapy for graves' ophthalmopathy. *Endocr J* (2010) 57:853–61. doi: 10.1507/endocrj.K10E-156

26. Falkowski B, Szczepanek-Parulska E, Sawicka-Gutaj N, Krygier A, Ruchala M. Evaluation of IL-29 in euthyroid patients with graves' orbitopathy: A preliminary study. *Mediators Inflammation* (2020) 2020:4748612. doi: 10.1155/2020/4748612

27. He M, Wang Y, Wang J, Sui J, Ding X, Chen Z, et al. The potential markers involved in newly diagnosed graves' disease and the development of active graves' orbitopathy. *Cytokine* (2020) 127:154998. doi: 10.1016/j.cyto.2020.154998

28. Martin CS, Sirbu AE, Betivoiu MA, Florea S, Barbu CG, Fica SV. Serum immunoglobulin G4 levels and graves' disease phenotype. *Endocrine* (2017) 55:478–84. doi: 10.1007/s12020-016-1157-5

29. Torimoto K, Okada Y, Kurozumi A, Narisawa M, Arao T, Tanaka Y. Clinical features of patients with basedow's disease and high serum IgG4 levels. *Intern Med Tokyo Jpn* (2017) 56:1009–13. doi: 10.2169/internalmedicine.56.7824

30. Tooley AA, Salomao DR, Bradley EA, Garrity JA. Distinguishing IgG4-related ophthalmic disease from graves orbitopathy. *Ophthal Plast Reconstr Surg* (2019) 35:170–6. doi: 10.1097/IOP.0000000000001201

31. Culver EL, Sadler R, Bateman AC, Makuch M, Cargill T, Ferry B, et al. Increases in IgE, eosinophils, and mast cells can be used in diagnosis and to predict relapse of IgG4-related disease. *Clin Gastroenterol Hepatol* (2017) 15:1444–1452.e6. doi: 10.1016/j.cgh.2017.02.007

32. Della Torre E, Mattoo H, Mahajan VS, Carruthers M, Pillai S, Stone JH. Prevalence of atopy, eosinophilia, and IgE elevation in IgG4-related disease. *Allergy* (2014) 69:269–72. doi: 10.1111/all.12320

33. Braunstahl G-J, Fokkens W. Nasal involvement in allergic asthma. *Allergy* (2003) 58:1235–43. doi: 10.1046/j.0105-4538.2003.00354.x

34. Simon D, Braathen LR, Simon H-U. Eosinophils and atopic dermatitis. *Allergy* (2004) 59:561–70. doi: 10.1111/j.1398-9995.2004.00476.x

35. Higuchi S, Kabeya Y, Uchida J, Kato K, Tsukada N. Low bilirubin levels indicate a high risk of cerebral deep white matter lesions in apparently healthy subjects. *Sci Rep* (2018) 8:6473. doi: 10.1038/s41598-018-24917-8

36. Song YS, Koo BK, Cho NH, Moon MK. Effect of low serum total bilirubin levels (≤0.32 mg/dl) on risk of coronary artery disease in patients with metabolic syndrome. *Am J Cardiol* (2014) 114:1695–700. doi: 10.1016/j.amjcard.2014.08.043

37. Kimm H, Yun JE, Jo J, Jee SH. Low serum bilirubin level as an independent predictor of stroke incidence. *Stroke* (2009) 40:3422–7. doi: 10.1161/STROKEAHA.109.560649

38. Kadl A, Pontiller J, Exner M, Leitinger N. Single bolus injection of bilirubin improves the clinical outcome in a mouse model of endotoxemia. *Shock Augusta Ga* (2007) 28:582–8. doi: 10.1097/shk.0b013e31804d41dd

39. Wei J, Zhao H, Fan G, Li J. Bilirubin treatment suppresses pulmonary inflammation in a rat model of smoke-induced emphysema. *Biochem Biophys Res Commun* (2015) 465:180–7. doi: 10.1016/j.bbrc.2015.07.133

40. Creeden JF, Gordon DM, Stec DE, Hinds TD. Bilirubin as a metabolic hormone: The physiological relevance of low levels. *Am J Physiol-Endocrinol Metab* (2021) 320:E191–207. doi: 10.1152/ajpendo.00405.2020

41. Shi H, Feng Y, Jiang J, Zhao J, Li X, Liu X. Correlations between the serum bilirubin level and ulcerative colitis: A case-control study. *Eur J Gastroenterol Hepatol* (2019) 31:992–7. doi: 10.1097/MEG.0000000000001466

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Influence of biological sex, age and smoking on Graves' orbitopathy – a ten-year tertiary referral center analysis

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Purpose: Severity of Graves' orbitopathy (GO) shows wide individual differences. For optimal treatment, it is important to be able to predict the natural course of the disease as accurate as possible to counteract with anti-inflammatory and surgical treatment. Therefore, we aimed to further elucidate the impact of sex, age and smoking on GO.

Methods: We collected the clinical and demographic data of all patients of our tertiary referral center from January 2008 till December 2018 and analyzed it with descriptive statistics. Only patients with a complete data set were included in the further analysis. Odds ratio's for moderate-to-severe and sight-threatening GO in relation to age, sex and smoking were calculated by means of multivariate logistic regression models.

Results: We evaluated the data of 4260 patient with GO and complete data sets. Most of these were women (83%). There were no significant differences between male and female patients regarding smoking habits and thyroid treatment. Men were significantly older at initial manifestation of TED (51.8 vs. 49.9y, p<0.01) and showed significant more often severe stages (61% vs. 53%, p<0.0001). Therefore, they needed significantly more intense treatment with steroids, irradiation, orbital decompression and muscle surgery. In multivariate logistic regression analyses age (OR 0.97, 95% CI:0.97-0.98, p<0.0001), male sex (OR 1.64, 95% CI:1.38-1.9, p<0.0001), smoking (OR 1.19, 95% CI:1.04-1.36, p=0.01), Grave's disease (OR 1.55, 95% CI:1.26-1.90, p<0.0001) and history of radioiodine treatment (RAI) (OR 2.44, 95% CI:2.10-2.86, p<0.0001) showed an significant association with severe stages of GO.

Discussion: Our retrospective analysis showed once more that women are more often afflicted by GO. In contrast, men seem to be more severely afflicted and in need of anti-inflammatory and surgical treatments. This might be due to a different approach to the health system and resilience to GO specific symptoms, as well as previously described worse thyroid control. Estrogen

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mediated effects might also play a role as in other autoimmune diseases and should be subject of further trials. Besides the biological sex, smoking could again be confirmed as serious risk factor for severe GO. Of note, RAI was associated with more severe stages of GO, which should be subject to further investigation.

KEYWORDS

Graves' disease, Graves' orbitopathy, thyroid eye disease (TED), TED, GO, RAI (radioiodine) ablation, sex, age

1 Introduction

Graves' orbitopathy (GO) is a disorder of autoimmune origin and the most common extrathyroidal manifestation of Graves' disease (GD) (1–3). The disease is mediated by TSH receptor autoantibodies (TRAb), which stimulate receptors on orbital fibroblasts. In conjunction with the crosstalk with IGF-1 receptors and the activation of several immunomodulatory cells (e.g. T-cells, macrophages) this leads to a cascade of inflammatory conditions (4, 5). The orbital fibroblasts are then stimulated to release inflammatory cytokines, to produce hyaluronic acid and to differentiate into adipocytes and myofibroblasts (6–10). Consequently, patients suffer from signs of soft tissue inflammation (pain, swelling), diplopia (due to fibrosis of extraocular muscles) and proptosis (due to adipogenesis) to a variable extent. Thus, GO has a serious impact on the quality of life of the affected patients (11, 12). Most severe cases develop sight threatening disease mainly due to optic nerve compression (13). The severity and prognosis of GO is reported to be affected by age, biological sex, genetic factors and habitual factors, mainly smoking (14, 15). The prevalence is higher in women, although the female-to-male ratio (F/M) varies depending on the study. However, all studies show that the F/M ratio is lower compared to GD (GD: 3.4-5.6; GO: 2.1-4.2) (16–19). Furthermore, F/M ratio gets lower with higher severity of GO (mild 9.3, moderate 3.2, sight threatening 1.4) (20, 21). This is in concordance with several studies who reported over the years that male GO patients are more severely afflicted (18, 20–25). However, there are also studies showing no significant difference in severity of the disease (26, 27). More recently a GO mouse study also showed no difference in severity between female and male mice, although male mice developed symptoms earlier (28). Clinical studies did not all check for the possible confounding factor of smoking. Smoking is the strongest habitual risk factor and showed in a meta-analysis a 4-fold increased risk of GO occurrence (23, 25, 29, 30). Furthermore, the severity and response to treatment is also known to be worse in smokers (23, 31). Besides smoking and sex, age is also a risk factor: Patients above 60 years seem to be at greater risk of developing severe disease (14). Since previous studies did not have enough statistical power to check for confounding risk factors or simply did not perform such analyses, we aimed to further elucidate the importance of sex, age and smoking on severity of GO. Therefore, we performed subgroup analyses to minimize confounding factors, as well as multivariate logistic regression analyses in our retrospective study in our tertiary GO referral center.

2 Patients and methods

2.1 Study population

For this retrospective study we retrospectively analyzed data from all patients who visited our EUGOGO (European Group On Graves' Orbitopathy) tertiary referral center from January 2008 till December 2018 and were referred as GO patients. Only patients with actual diagnosis of GO and complete data sets were included in this study. Baseline characteristics and the course of the disease (treatments, surgeries) were assessed. The retrospective study was performed in accordance with the Declaration of Helsinki and approved by the Ethics Commission of the University of Essen (reference number: 22-10729-BO).

2.2 Clinical assessment

Eye examinations were performed at our center using a modified EUGOGO case record form and Color Atlas in a standardized manner (32). All patients were evaluated by a highly trained orthoptist and by one of the specialized ophthalmologists (AE,MO,YC,MS). GO was diagnosed in accordance with the published EUGOGO criteria and mainly based on typical clinical signs (e.g. lid retraction, exophthalmos, restrictive motility disorder, soft tissue involvement) on examination, which was comprised of BCVA, slit-lamp biomicroscopy, applanation tonometry, funduscopy, Hertel exophthalmometry, assessment of subjective diplopia and objective measurement of deviation using the prism-cover-test and measurement of monocular excursions (15). Thyroid disease was categorized into Graves' disease (active hyperthyroidism or already treated), primary hypothyroidism and euthyroidism (no thyroid disease in follow-up examinations). In case of such an absence of a thyroid disease the clinical signs, MRI or CT images and thyroid specific antibody levels (TRAb, Anti-TPO) were used to diagnose a euthyroid GO. GO activity was evaluated using the CAS (Clinical activity score) classification system established by Mourits et al. (33, 34). GO was classified active with CAS values of ≥3/7 points. Severity assessment was

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performed according to the EUGOGO guidelines into mild, moderate-to-severe and sight threatening (dysthyroid optic neuropathy [DON] and/or corneal breakdown) (15).

2.3 Statistical evaluation

For metric data, median values ($\tilde{x}$) and range or the mean and standard deviation (SD±) were calculated and differences between groups were evaluated with Student's t-test (two-tailed) if D'Agostino-Pearson omnibus-normality-test showed normal distribution, if not with Mann-Whitney Test. Fisher's exact test was used to evaluate group distributions of binary variables. Multivariable logistic regression analyses were carried out to evaluate the independent relationship of significant risk factors for severe stages of GO. Here, a first model analyzed the association between age, male sex, smoking, Graves' disease (vs. hypo-/eutyhroidism) and history of RAI with the occurrence of moderate-to-severe GO. A second model was employed to analyze the association of these covariates with sight-threatening GO. Level of statistical significance was defined two-tailed as $2\alpha<0.05$. All calculations were performed with SPSS (IBM SPSS Statistics, Chicago, IL, USA, Version 22.0.0), and Graph Pad Prism (Prism 9 for Windows, Software Inc., San Diego, CA, USA, Version 9.0.0). P-values are given descriptively without α-adjustment for multiple testing.

3 Results

3.1 Study population

Of all 4641 who were referred to our center as (possible) GO patients, 4381 patients were diagnosed as GO. The other 260 patients who were referred as possible GO showed either unspecific symptoms (slight lid or proptosis asymmetry) or other ocular diseases (e.g., ptosis, strabismus of other origin). After excluding patients with incomplete data sets 4260 patients were included in the analysis. Females were more frequent (n=3502) than men (n=758), resulting in F/M ratio of 4.6. Most patients showed a moderate-to-severe GO (n=2307, 55%), followed by mild cases (n=1777, 41%) and least sight threatening cases (n=176, 4%). The mean age (SD) was 50.3 ± 14 (29-80) years (an overview of baseline characteristics is provided in Table 1).

3.2 Sex specific characteristics

Our analysis showed already significant differences of the baseline characteristics between males and females: Male patients presented more often with euthyroid and hypothyroid GO, whereas females were significantly more often afflicted by Graves' disease

TABLE 1 Characteristics of study population.

	All (n=4260)	Males (n=758)	Females (n=3502)	*p*
Age at onset	50.3 ± 14	51.8 ± 14	49.9 ± 14	0.003[a]
Thyroid disease				
Graves' disease	89%	87%	89%	0.01[b]
Hypothyroidism	7%	5%	8%	0.004[b]
Eutyhroidism	4%	8%	3%	<0.001[b]
Thyroid treatment				
ATD	40%	44%	39%	0.005[b]
Thyroidectomy	34%	37%	40%	0.32[b]
Primary RAI	24%	21%	25%	0.04[b]
RAI after Tx	5%	3%	5%	0.08
GO status at baseline				
Mild	41%	33%	43%	<0.001[b]
Moderate-to-severe	55%	62%	54%	<0.001[b]
Sight threatening	4%	6%	4%	0.009[b]
Treatment period	13.3 ± 19	12 ± 18	13.5 ± 20	0.17[a]
Smoking status				
Non-smoker	63%	64%	63%	0.14[b]
Smoker	28%	27%	28%	0.53[b]
Past smoker	9%	9%	9%	0.72[b]
Cigarettes per day	13.4 ± 8	14.8 ± 10	13.1 ± 8	0.06[a]

Unless otherwise stated data are means ± SD or proportions (%) or median ($\tilde{x}$) [range]; a: t-test/Mann-Whitney-test, b: Fishers exact test.

and were more often treated with antithyroid drugs and radioiodine ablation (see Table 1). Mean age at presentation was significantly higher among the male patients, but smoking status showed no significant differences between the two groups. Men showed significantly more often moderate-to-severe and sight threatening GO (see Figure 1) and needed consequently more often steroids, orbital irradiation, orbital decompression surgery and rehabilitative muscle surgery (see Figure 2). Still, women received more lid surgery (56% vs 32%, p=0.0001).

3.3 Smoking subgroup analysis

To further elucidate the influence of smoking we performed a subgroup analysis stratified by smoking status (current smoker vs. non-smoker). Only patients with complete data on the quantity of smoking were included (n=3890). Among non-smokers (n=2696) mild cases were significantly more often, whereas moderate-to-severe cases were significantly more common among smokers (see Table 2). Most significant was the difference regarding the occurrence of sight threatening cases, which was much more often in smokers (6% vs. 3%). Furthermore, smokers (n=1194) needed significantly more often orbital decompression as well as steroid treatment, despite being significantly younger. Furthermore, the treatment duration was significantly increased compared to non-smokers. Orbital irradiation, eye muscle and lid surgery showed no significant difference between groups.

To rule out the influence of smoking on differences in GO severity between males and females we further analyzed the smoking subgroups stratified by sex. Among non-smokers male patients (n=484) showed significantly more often moderate-to-severe (59% vs 53%, p=0.01) and less of often mild GO (37% vs 44%, p=0.002 see Table 3). Sight threatening cases were more common among males without reaching statistical significance (4% vs 3%, p=0.15). Consequently, male patients needed significantly more often steroids, orbital irradiation, eye muscle and orbital decompression surgery. Furthermore, they needed a significantly higher amount of eye muscle procedures and were significantly older compared to the female patients (53 vs 50 years, p=0.0006). Still, female patients needed significantly more often lid surgery (19% vs. 13%, p=0.001).

In the smoking subgroup there was no significant age difference, but other significant differences in severity between males (n=206) and females (n=989) as displayed in Supplemental Table 1. Males suffered significantly more often by moderate-to-severe GO (65% vs 52%, p<0.001), and less often by mild GO compared to females (26% vs 42%, p<0.001). Sight threatening GO showed a markedly higher incidence among males (9% vs 5%, p=0.15), without reaching statistical significance. Males needed consequently significantly more often steroids and orbital irradiation, but surgeries were not significantly different compared to females.

3.4 Age and severity

To evaluate the influence of age on severity of GO we performed a subgroup analysis and divided into patients ≥50 and below 50 years. In the older group (n=2246), patients showed significantly more often moderate-to-severe and sight threatening GO (61% vs 47%; 6% vs 3%, p=0.0001, see Table 4) and significantly less often mild forms. Steroids, irradiation, lid and orbital surgery were significantly more often required in the older group, in contrast to strabismus surgery which showed no significant difference.

3.5 Multiple logistic regression

To further elucidate the effects of age, sex and smoking we used multivariate logistic regression analyses. Due to their known influence, we added the thyroid disease (GD vs euthyroid and hypothyroid cases) and history of Radioiodine treatment to the multivariate regression. Whereas the first model analyzed the association between these five factors and moderate-to-severe GO, the second model was focused on sight threatening cases (both models used mild cases as default). Model 1 showed that age (OR 0.97, 95% CI: 0.97 to 0.98, p<0.0001), male sex (OR 1.64, 95% CI: 1.38 to 1.97, p<0.0001), smoking (OR 1.19, 95% CI: 1.04 to 1.36, p=0.01), Grave's disease (OR 1.55, 95% CI: 1.26 to 1.90,

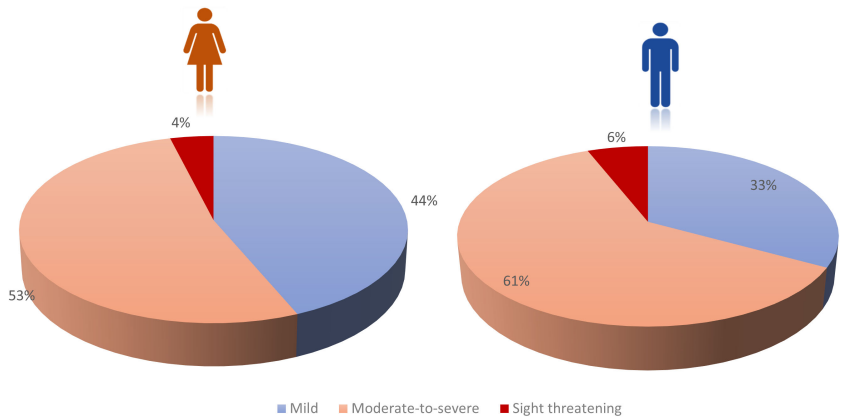

FIGURE 1
Mild, Moderate-to-severe and Sight-threatening GO in female (n=3502) and male patients (n=758) in a tertiary referral center.

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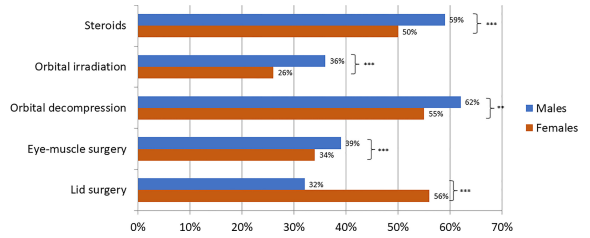

FIGURE 2
Treatments for GO patients stratified by sex as proportions. *(Fisher's exact test, **<0.01 ***< 0.001).*

p<0.0001) and history of RAI (OR 2.44, 95% CI: 2.10 to 2.86, p<0.0001) are significantly associated with moderate-to-severe GO. The second model showed that age (OR 0.96, 95% CI: 0.94 to 0.97, p<0.0001), male sex (OR 2.11, 95% CI: 1.43 to 3.07, p<0.0001), smoking (OR 2.07, 95% CI: 1.49 to 2.89, p=0.0001), Grave's disease (OR 2.18, 95% CI: 1.19 to 4.39, p=0.018) and history of RAI (OR 1.68, 95% CI: 1.16 to 2.30, p=0.005) are associated also with sight threatening GO (see Figure 3). Multicollinearity analysis was employed to ensure the independence of the three variables, which was the case in both models. Goodness-of fit analysis showed a Nagelkerke's R^2 of 0.12 for both and a Log-likelihood ratio (G squared) of 377.4 and 106.7, respectively (both p<0.0001) indicating a good prediction model. The Area under the receiver operating characteristic curve (AUC) was observed as 0.68 (95% CI: 0.66 to 0.69) for Model 1 and 0.74 (95% CI: 0.71 to 0.78, see Figure 4).

4 Discussion

The results of this retrospective study in our tertiary referral center show a higher risk of developing a more severe GO for men and smokers which is in concordance with many previous studies (18, 20–24, 29–31). These patients should be critically monitored and patients vigorously encouraged to stop smoking.

4.1 Influence of biological sex on severity of GO

In our retrospective analysis of a large single-center cohort female GO patients were much more common as in previous studies and similar to recent reports of tertial referral centers (PREGO III: 79.2% females vs. 82.2% here) (35). Our evaluation reaffirms the association of male sex with more severe stages of GO (18, 20–25). This in contrast to Kavoussi et al. (26) who reported in a chart review of 62 patients no significant difference in NOSPECS and CAS between men and women (26). Only difference they found was that men showed more often asymmetric disease and exophthalmos than females. Furthermore, an Australian case-control study by Khong et al. (27) reported no significant association of sex and development of GO in 1004 patients in simple and multiple logistic regression models (27). In contrast to our study they compared GO patients (n=604) to GD patients without GO. They did not report how many patients showed mild and moderate-to-severe stages. Assuming a typical distribution (77% mild Tanda 2013 et al.) - their lack of a significant association might be due to mostly mild cases, which seem not to be associated with the male sex (36).

Interestingly, there were in our cohort no significant differences in the needed treatments between male and female non-smokers despite the more moderate-to-severe cases among men. This might indicate that there is a different approach to the health system or even a different resilience to the same symptoms. Women might suffer more under lid related symptoms which might explain that there were even more Lid surgeries among women in this subgroup.

TABLE 2 Subgroup analysis of current smokers vs. non-smokers.

	Smoker (n=1194)	Non-smoker (n=2696)	*p*
Age at onset	49.1 ± 11	50.8 ± 15	0.0003[a]
GO status at baseline			
Mild	39%	43%	0.02[b]
Moderate-to-severe	55%	54%	0.02[b]
Sight threatening	6%	3%	0.0001[b]
Treatment period	6.2 [0-107]	4.8 [0-106]	0.04[a]
Treatments			
Steroids	54%	51%	0.04[b]
Orbital irradiation	27%	29%	0.26[b]
Lid-surgery	17%	18%	0.44[b]
Eye muscle surgery	19%	18%	0.62[b]
No. of procedures	1.65	1.64	0.45
Orbital decompression	23%	18%	0.0013[b]

Unless otherwise stated data are means ± SD or proportions (%) or median ($\tilde{x}$) [range]; a: t-test/Mann-Whitney-test, b: Fishers exact test.

TABLE 3 Subgroup analysis of non-smoking male vs. female.

	Male (n=484)	Female (n=2212)	*p*
Age at onset	53.0 ± 15	50.3 ± 15	0.0006
GO status at baseline			
Mild	37%	44%	0.002[b]
Moderate-to-severe	59%	53%	0.014[b]
Sight threatening	4%	3%	0.15[b]
Treatments			
Steroids	55%	50%	0.02[b]
Orbital irradiation	37%	27%	0.0001[b]
Lid-surgery	13%	19%	0.001[b]
Eye muscle surgery	25%	17%	0.0001[b]
No. of procedures	1.75	1.60	0.03[a]
Orbital decompression	23%	18%	0.003[b]

Unless otherwise stated data are means ± SD or proportions (%) or median ($\tilde{x}$) [range]; a: t-test/Mann-Whitney-test, b: Fishers exact test.

Indeed a study by Ponto et al. (37) reported that men were less willing to accept long distances to the center despite being more affected (37). Furthermore, they reported that significantly more women used psychosocial support, which might indicate that female patients suffer by a greater impact on quality of life. However, quality of life studies did not report QoL values divided by sex, which is why this aspect should be evaluated in future prospective studies. However, there have been reports that men demonstrate decreased cosmetic impetus for medical treatment compared to females (14). In addition to the reported reluctance to accept longer access routes, male GD patients have reportedly a worse compliance and follow-up situation, which is why their response to treatment of hyperthyroidism is reportedly worse (38). Since the effect of uncontrolled thyroid status on GO is well known, this might also explain the sex different severity of GO. Furthermore, Radioiodine treatment is significantly more often used in females and a known risk factor in case of insufficient prophylaxis for progression of GO (15, 39). Still, our multiple logistic regression revealed a significant association of sex despite including thyroid status and RAI, which independently contributed to the development of severe GO. However, our study did not included TRab and thyroid hormone levels, which is why the effect of an uncontrolled thyroid more often present in men cannot be ruled out. Another possible explanation might be the effect of estrogen on inflammatory processes as suggested (40). In other autoimmune diseases this effect has already been shown, e.g. in Systemic sclerosis a female predominant disease also showing more severe cases in men (41). However, this theory has not been tested

TABLE 4 Subgroup analysis stratified by age (≥50 vs<50 years).

	≥50 (n=2246)	<50 (n=2014)	*p*
Age at onset	60.6 ± 8	38.8 ± 9	0.0001[a]
GO status at baseline			
Mild	33%	50%	0.0001[b]
Moderate-to-severe	61%	47%	0.0001[b]
Sight threatening	6%	3%	0.0001[b]
Treatments			
Steroids	58%	45%	0.0001[b]
Orbital irradiation	36%	20%	0.0001[b]
Lid-surgery	10%	15%	0.0001[b]
Eye muscle surgery	14%	13%	0.27[b]
No. of procedures	1.65	1.66	0.72[a]
Orbital decompression	10%	19%	0.0001[b]

Unless otherwise stated data are means ± SD or proportions (%) or median ($\tilde{x}$) [range]; a: t-test/Mann-Whitney-test, b: Fishers exact test.

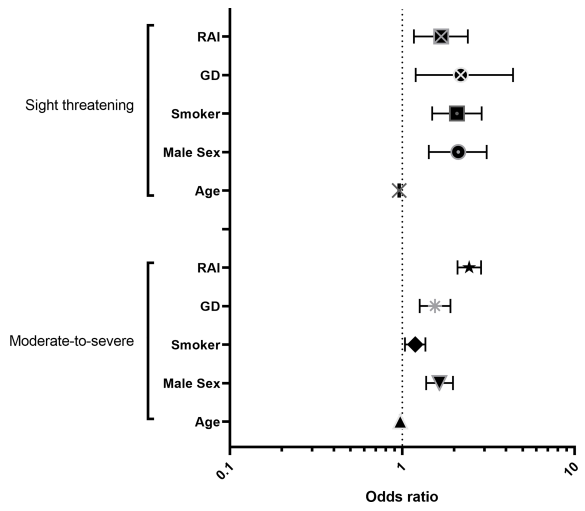

FIGURE 3
Odds ratio plot for the multiple logistic regression models depicting Odds ratios for the predicting factors and their 95% confidence interval; Model 1 is predicting occurence of moderate-to-severe GO, and Model 2 of sight-threatening GO.

in GO, yet. In conclusion, men have a greater risk of developing moderate-to-severe and sight-threatening GO and should be carefully monitored and even more encouraged to regularly follow-up and stop smoking. Further experimental and prospective studies are needed to further elucidate the reasons for this predisposition of men for more severe GO.

4.2 Influence of smoking

In our analysis we confirmed the significant association of smoking with a more severe course of GO as reported before in clinical and experimental studies (23, 29–31, 42). As in a recent EUGOGO report about a quarter of patients were current smokers (24.2% vs 28% here) (35). Our multivariate logistic regression showed a significant association but lower Odd's ratios (OR= 1.2 and 2.1, respectively) compared to Lee et al. (43), who reported smoking as a

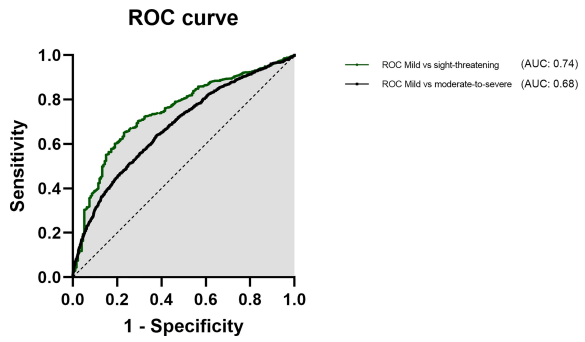

FIGURE 4
Area under the receiver operating characteristic curve for age, male sex and smoking as predictors for severe (black) and sight threatening GO (green).

predictive risk factor for a severe course of GO and the development of optic neuropathy (OR = 6.57 and 10.00, respectively) in a cohort of 99 patients (43). In contrast, other factors such as age, gender, free T4 level, thyroid binding-inhibiting immunoglobulin, and a history of diabetes were not predictive of severe GO or optic neuropathy in their study. A systematic review concluded that all evidence supports the theory of a causal link, because of the constant association of smoking with the occurrence of GO across all studies, a dose–response effect, a reduced risk of GO in ex-smokers, and the reported temporal relationship (44). Still, most studies focused on the incidence of GO reporting in comparison to GD patients OR between 1.94 and 10.1, and in comparison to control subjects without thyroid disease OR between 1.22 and 20.2. Only 2 studies investigated the association with severe GO (27, 43). In contrast to Lee et al., Khong et al. (27) reported in their Australian cohort (n=1004) a significant association of smoking with the occurrence of GO but not with development of DON. This is in contrast with our results showing smoking to be significantly associated with the occurrence of sight-threatening GO and showing higher OR in the multiple logistic regression compared to moderate-to-severe GO, indicating a larger effect on development of DON. To conclude, smoking is as demonstrated before significantly associated with the development of GO and patients should be advised to quit smoking. In addition, smoking appears to be a risk factor for sight-threatening GO.

4.3 Influence of age

In our study the mean age was comparable to other reports (50.3y vs. 50.5y in PREGOIII) (35). However, the influence of age was less pronounced compared to previous reports. Whereas, the median age of more severe stages was higher and the subgroup analysis showed more severe stages in the older group, the multiple logistic regression analyses showed surprisingly younger patients slightly more at risk. This association was smaller compared to smoking and sex. Similar results were found by Woo et al. (45) among 1,632 dysthyroid patients (45). They reported as result from multiple logistic regression analyses that young age, Graves' disease, dermopathy, anti-thyroid medication treatment, and radioiodine treatment were independent risk factors for the occurrence of thyroid eye disease. However, the study did not differ between different severity stages as in our report. This might be linked to a lower remission rate of younger patients after antithyroid medication (38). Lee et al. (43) reported similarly to our results that patients with more severe GO were older, but no significant association in multiple logistic regression. Smoking was there the only significant predictive factor (43). In conclusion, age seems to have a smaller association to severe stages of GO than sex, smoking and thyroid status.

4.4 Multiple logistic regression and further influential factors

The AUC for both models indicate unsurprisingly, that there are further influential factors. Still, the model performed pretty well (AUC 0.68 and 0.74) considering, that only basic factors were included. The

addition of TRAb and thyroid hormone levels could further improve the models. RAI had a significant association with moderate-to-severe GO and sight-threatening GO patients as described before (46). The main reason for this association is certainly the fact that patients with poorly controlled thyroid function are of course send for definitive therapy. And these are usually the patients who are at risk for a more severe course of GO (Wiersinga 2018). However Radioiodine therapy itself can be followed by a deterioration or new onset of GO (Törring 1996, Traisk 2009, Dederichs 2006, Bartalena 1997). It has been published that this can be prevented in most of the cases by steroid prophylaxis (Bartalena 1997). However GO can deteriorate in some cases especially with high TRAb and recurrence of hyperthyroidism (Vanucci 2019) and of course also with insufficient prophylaxis for progression of GO (15, 38). The increase of TRAb levels after radioiodine Therapy (Laurberg 2008) is discussed as a major factor for deterioration of GO. Previous reports showed a high association in simple logistic regression models, but no significant in multiple logistic regression when combined with age, smoking and antithyroid medication (27). This might indicate, that RAI is no in general harmful (with sufficient steroid prophylaxis) but should not be considered in patients presenting further risk factors. In our cohort most patients suffered as in previous reports of GD (89% vs 89.9 PREGO III) (35), whereas hypothyroid and euthyroid cases comprised the remaining 11%. The latter seem not be associated with more severe GO, but might be associated with a delayed diagnosis of GO.

5 Limitations

Our results could possibly be confounded by other factors such as genetic, ethnic, thyroid related and possibly further unknown associated factors. Still, genetics seem to have the lesser role and our population was mainly Caucasian (47). Furthermore, one should note that our center has an ophthalmological focus, which might be why the cohort comprised of more moderate-to-severe cases than in PREGO III report of other tertiary referral centers (55% vs 39.9%) (35). This is also why LDL cholesterol levels where no regularly assessed, though there are a known risk factor (48). In addition, GD duration was not part of the model, despite a significant role in a previous study (27).

6 Conclusion

We could show in our large cohort comprised of 4260 patients of a single tertiary referral center that there is a strong association of male sex, smoking and RAI with more severe stages of GO. Besides stable euthyroidism, cessation of smoking should be a primary goal especially for male patients to avoid severe GO and consecutive medical and surgical treatments.

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 human participants were reviewed and approved by Ethikkommission Universitätsklinikum Essen. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

Conceptualization: MO, AE, and YC. Methodology: MO, AE, YC, and MS. Software: MO. Validation: MO, AE, YC, LW, NB, AD, and KS. Formal analysis: MO, AE, and LW. Investigation: MO, KS, AD, MS, AE, and YC. Resources: NB, AE, and MO. Data curation: MO and LW. Writing-original draft preparation: MO, AE, and YC. Writing-review and editing: MO, LW, AD, MS, KS, NB, AE, YC. Visualization: MO and LW. Supervision: NB, AE, MO. Project administration: LW, MS, and MO. Funding acquisition: MO, AE, and NB. All authors have read and agreed to the published version of the manuscript.

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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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2023.1160172/full#supplementary-material

References

1. Shan SJ, Douglas RS. The pathophysiology of thyroid eye disease. *J Neuroophthalmol* (2014) 34(2):177–85. doi: 10.1097/WNO.0000000000000132

2. Bahn RS. Current insights into the pathogenesis of graves' ophthalmopathy. *Horm Metab Res* (2015) 47(10):773–8. doi: 10.1055/s-0035-1555762

3. Davies TF, Andersen S, Latif R, Nagayama Y, Barbesino G, Brito M, et al. Graves' disease. *Nat Rev Dis Primers* (2020) 6(1):52. doi: 10.1038/s41572-020-0184-y

4. Krieger CC, Place RF, Bevilacqua C, Marcus-Samuels B, Abel BS, Skarulis MC, et al. TSH/IGF-1 receptor cross talk in graves' ophthalmopathy pathogenesis. *J Clin Endocrinol Metab* (2016) 101(6):2340–7. doi: 10.1210/jc.2016-1315

5. Hai YP, Saeed MEM, Ponto KA, Elflein HM, Lee ACH, Fang S, et al. A multicenter, single-blind, case-control, immunohistochemical study of orbital tissue in thyroid eye disease. *Thyroid* (2022) 32(12):1547–58. doi: 10.1089/thy.2022.0173

6. Morshed SA, Davies TF. Graves' disease mechanisms: The role of stimulating, blocking, and cleavage region TSH receptor antibodies. *Horm Metab Res* (2015) 47 (10):727–34. doi: 10.1055/s-0035-1559633

7. Tsui S, Naik V, Hoa N, Hwang CJ, Afifiyan NF, Sinha Hikim A, et al. Evidence for an association between thyroid-stimulating hormone and insulin-like growth factor 1 receptors: a tale of two antigens implicated in graves' disease. *J Immunol* (2008) 181 (6):4397–405. doi: 10.4049/jimmunol.181.6.4397

8. Krieger CC, Neumann S, Place RF, Marcus-Samuels B, Gershengorn MC. Bidirectional TSH and IGF-1 receptor cross talk mediates stimulation of hyaluronan secretion by graves' disease immunoglobins. *J Clin Endocrinol Metab* (2015) 100 (3):1071–7. doi: 10.1210/jc.2014-3566

9. Stohr M, Oeverhaus M, Lytton SD, Horstmann M, Zwanziger D, Moller L, et al. Predicting the course of graves' orbitopathy using serially measured TSH-receptor autoantibodies by automated binding immunoassays and the functional bioassay. *Horm Metab Res* (2021) 53(7):435–43. doi: 10.1055/a-1525-2070

10. Plohn S, Edelmann B, Japtok L, He X, Hose M, Hansen W, et al. CD40 enhances sphingolipids in orbital fibroblasts: Potential role of sphingosine-1-Phosphate in inflammatory T-cell migration in graves' orbitopathy. *Invest Ophthalmol Vis Sci* (2018) 59(13):5391–7. doi: 10.1167/iovs.18-25466

11. Gerding MN, Terwee CB, Dekker FW, Koornneef L, Prummel MF, Wiersinga WM, et al. Quality of life in patients with graves' ophthalmopathy is markedly decreased: measurement by the medical outcomes study instrument. *Thyroid* (1997) 7(6):885–9. doi: 10.1089/thy.1997.7.885

12. Burch HB, Wartofsky L. Graves' ophthalmopathy: current concepts regarding pathogenesis and management. *Endocr Rev* (1993) 14(6):747–93. doi: 10.1210/edrv-14-6-747

13. Dunne JW, Edis RH. Optic nerve involvement in graves' ophthalmopathy: a case report and review. *Aust N Z J Med* (1985) 15(2):258–61. doi: 10.1111/j.1445-5994.1985.tb04021.x

14. Perros P, Crombie AL, Matthews JN, Kendall-Taylor P. Age and gender influence the severity of thyroid-associated ophthalmopathy: a study of 101 patients attending a combined thyroid-eye clinic. *Clin Endocrinol (Oxf)* (1993) 38(4):367–72. doi: 10.1111/j.1365-2265.1993.tb00516.x

15. Bartalena L, Kahaly GJ, Baldeschi L, Dayan CM, Eckstein A, Marcocci C, et al. The 2021 European group on graves' orbitopathy (EUGOGO) clinical practice guidelines for the medical management of graves' orbitopathy. *Eur J Endocrinol* (2021) 185(4):G43–67. doi: 10.1530/EJE-21-0479

16. Zaletel K, Gaberscek S, Pirnat E. Ten-year follow-up of thyroid epidemiology in Slovenia after increase in salt iodization. *Croat Med J* (2011) 52(5):615–21. doi: 10.3325/cmj.2011.52.615

17. Piantanida E, Tanda ML, Lai A, Sassi L, Bartalena L. Prevalence and natural history of graves' orbitopathy in the XXI century. *J Endocrinol Invest* (2013) 36(6):444–9. doi: 10.3275/8937

18. Abraham-Nordling M, Bystrom K, Torring O, Lantz M, Berg G, Calissendorff J, et al. Incidence of hyperthyroidism in Sweden. *Eur J Endocrinol* (2011) 165(6):899–905. doi: 10.1530/EJE-11-0548

19. Boulakh L, Nygaard B, Bek T, Faber J, Heegaard S, Toft PB, et al. Nationwide incidence of thyroid eye disease and cumulative incidence of strabismus and surgical interventions in Denmark. *JAMA Ophthalmol* (2022) 140(7):667–73. doi: 10.1001/jamaophthalmol.2022.1002

20. Laurberg P, Berman DC, Bulow Pedersen I, Andersen S, Carle A. Incidence and clinical presentation of moderate to severe graves' orbitopathy in a Danish population before and after iodine fortification of salt. *J Clin Endocrinol Metab* (2012) 97(7):2325–32. doi: 10.1210/jc.2012-1275

21. Bartley GB, Fatourechi V, Kadrmas EF, Jacobsen SJ, Ilstrup DM, Garrity JA, et al. The incidence of graves' ophthalmopathy in Olmsted county, Minnesota. *Am J Ophthalmol* (1995) 120(4):511–7. doi: 10.1016/S0002-9394(14)72666-2

22. Perros P, Hegedus L, Bartalena L, Marcocci C, Kahaly GJ, Baldeschi L, et al. Graves' orbitopathy as a rare disease in Europe: a European group on graves' orbitopathy (EUGOGO) position statement. *Orphanet J Rare Dis* (2017) 12(1):72. doi: 10.1186/s13023-017-0625-1

23. Vestergaard P. Smoking and thyroid disorders–a meta-analysis. *Eur J Endocrinol* (2002) 146(2):153–61. doi: 10.1530/eje.0.1460153

24. Manji N, Carr-Smith JD, Boelaert K, Allahabadia A, Armitage M, Chatterjee VK, et al. Influences of age, gender, smoking, and family history on autoimmune thyroid disease phenotype. *J Clin Endocrinol Metab* (2006) 91(12):4873–80. doi: 10.1210/jc.2006-1402

25. Lee MH, Chin YH, Ng CH, Nistala KRY, Ow ZGW, Sundar G, et al. Risk factors of thyroid eye disease. *Endocrine Pract* (2021) 27(Issue 3):245–53. doi: 10.1016/j.eprac.2020.11.011

26. Kavoussi SC, Giacometti JN, Servat JJ, Levin F. The relationship between sex and symmetry in thyroid eye disease. *Clin Ophthalmol* (2014) 8:1295–300. doi: 10.2147/OPTH.S61041

27. Khong JJ, Finch S, De Silva C, Rylander S, Craig JE, Selva D, et al. Risk factors for graves' orbitopathy; the Australian thyroid-associated orbitopathy research (ATOR) study. *J Clin Endocrinol Metab* (2016) 101(7):2711–20. doi: 10.1210/jc.2015-4294

28. Schluter A, Flogel U, Diaz-Cano S, Gortz GE, Stahr K, Oeverhaus M, et al. Graves' orbitopathy occurs sex-independently in an autoimmune hyperthyroid mouse model. *Sci Rep* (2018) 8(1):13096. doi: 10.1038/s41598-018-31253-4

29. Hagg E, Asplund K. Is endocrine ophthalmopathy related to smoking? *Br Med J (Clin Res Ed)* (1987) 295(6599):634–5. doi: 10.1136/bmj.295.6599.634

30. Shine B, Fells P, Edwards OM, Weetman AP. Association between graves' ophthalmopathy and smoking. *Lancet* (1990) 335(8700):1261–3. doi: 10.1016/0140-6736(90)91315-2

31. Bartalena L, Pinchera A, Marcocci C. Management of graves' ophthalmopathy: reality and perspectives. *Endocr Rev* (2000) 21(2):168–99. doi: 10.1210/edrv.21.2.0393

32. Dickinson AJ, Perros P. Controversies in the clinical evaluation of active thyroid-associated orbitopathy: use of a detailed protocol with comparative photographs for objective assessment. *Clin Endocrinol (Oxf)* (2001) 55(3):283–303. doi: 10.1046/j.1365-2265.2001.01349.x

33. Mourits MP, Koornneef L, Wiersinga WM, Prummel MF, Berghout A, van der Gaag R. Clinical criteria for the assessment of disease activity in graves' ophthalmopathy: a novel approach. *Br J Ophthalmol* (1989) 73(8):639–44. doi: 10.1136/bjo.73.8.639

34. Mourits MP, Prummel MF, Wiersinga WM, Koornneef L. Clinical activity score as a guide in the management of patients with graves' ophthalmopathy. *Clin Endocrinol (Oxf)* (1997) 47(1):9–14. doi: 10.1046/j.1365-2265.1997.2331047.x

35. Schuh A, Ayvaz G, Baldeschi L, Baretic M, Bechtold D, Boschi A, et al. Presentation of graves' orbitopathy within European group on graves' orbitopathy (EUGOGO) centres from 2012 to 2019 (PREGO III). *Br J Ophthalmol* (2023) bjo-2022-322442. doi: 10.1136/bjo-2022-322442

36. Tanda ML, Piantanida E, Liparulo L, Veronesi G, Lai A, Sassi L, et al. Prevalence and natural history of graves' orbitopathy in a large series of patients with newly diagnosed graves' hyperthyroidism seen at a single center. *J Clin Endocrinol Metab* (2013) 98(4):1443–9. doi: 10.1210/jc.2012-3873

37. Ponto KA, v. d. Osten-Sacken S, Elflein H, Koutsimpelas D, Pfeiffer N, Kahaly GJ. [Healthcare relevant data from an interdisciplinary consultation for endocrine orbitopathy]. *Ophthalmologe* (2020) 117(11):1105–11. doi: 10.1007/s00347-020-01050-4

38. Allahabadia A, Daykin J, Holder RL, Sheppard MC, Gough SC, Franklyn JA. Age and gender predict the outcome of treatment for graves' hyperthyroidism. *J Clin Endocrinol Metab* (2000) 85(3):1038–42. doi: 10.1210/jcem.85.3.6430

39. Tallstedt L, Lundell G, Torring O, Wallin G, Ljunggren JG, Blomgren H, et al. Occurrence of ophthalmopathy after treatment for graves' hyperthyroidism. the thyroid study group. *N Engl J Med* (1992) 326(26):1733–8. doi: 10.1056/NEJM199206253262603

40. FitzPatrick AM. Is estrogen a missing culprit in thyroid eye disease? sex steroid hormone homeostasis is key to other fibrogenic autoimmune diseases - why not this one? *Front Immunol* (2022) 13:898138. doi: 10.3389/fimmu.2022.898138

41. Baker Frost D, Wolf B, Peoples C, Fike J, Silver K, Laffoon M, et al. Estradiol levels are elevated in older men with diffuse cutaneous SSc and are associated with decreased survival. *Arthritis Res Ther* (2019) 21(1):85. doi: 10.1186/s13075-019-1870-6

42. Gortz GE, Philipp S, Bruderek K, Jesenek C, Horstmann M, Henning Y, et al. Macrophage-orbital fibroblast interaction and hypoxia promote inflammation and adipogenesis in graves' orbitopathy. *Endocrinology* (2022) 164(2):bqac203. doi: 10.1210/endocr/bqac203

43. Lee JH, Lee SY, Yoon JS. Risk factors associated with the severity of thyroid-associated orbitopathy in Korean patients. *Korean J Ophthalmol* (2010) 24(5):267–73. doi: 10.3341/kjo.2010.24.5.267

44. Thornton J, Kelly SP, Harrison RA, Edwards R. Cigarette smoking and thyroid eye disease: A systematic review. *Eye (Lond)* (2007) 21(9):1135–45. doi: 10.1038/sj.eye.6702603

45. Woo KI, Kim YD, Lee SY. Prevalence and risk factors for thyroid eye disease among Korean dysthyroid patients. *Korean J Ophthalmol* (2013) 27(6):397–404. doi: 10.3341/kjo.2013.27.6.397

46. Ponto KA, Zang S, Kahaly GJ. The tale of radioiodine and graves' orbitopathy. *Thyroid* (2010) 20(7):785–93. doi: 10.1089/thy.2010.1640

47. Prabhakar BS, Bahn RS, Smith TJ. Current perspective on the pathogenesis of graves' disease and ophthalmopathy. *Endocr Rev* (2003) 24(6):802–35. doi: 10.1210/er.2002-0020

48. Lanzolla G, Sabini E, Profilo MA, Mazzi B, Sframeli A, Rocchi R, et al. Relationship between serum cholesterol and graves' orbitopathy (GO): A confirmatory study. *J Endocrinol Invest* (2018) 41(12):1417–23. doi: 10.1007/s40618-018-0915-z

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Decreased macular choriocapillaris in thyroid-associated ophthalmopathy: focusing on chorioretinal folds with and without optic disc edema

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Purpose: The aim of this study was to evaluate the vessel density (VD) of the macular choriocapillaris (CC) and retina in thyroid-associated ophthalmopathy (TAO) patients with chorioretinal folds (CRFs) with and without optic disc edema (ODE) and the correlations of these characteristics with visual function.

Method: This was a cross-sectional study. Twenty TAO patients with CRFs (35 eyes) and 20 normal subjects (normal group, 40 eyes) were recruited at the Ophthalmology Department of the Sun Yat-sen Memorial Hospital from March 2018 to October 2022. Then, CRF patients were divided into two groups, the ODE and non-ODE groups (NODE), based on the presence or absence of ODE. All the patients underwent optical coherence tomography angiography (OCTA) and the VD of the macular CC and retina was computed. The correlation of VD and visual function was analyzed.

Results: Compared with the normal group, the macular whole-image VD in the retinal superficial layer (SLR-mwiVD: 49.82 ± 3.38 in the normal group, 42.44 ± 5.40 in the NODE group, and 42.51 ± 5.37 in the ODE group), deep layer (DLR-mwiVD: 51.05 ± 6.23 in the normal group, 45.71 ± 6.66 in the NODE group, and 46.31 ± 5.48 in the ODE group), and CC (CC-mwiVD: 70.23 ± 2.47 in the normal group, 68.04 ± 3.73 in the NODE group, and 63.09 ± 6.51 in the ODE group) was decreased in the NODE (all $p < 0.05$) and ODE group (all $p < 0.01$). There was no difference in these parameters except CC-mwiVD between the ODE and NODE groups. The CC-mwiVD in the ODE group (63.09 ± 6.51) was significantly reduced compared with that in the NODE group (68.04 ± 3.73, $p = 0.004$). All these VD parameters were negatively correlated with BCVA, VF-PSD, and P100 latency and positively associated with VF-MD, P100 amplitude, and HRR scores (all $p < 0.05$).

Conclusions: There was a significant decrease in the VD of the macular CC and retina of patients with CRFs with or without ODE, which was correlated with visual dysfunction. The VD of the macular CC in CRF patients with ODE was significantly reduced compared with that in the NODE group, but similar results were not observed in the retina.

KEYWORDS

thyroid-associated ophthalmopathy, chorioretinal folds, optic disc edema, choriocapillaris, vessel density

Introduction

Thyroid-associated ophthalmopathy (TAO) is an autoimmune disorder related to thyroid dysfunction that can threaten the vision in severe stages. Chorioretinal folds (CRFs), corrugations at the level of the choroid, Bruch's membrane, retinal pigment epithelium, and the overlying neurosensory retina, have been described in a wide range of ophthalmic and systemic diseases, including age-related macular degeneration (1), posterior scleritis (2), orbital tumors (3), hypotony (4), hyperopia (5), central serous chorioretinopathy (6), and TAO (7). Previous studies have demonstrated that CRFs are often an indicator of conditions that threaten vision in patients with TAO (7–11). The mechanism underlying CRF formation in TAO is not clearly understood but is hypothesized to be related to orbital hypertension, which may place compressive stress on the choroid, Bruch's membrane, and optic nerve; the latter results may be related to retinal and choroidal microvascular changes (1).

Optical coherence tomography angiography (OCTA), a noninvasive and quantitative technique, has been used to evaluate retinal and choroidal microvascular density (VD) in TAO patients (12–17) and has been used to diagnose and monitor the early stage of vision-threatening TAO (18–21). Our previous study on OCTA reported that the vessel density (VD) of the retinal macula and radial peripapillary capillaries (RPCs) was decreased in CRF patients compared with TAO patients without CRFs (11). However, these CRF patients were unselected in a previous study, including CRF patients with or without optic disc edema (ODE). As is known, ODE is a specific sign to diagnose dysthyroid optic neuropathy (DON) (22–24). A recent study has shown a reduction in VD of choroidal RPC in DON eyes, and this is correlated with visual field (VF) defects (18). Therefore, CRF patients with ODE should be diagnosed as DON and there is a logical reason to suggest that CRF patients with or without ODE may influence the retinal and choroidal VD changes in TAO patients. However, as far as we know, no report has described changes in the macular choroidal VD in TAO patients with CRFs with or without ODE. Therefore, OCTA was implemented to detect the changes in the VD of macular retina and choriocapillaris (CC) in TAO patients with CRFs with and without ODE and to analyze the relationship between these changes and visual function parameters in this study.

Patients and methods

The cross-sectional study was conducted at Sun Yat-sen Memorial Hospital, Sun Yat-sen University, from March 2018 to October 2022. This study was conducted in accordance with the tenets of the Declaration of Helsinki, and the protocol of this study was approved by the Sun Yat-sen University Sun Yat-sen Memorial Hospital Ethical Committee in the People's Republic of China.

Twenty TAO patients with CRFs were diagnosed in the Department of Endocrinology and Ophthalmology at Sun Yat-sen Memorial Hospital, Sun Yat-sen University based on the European Group on Graves' Orbitopathy (EUGOGO) criteria (22, 25). Twenty normal subjects (40 eyes) were enrolled as controls in this study. The inclusion criteria of CRF patients were as follows: (1) age >18 years; (2) refractive errors with spherical equivalent (SE) < −6 diopters; (3) clear refracting media; and (4) no history of treatment with large-dose systemic glucocorticoids, immunosuppressive agents, or ocular radiation therapy. The exclusion criteria were as follows: (1) any other systemic diseases except TAO, such as diabetes and systemic hypertension; and (2) any history of ocular diseases, prior ophthalmic surgery, or trauma.

The clinical data included age; sex; thyroid function, including free triiodothyronine (FT3), free thyroxine (FT4), thyroid-stimulating hormone (TSH), and thyrotrophin receptor antibody (TRab); signs, symptoms, and duration of TAO; history and duration of thyroid disease; and the presence of other systemic and eye diseases. Ophthalmic examinations included best-corrected visual acuity (BCVA) measured with a standardized logMAR visual acuity chart, slit lamp examination of the anterior segment, and fundus examination. Proptosis was measured with a Hertel exophthalmometer (Oculus, Germany), and intraocular pressure (IOP) measurements (Canon TX-20, YZB/JAP3501-2012, Tokyo, Japan) were obtained in the primary position. Standard automated VF and pattern visual evoked potential tests were performed using the Humphrey automated visual field analyzer (Program 30-2,

Humphrey Field Analyzer II 750; Carl Zeiss Meditec, Inc., Dublin, CA, USA) and a pattern visual evoked potential analyzer (ESPION; Diagnosys LLC, Inc., Cambridge, UK), respectively. Color vision scores were tested by the Hardy-Rand-Rittler color plates (HRR, Richmond products, Inc. Albuquerque, NM, USA). Blood pressure and heart rate were measured after participants rested for at least 5 min. Mean arterial blood pressure (MABP) was computed as diastolic blood pressure (DBP) plus one-third of the patient's pulse pressure.

OCTA images were obtained using prototype AngioVue software 2.0 of the RTVue XR Avanti spectral domain OCT device (Optovue, Inc., Fremont, CA, USA). The VD parameters of the macular retinal superficial layer (SLR), deep layer (DLR), and CC were obtained from the 6 mm × 6 mm area of scan centered on the fovea. The area of macular scanning was segmented by an annular grid into three fields: the foveal, parafoveal, and perifoveal zones. Representative partition images in the CC are shown in Figure 1. In addition, the nerve fiber thickness of the macula and optic disc were assessed using ganglion cell complex (GCC) mode and optic nerve head mode, respectively. All OCTA imaging was performed by a trained ophthalmic examiner. Low-quality OCTA images (SSI < 60 or scan quality < 6) were excluded.

Statistical analysis

Statistical analysis was performed using SPSS (Statistical Package for Social Sciences; SPSS Inc. IBM, Armonk, NY) version 26.0. The mean ± standard deviation was used for continuous variables and frequency (%) was used for classification variables. Data with a normal distribution were evaluated by independent sample *t*-tests, data with nonnormal distribution were evaluated by Mann–Whitney test, and categorical variables were evaluated by chi-square analysis. Clinical data were compared and each eye was included in the study as an independent sample. Considering the correlation between the eyes of individual patients, a generalized estimation equation (GEE) was used to increase the statistical power. Pearson correlation analysis was used to analyze the correlation between visual function and VD parameters. Differences were considered statistically significant at $p \leq 0.05$.

Results

Demographic and clinical data

A total of 20 normal subjects (normal group) and 20 CRF patients (CRF group) were enrolled in the study, and their clinical data are listed in Table 1. More than two-thirds in CRF patients were male (17 patients, 85%), smoked (14 patients, 70%), and had onset in both eyes (15 patients, 75%). The most common primary thyroid disease of CRF patients was hyperthyroidism. The durations of autoimmune thyroid diseases and TAO were 12.65 ± 7.82 and 9.40 ± 4.68 months, respectively. CRF patients had significantly higher TSH and TRab level than the normal group (all $p < 0.05$). There was no significant difference in age, sex, systolic blood pressure (SBP), DBP, MABP, heart rate, FT3, or FT4 between the two groups.

Comparisons of ophthalmic parameters

Twenty normal subjects (40 eyes) and 20 CRF patients (35 eyes) were divided into the normal group (40 eyes), CRFs with ODE group (ODE group, 18 eyes), and CRFs without ODE group (NODE group, 17 eyes), and the groups are described in Table 2. Regardless of ODE status, CRF patients had significant differences in BCVA, IOP, proptosis, VF-MD, P100 latency, P100 amplitude, and HRR scores compared with control group (all $p < 0.05$), and these parameters were not different between the ODE and NODE groups (all $p > 0.05$). The VF-PSD in the ODE group was significantly higher than that in the NODE ($p = 0.037$) and normal groups ($p < 0.001$). The thickness of the RNFL and GCCL in the ODE group was obviously thicker than that in the NODE and normal groups (all $p < 0.05$), and these parameters were not different between the ONDE and normal groups. There was no difference in CAS scores between the ODE and NODE groups.

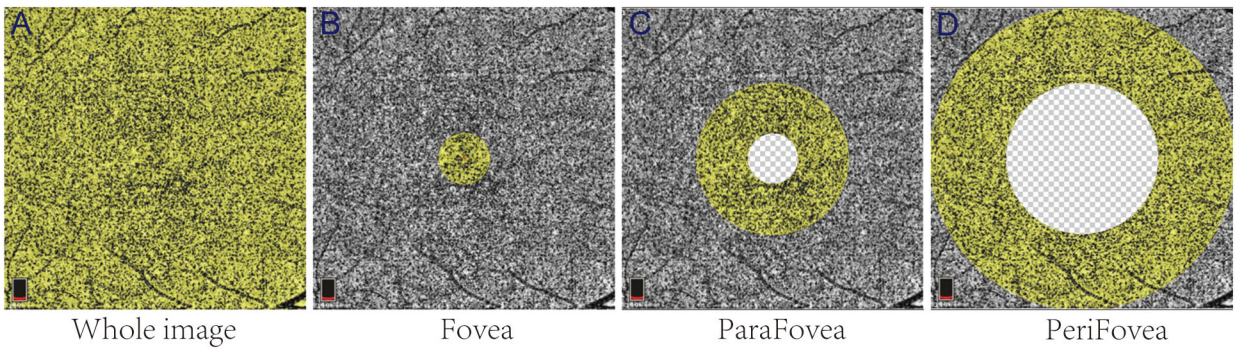

FIGURE 1
Representative partition images of the macular choriocapillaris. The yellow areas in **(A–D)** represent the whole-image, Fovea, ParaFovea, and PeriFovea regions, respectively.

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TABLE 1 Demographic and clinical data.

Variables	Normal	CRFs	*p*
N	20	20	NA
Sex, male, *n* (cases, %)	17, 85%	17, 85%	NA
Age (years, mean ± SD)	46.40 ± 10.54	47.95 ± 12.00	0.667
SBP, mmHg	124.05 ± 11.22	123.00 ± 6.10	0.715
DBP, mmHg	78.60 ± 7.54	79.10 ± 5.21	0.808
MABP, mmHg	93.75 ± 8.19	93.73 ± 4.73	0.994
Heart rate, times/min	83.20 ± 10.12	82.95 ± 9.08	0.935
Smoking status (smoker, %)	0, 0%	14, 70%	NA
Primary thyroid disease (hyperthyroidism, %)	–	20,100%	–
Duration of autoimmune thyroid disease, months	–	12.65 ± 7.82	–
TAO duration, months	–	9.40 ± 4.68	–
Thyroid function **test at presentation**			
FT3, pmol/L	5.16 ± 0.51	6.81 ± 6.20	0.243
FT4, pmol/L	15.56 ± 2.28	22.72 ± 24.43	0.200
TSH, mU/L	1.85 ± 1.17	1.33 ± 1.84	0.030
TRab, U/L	0.88 ± 0.23	14.13 ± 11.65	<0.001

Data are shown as the mean ± SD. N, number of patients; SBP, systolic blood pressure; DBP, diastolic blood pressure; MABP, mean arterial blood pressure; FT3, free triiodothyronine; FT4, free thyroxine; TSH, thyroid-stimulating hormone; TRab, thyrotrophin receptor antibody; NA, not applicable.

Comparisons of the VD in macular retina and choriocapillaris

Representative OCTA images of the three groups are shown in Figure 2. The VD parameters of the macular retina and CC in the normal, NODE, and ODE groups are shown in Table 3 and Figure 3. In the SLR, the VD of the whole image (both $p < 0.001$), ParaFovea (both $p < 0.01$), and PeriFovea (both $p < 0.001$) but not the Fovea (both $p > 0.05$) was significantly decreased in the ODE and NODE groups compared with the normal group. There was no difference in these parameters between the ODE and NODE groups (all $p > 0.05$). In the DLR, the whole image and PeriFovea VD were significantly decreased in the ODE

TABLE 2 The comparisons of ophthalmic parameters.

Variables		CRFs		Post-Hoc Analysis *p*-Values			
	Normal *n* = 40 eyes	NODE *n* = 17 eyes	ODE *n* = 18 eyes	*p*	Normal vs. NODE	Normal vs. ODE	NODE vs. ODE
BCVA, logMAR	−0.03 ± 0.06	0.20 ± 0.34	0.29 ± 0.28	<0.001	0.004	<0.001	0.384
SE, diopter	0.03 ± 0.56	0.29 ± 1.50	0.14 ± 1.48	0.729	0.458	0.742	0.745
IOP, mmHg	14.87 ± 2.21	23.35 ± 7.56	20.78 ± 7.04	<0.001	<0.001	<0.001	0.283
Proptosis, mm	15.78 ± 1.82	21.64 ± 2.26	20.78 ± 4.40	<0.001	<0.001	<0.001	0.438
VF-MD, Db	−0.16 ± 0.63	−6.20 ± 6.52	−8.65 ± 5.68	<0.001	<0.001	<0.001	0.211
VF-PSD, Db	1.53 ± 0.30	3.46 ± 2.27	5.14 ± 2.77	<0.001	<0.001	<0.001	0.037
P100 latency, ms	100.96 ± 4.27	111.24 ± 7.49	118.86 ± 9.67	<0.001	<0.001	<0.001	0.838
P100 amplitude, lV	13.62 ± 4.68	5.52 ± 2.73	5.33 ± 1.33	<0.001	<0.001	<0.001	0.799
HRR scores	19.50 ± 0.51	9.64 ± 9.12	11.47 ± 8.31	<0.001	<0.001	<0.001	0.529
RNFL, μm	113.62 ± 13.79	112.35 ± 15.86	180.94 ± 76.13	<0.001	0.791	<0.001	<0.001
GCCL, μm	95.99 ± 12.99	95.65 ± 8.63	104.67 ± 15.44	0.068	0.900	0.033	0.028
CAS	–	2.47 ± 1.77	3.11 ± 1.97	0.320	–	–	–

Data are shown as the mean ± SD.

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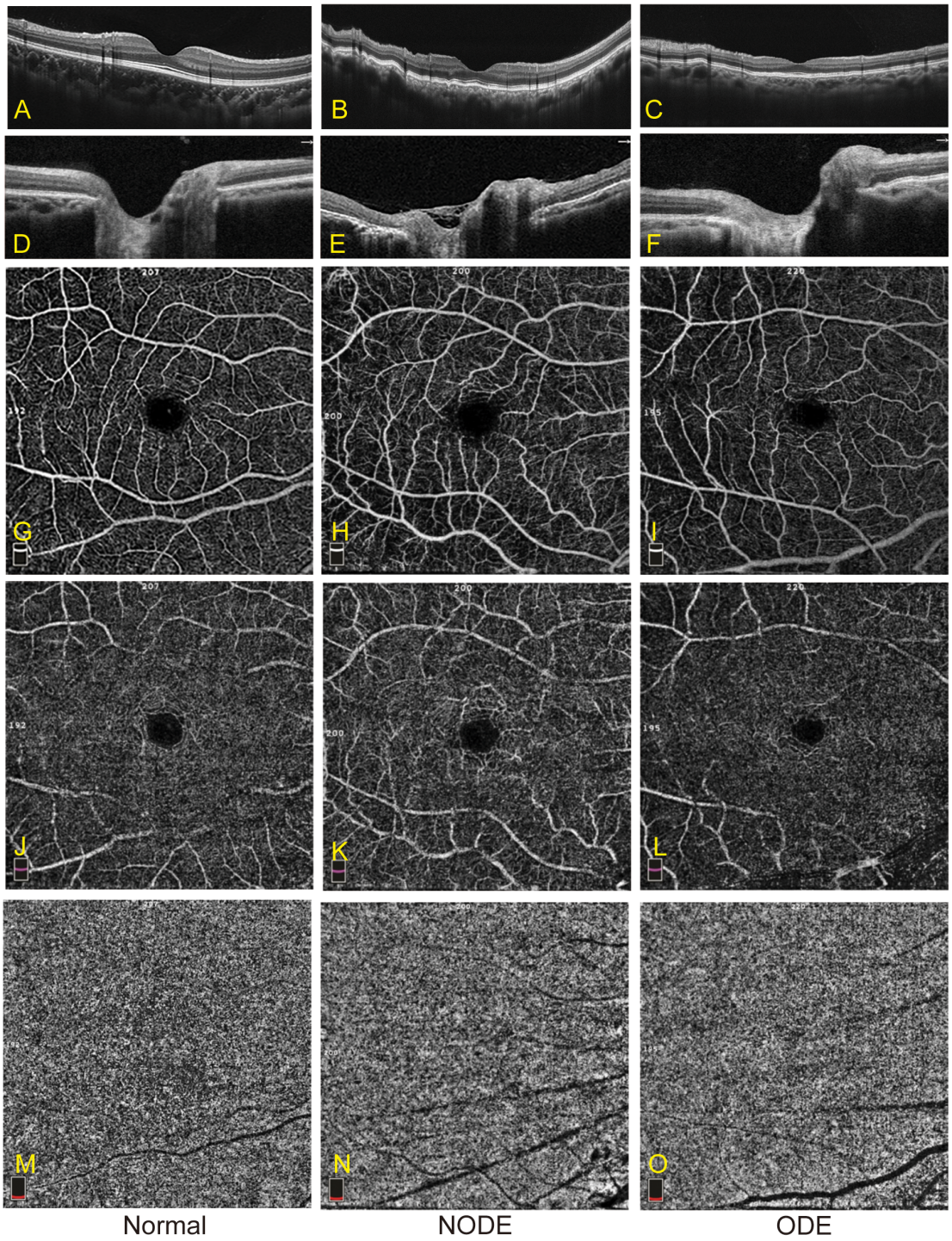

FIGURE 2
Representative images of OCTA in the normal, NODE, and ODE groups. **(A–C)** show optical coherence tomography (OCT) images of the macula in the normal, NODE, and ODE groups, respectively. The optical coherence tomography (OCT) images of the optic nerve head in the normal, NODE, and ODE groups are displayed in **(D–F)**, respectively. Macular SLR vessel density map is displayed with the normal **(G)**, NODE **(H)**, and ODE **(I)** groups. **(J–L)** exhibit macular DLR vessel density map in the normal, NODE, and ODE groups, respectively. **(M–O)** show macular CC vessel density in the normal, NODE, and ODE groups, respectively. SLR, superficial layer; DLR, deep layer; CC, choriocapillaris.

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TABLE 3 The comparisons of macular retinal and choroidal microvascular density.

Variables		CRFs		Post-Hoc Analysis *p*-Values			
	Normal	NODE	ODE	*p*	Normal vs. NODE	Normal vs. ODE	NODE vs. ODE
SLR							
Whole Image	49.82 ± 3.38	42.44 ± 5.40	42.51 ± 5.37	<0.001	<0.001	<0.001	0.979
Fovea	18.92 ± 11.12	16.05 ± 4.66	15.34 ± 5.26	0.225	0.160	0.090	0.671
ParaFovea	50.33 ± 9.43	43.14 ± 8.06	43.50 ± 6.25	0.001	0.003	0.001	0.883
PeriFovea	50.70 ± 3.57	44.21 ± 5.12	44.78 ± 4.98	<0.001	<0.001	<0.001	0.748
DLR							
Whole Image	51.05 ± 6.23	45.71 ± 6.66	46.31 ± 5.48	0.001	0.004	0.003	0.772
Fovea	34.37 ± 9.36	33.51 ± 8.77	33.48 ± 8.78	0.911	0.730	0.731	0.996
ParaFovea	54.16 ± 6.83	52.08 ± 4.10	53.09 ± 4.90	0.349	0.147	0.488	0.495
PeriFovea	51.86 ± 6.96	44.59 ± 7.00	46.46 ± 5.15	<0.001	<0.001	0.001	0.355
CC							
Whole Image	70.23 ± 2.47	68.04 ± 3.73	63.09 ± 6.51	<0.001	0.029	<0.001	**0.004**
Fovea	70.17 ± 3.29	65.64 ± 6.14	58.99 ± 9.64	<0.001	0.003	<0.001	**0.010**
ParaFovea	68.21 ± 3.63	66.15 ± 4.15	66.01 ± 5.62	0.108	0.072	0.118	0.923
PeriFovea	70.88 ± 2.52	69.04 ± 3.67	66.17 ± 3.50	<0.001	0.042	<0.001	**0.007**

Data are shown as the mean ± SD. SLR, superficial layer; DLR, deep layer; CC, choriocapillaris.

(both $p < 0.01$) and NODE groups (both $p < 0.01$), compared with the normal group. There was no difference in the VD of the Fovea and ParaFovea among three groups (all $p > 0.05$). In the CC, compared to the normal group, the VD of the whole image (both $p < 0.05$), Fovea (both $p < 0.01$), and Perifovea (both $p < 0.05$) except the ParaFovea (both $p > 0.05$) was significantly reduced in the NODE and ODE groups, and the VD of the whole image, Fovea, and Perifovea was obviously decreased in the ODE group compared with the NODE group (all $p < 0.05$).

The correlation between vessel densities and visual functional parameters

The correlation of macular whole-image VD in the SLR (SLR-mwiVD), DLR (DLR-mwiVD), and CC (CC-mwiVD) with visual functional parameters is shown in Table 4. The BCVA, VF-PSD, and P100 latency were negatively correlated with all parameters of VD (all $p < 0.01$). The VF-MD, P100 amplitude, and HRR scores were positively associated with all parameters of VD (all $p < 0.05$)

Discussion

Our study demonstrated that SLR-mwiVD, DLR-mwiVD, and CC-mwiVD were decreased in CRF patients with or without ODE compared with normal, and there was no difference in these parameters, except CC-mwiVD between the ODE and NODE groups. The CC-mwiVD in the ODE group was significantly reduced compared with that in the NODE group. All these VD parameters were negatively correlated with BCVA, VF-PSD, and

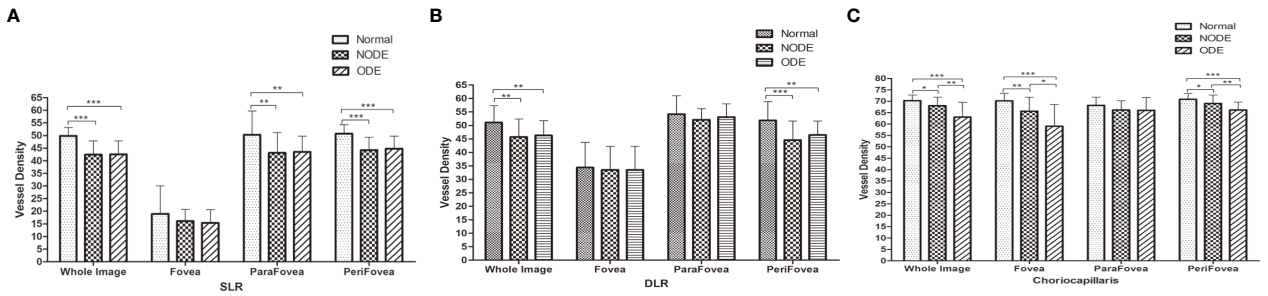

FIGURE 3
Macular VD of SLR, DLR and CC in different groups were listed in **(A)**, **(B)** and **(C)** respectively. Compared with normal group, there is a significant decreased in VD of macular CC and retina in NODE and ODE group. The VD of macular CC in ODE group was significantly reduced than that of NODE group, while not in macular retina. SLR, superficial layer; DLR, deep layer; CC, choriocapillaris. (* indicates p<0.05, ** indicates p<0.01 and ***indicates p<0.001).

TABLE 4 The correlation between microvascular density and visual function parameters.

Variables	SLR-mwiVD	DLR-mwiVD	CC-mwiVD
BCVA	**−0.536 (<0.001)**	**−0.545 (<0.001)**	**−0.398 (<0.001)**
VF-MD	**0.373 (0.001)**	**0.440 (<0.001)**	**0.378 (0.001)**
VF-PSD	**−0.425 (<0.001)**	**−0.436 (<0.001)**	**−0.534 (<0.001)**
P100 latency	**−0.441 (<0.001)**	**−0.328 (0.004)**	**−0.337 (0.003)**
P100 amplitude	**0.512 (<0.001)**	**0.268 (<0.020)**	**0.310 (<0.007)**
HRR scores	**0.571 (<0.001)**	**0.564 (<0.001)**	**0.417 (<0.001)**

Data are shown as the mean ± SD. SLR, superficial layer; DLR, deep layer; CC, choriocapillaris; mwiVD, macular whole-image vessel density.

P100 latency and positively associated with VF-MD, P100 amplitude, and HRR scores.

CRFs were first described in 1884 by Nettleship and associated with a wide variety of pathological conditions, such as tumors, central serous retinopathy, choroidal naevi, and papilloedema (26). CRFs have rarely been reported in TAO patients and are often considered as an indicator of conditions that threaten vision in TAO patients, such as DON, which is the most common vision-threatening condition of TAO (7). ODE, a specific sign of DON, was reported in 56% of eyes affected by DON, and the possible mechanism was the inflammation and edema that coexist in the orbit (23, 24). Therefore, there is a logical reason to speculate that CRFs with ODE may be more serious manifestations than CRFs alone. Although many visual functional parameters in the ODE group were indeed worse than those in the NODE group, there was no significant difference in the visual functional parameters, including BCVA, VF-MD, P100 latency, and HRR scores between two groups, with the exception of VF-PSD. Considering the effect of some systemic or ophthalmic diseases on OCTA parameters, such as hypertension and high myopia, these patients were not included in this study due to the inclusion and exclusion criteria, although these diseases may have a low impact on vision. Therefore, a possible explanation is that not all patients could be included due to the inclusion and exclusion criteria in this study.

OCTA, a novel noninvasive technique, was recently adopted to quantitatively measure retinal and choroidal microvasculature in different ocular and systemic diseases, such as glaucoma (27, 28), age-related macular degeneration (29–31), optic neuropathies (32–35), leukemia (36), diabetic retinopathy (37–40), and TAO (14, 19, 20, 41, 42), and to evaluate the severity and prognosis of these diseases. Our study showed that the macular retinal VD was significantly decreased in the ODE and NODE groups compared with the normal group. Moreover, macular retinal VD was correlated with visual dysfunction in this study. Similar results have been reported in DON patients in previous studies (18, 20, 21). Not all CRF patients have DON symptoms, which are present in 47%–50% of eyes with CRFs (7) and ODE is a specific diagnostic marker of DON and could be used to diagnose as DON in this study. Our study showed no difference in the VD of the macular retina between the ODE and NODE groups. Therefore, these studies may suggest that decreased macular retinal VD in CRF patients may be valid evidence to diagnose vision-threatening TAO.

A recent study showed that choroidal RPC was significantly reduced in DON, which is correlated with VF defects (18). However, to the best of our knowledge, no study on macular choroidal changes has been reported in TAO patients with CRFs. In this study, the VD of the macular CC was significantly reduced in CRF patients with or without ODE and correlated with visual dysfunction. Therefore, decreased choroidal VD in CRF patients may be valid evidence to diagnose vision-threatening TAO. In addition, our study showed that compared with the NODE group, the macular choroidal VD was significantly reduced in the ODE group, while the retinal VD was not different. It is powerful evidence to suggest that CRFs with ODE may be more serious than CRFs alone.

The current study has some limitations. First, this was a cross-sectional study, which makes it difficult to evaluate dynamic changes in VD over the course of the disease and understand its role in the development of disease. Second, the macular choroidal VD with OCTA is determined by projection artifacts, which may interfere with the results of the study. Third, the sample size of CRF-affected eyes was also small because CRFs were rare in TAO patients, and more samples would make the results stronger.

Conclusion

In summary, our results demonstrated a notable decrease in choroidal and retinal macular VD in patients with CRFs with or without ODE, which is correlated with visual dysfunction. The macular choroidal VD in CRF patients with ODE was significantly reduced compared with that in NODE patients and may be an alternative index to diagnose vision-threatening TAO.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding authors.

Ethics statement

The protocol of this study was approved by the Sun Yat-sen University Sun Yat-sen Memorial Hospital Ethical Committee in the People's Republic of China. The patients/participants provided their written informed consent to participate in this study.

Author contributions

PZ, J-QL and Y-YP have contributed equally to the work. All authors contributed to the article and approved the submitted version.

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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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References

1. Olsen TW, Palejwala NV, Lee LB, Bergstrom CS, Yeh S. Chorioretinal folds: associated disorders and a related maculopathy. *Am J Ophthalmol* (2014) 157(5):1038–47. doi: 10.1016/j.ajo.2014.02.021

2. Haruyama M, Yuzawa M, Kawamura A, Yamazaki C, Matsumoto Y. Indocyanine green angiographic findings of chorioretinal folds. *Japanese J Ophthalmol* (2001) 45 (3):293–300. doi: 10.1016/S0021-5155(01)00323-9

3. Khairallah M, Ladjimi A, Messaoud R, Gharsallah R, Ben Yahia S. Sectorial choroidal ischemia associated with ipsilateral lacrimal gland tumor. *Am J Ophthalmol* (1997) 124(2):263–5. doi: 10.1016/S0002-9394(14)70803-7

4. Fannin LA, Schiffman JC, Budenz DL. Risk factors for hypotony maculopathy. *Ophthalmology* (2003) 110(6):1185–91. doi: 10.1016/S0161-6420(03)00227-6

5. Leahey AB, Brucker AJ, Wyszynski RE, Shaman P. Chorioretinal folds. a comparison of unilateral and bilateral cases. *Arch Ophthalmol (Chicago Ill 1960)* (1993) 111(3):357–9. doi: 10.1001/archopht.1993.01090030075042

6. Cohen SY, Ducos de Lahitte G, Gaudric A, Mrejen S. CHORIORETINAL FOLDS IN PATIENTS WITH CENTRAL SEROUS CHORIORETINOPATHY. *Retinal cases Brief Rep* (2022) 16(2):242–5. doi: 10.1097/ICB.0000000000000944

7. Tran AQ, Zhang-Nunes SX, Cahill K, Alabiad CR, Shriver EM, Ho T, et al. Thyroid eye disease with choroidal folds. *Orbit (Amsterdam Netherlands)* (2021) 40 (3):206–14. doi: 10.1080/01676830.2020.1756347

8. DeMaria LN, Tran AQ, Tooley AA, Elmalem VI, Belinsky I. Partial vision loss after orbital decompression in a patient with thyroid eye disease, chorioretinal folds, and disc edema. *J Neuroophthalmol* (2021) 41(3):e366–8. doi: 10.1097/WNO.0000000000001174

9. Vahdani K, Rose GE. Chorioretinal folds in thyroid eye disease. *Ophthalmology* (2019) 126(8):1106. doi: 10.1016/j.ophtha.2019.04.045

10. Jorge R, Scott IU, Akaishi PM, Velasco Cruz AA, Flynn HWJr. Resolution of choroidal folds and improvement in visual acuity after orbital decompression for graves orbitopathy. *Retina (Philadelphia Pa)* (2003) 23(4):563–5. doi: 10.1097/00006982-200308000-00025

11. Zeng P, Wang J, Tian P, Peng YY, Liang JQ, Wang M, et al. Macular and peripapillary optical coherence tomography angiography metrics in thyroid-associated ophthalmopathy with chorioretinal folds. *Photodiagnosis Photodyn Ther* (2022), 42:103146. doi: 10.1016/j.pdpdt.2022.103146

12. Ye L, Zhou SS, Yang WL, Bao J, Jiang N, Min YL, et al. RETINAL MICROVASCULATURE ALTERATION IN ACTIVE THYROID-ASSOCIATED OPHTHALMOPATHY. *Endocrine Pract* (2018) 24(7):658–67. doi: 10.4158/EP-2017-0229

13. Yu L, Jiao Q, Cheng Y, Zhu Y, Lin Z, Shen X. Evaluation of retinal and choroidal variations in thyroid-associated ophthalmopathy using optical coherence tomography angiography. *BMC Ophthalmol* (2020) 20:421. doi: 10.1186/s12886-020-01692-7

14. Del Noce C, Roda M, Valsecchi N, Guandalini S, Di Geronimo N, Schiavi C, et al. Evaluation of peripapillary vascular flow in patients with thyroid-associated ophthalmopathy (TAO) by OCT angiography. *Graefe's Arch Clin Exp Ophthalmol* (2022) 260(8):2711–6. doi: 10.1007/s00417-022-05551-7

15. Jian H, Wang Y, Ou L, He W. Altered peripapillary vessel density and nerve fiber layer thickness in thyroid-associated ophthalmopathy using optical coherence tomography angiography. *Int Ophthalmol* (2022) 42(3):855–62. doi: 10.1007/s10792-021-02051-1

16. Ye J, Liu W, Hu X, Jiang H, Xu M, Jin H, et al. Elevated pulse pressure correlated with reduced retinal peripapillary capillary in thyroid-associated ophthalmology with visual field defect. *Front Endocrinol* (2022) 13:941051. doi: 10.3389/fendo.2022.941051

17. Del Noce C, Roda M, Ferro Desideri L, Traverso CE, Vagge A. Evaluation of macular blood flow after intermittent intravenous infusion of high-dose corticosteroids (pulse therapy) in patients with thyroid-associated orbitopathy (TAO) using angio-OCT. *Graefe's Arch Clin Exp Ophthalmol* (2022) 260(2):571–6. doi: 10.1007/s00417-021-05336-4

18. Wu JH, Luo LY, Zhou H, Wu Y, Zhang J, Cheng JW. Reduced choroidal peripapillary capillaries in thyroid-associated ophthalmopathy with early stage of dysthyroid optic neuropathy. *Int J Ophthalmol* (2022) 15(7):1135–41. doi: 10.18240/ijo.2022.07.14

19. Wu Y, Tu Y, Wu C, Bao L, Wang J, Lu F, et al. Reduced macular inner retinal thickness and microvascular density in the early stage of patients with dysthyroid optic neuropathy. *Eye Vision* (2020) 7:16. doi: 10.1186/s40662-020-00180-9

20. Zhang T, Xiao W, Ye H, Chen R, Mao Y, Yang H. Peripapillary and macular vessel density in dysthyroid optic neuropathy: an optical coherence tomography angiography study. *Invest Ophthalmol Visual Sci* (2019) 60(6):1863–9. doi: 10.1167/iovs.18-25941

21. Wu Y, Yang Q, Ding L, Tu Y, Deng X, Yang Y, et al. Peripapillary structural and microvascular alterations in early dysthyroid optic neuropathy. *Eye Vision* (2022) 9 (1):30. doi: 10.1186/s40662-022-00301-6

22. Bartalena L, Kahaly GJ, Baldeschi L, Dayan CM, Eckstein A, Marcocci C, et al. The 2021 European group on graves' orbitopathy (EUGOGO) clinical practice guidelines for the medical management of graves' orbitopathy. *Eur J Endocrinol* (2021) 185(4):G43–g67. doi: 10.1530/EJE-21-0479

23. Blum Meirovitch S, Leibovitch I, Kesler A, Varssano D, Rosenblatt A, Neudorfer M. Retina and nerve fiber layer thickness in eyes with thyroid-associated ophthalmopathy. *Israel Med Assoc J IMAJ* (2017) 19(5):277–81.

24. McKeag D, Lane C, Lazarus JH, Baldeschi L, Boboridis K, Dickinson AJ, et al. Clinical features of dysthyroid optic neuropathy: a European group on graves' orbitopathy (EUGOGO) survey. *Br J Ophthalmol* (2007) 91(4):455–8. doi: 10.1136/bjo.2006.094607

25. Bartalena L, Baldeschi L, Boboridis K, Eckstein A, Kahaly GJ, Marcocci C, et al. The 2016 European thyroid Association/European group on graves' orbitopathy guidelines for the management of graves' orbitopathy. *Eur Thyroid J* (2016) 5(1):9–26. doi: 10.1159/000443828

26. Jaworski A, Wolffsohn JS, Napper GA. Aetiology and management of choroidal folds. *Clin Exp optometry* (1999) 82(5):169–76. doi: 10.1111/j.1444-0938.1999.tb06638.x

27. Rao HL, Pradhan ZS, Suh MH, Moghimi S, Mansouri K, Weinreb RN. Optical coherence tomography angiography in glaucoma. *J glaucoma* (2020) 29(4):312–21. doi: 10.1097/IJG.0000000000001463

28. Takusagawa H, Liu L, Ma KN, Jia Y, Gao S, Zhang M, et al. Projection-resolved optical coherence tomography angiography of macular retinal circulation in glaucoma. *Ophthalmology* (2017) 124(11):1589–99. doi: 10.1016/j.ophtha.2017.06.002

29. Braun PX, Mehta N, Gendelman I, Alibhai AY, Baumal CR, Duker JS, et al. Using the pathophysiology of dry AMD to guide binarization of the choriocapillaris on OCTA: a model. *Trans Vision Sci Technol* (2020) 9(8):44. doi: 10.1167/tvst.9.8.44

30. Yuan MZ, Chen LL, Yang JY, Luo MY, Chen YX. Comparison of OCT and OCTA manifestations among untreated PCV, neovascular AMD, and CSC in Chinese population. *Int J Ophthalmol* (2020) 13(1):93–103. doi: 10.18240/ijo.2020.01.14

31. Levine ES, Custo Greig E, Mendonça LSM, Gulati S, Despotovic IN, Alibhai AY, et al. The long-term effects of anti-vascular endothelial growth factor therapy on the optical coherence tomography angiographic appearance of neovascularization in age-related macular degeneration. *Int J Retina Vitreous* (2020) 6:39. doi: 10.1186/s40942-020-00242-z

32. Micieli JA, Newman NJ, Biousse V. The role of optical coherence tomography in the evaluation of compressive optic neuropathies. *Curr Opin Neurol* (2019) 32(1):115–23. doi: 10.1097/WCO.0000000000000636

33. Moon Y, Song MK, Shin JW, Lim HT. Optical coherence tomography angiography characteristics and predictors of visual outcomes in patients with acute and chronic nonarteritic anterior ischemic optic neuropathy. *J Neuroophthalmol* (2021) 41(4):e440–50. doi: 10.1097/WNO.0000000000001102

34. Augstburger E, Zéboulon P, Keilani C, Baudouin C, Labbé A. Retinal and choroidal microvasculature in nonarteritic anterior ischemic optic neuropathy: an optical coherence tomography angiography study. *Invest Ophthalmol Visual Sci* (2018) 59(2):870–7. doi: 10.1167/iovs.17-22996

35. Aghsaei Fard M, Salabati M, Mahmoudzadeh R, Kafieh R, Hojati S, Safizadeh M, et al. Automated evaluation of parapapillary choroidal microvasculature in ischemic optic neuropathy and open angle glaucoma. *Invest Ophthalmol Visual Sci* (2020) 61 (3):35. doi: 10.1167/iovs.61.3.35

36. Cicinelli MV, Mastaglio S, Menean M, Marchese A, Miserocchi E, Modorati G, et al. RETINAL MICROVASCULAR CHANGES IN PATIENTS WITH ACUTE LEUKEMIA. *Retina (Philadelphia Pa)* (2022) 42(9):1762–71. doi: 10.1097/IAE.0000000000003504

37. Auvazian SL, Cano J, Leahy S, Karamian P, Kashani A, Moshfeghi A, et al. Relating retinal vascular oxygen saturation and microvasculature morphology at progressive stages of diabetic retinopathy. *Trans Vision Sci Technol* (2021) 10(6):4. doi: 10.1167/tvst.10.6.4

38. Kaoual H, Zhioua Braham I, Boukari M, Zhioua R. Evaluation of the effect of the severity of diabetic retinopathy on microvascular abnormalities and vascular density using optical coherence tomography angiography. *Acta diabetologica* (2021) 58 (12):1683–8. doi: 10.1007/s00592-021-01774-y

39. Ashraf M, Sampani K, Clermont A, Abu-Qamar O, Rhee J, Silva PS, et al. Vascular density of deep, intermediate and superficial vascular plexuses are differentially affected by diabetic retinopathy severity. *Invest Ophthalmol Visual Sci* (2020) 61(10):53. doi: 10.1167/iovs.61.10.53

40. Suciu CI, Suciu VI, Nicoara SD. Optical coherence tomography (Angiography) biomarkers in the assessment and monitoring of diabetic macular edema. *J Diabetes Res* (2020) 2020:6655021. doi: 10.1155/2020/6655021

41. Wang YH, Ma J, Li H, Xu HY, Gan LY, Zhang X, et al. [Peripapillary and macular vessel density in eyes with different phases of thyroid-associated ophthalmopathy]. *[Zhonghua yan ke za zhi] Chin J Ophthalmol* (2020) 56(11):824–31. doi: 10.3760/cma.j.cn112142-20191115-00574

42. Del Noce C, Roda M, Ferro Desideri L, Traverso CE, Vagge A. Evaluation of macular blood flow after intermittent intravenous infusion of high-dose corticosteroids (pulse therapy) in patients with thyroid-associated orbitopathy (TAO) using angio-OCT. *Graefe's Arch Clin Exp Ophthalmol* (2021) 260(2):571-576. doi: 10.1007/s00417-021-05336-4

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Efficacy and Safety of intravenous monoclonal antibodies in patients with moderate-to-severe active Graves'ophthalmopathy: a systematic review and meta-analysis

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Backgrounds: The effects of various treatments on Graves' ophthalmopathy (GO) have been studied. As monoclonal antibodies (mAbs) have been proposed for the treatment of moderate to severe GO, direct comparisons between different mAbs are lacking.We therefore conducted this meta-analysis to objectively compare the efficacy and safety of intravenous mAbs.

Methods: To identify eligible trials, references published before September 2022 were electronically searched in PubMed, Web of Science, Pubmed, Embase, Cochrane Library, CBM, CNKI,Wan-Fang and ICTRP databases.The Newcastle-Ottawa scale (NOS) and the Cochrane Risk of Bias Assessment Tool were used to assess the risk of bias of the original studies.The primary and secondary outcomes were the response and inactivation rates, with the secondary outcomes being the clinical activity score (CAS),the improvement of proptosis and diplopia improvement,and the adverse event rate. Publication bias was evaluated, along with subgroup and sensitivity analyses.

Results: A total of 12 trials with 448 patients were included. The meta-analysis showed that TCZ (tocilizumab) was most likely to be the best treatment in terms of response according to indirect contrast, followed by TMB (teprotumumab) and RTX (rituximab).TCZ, followed by TMB and RTX, was also most likely to be the best treatment in terms of reducing proptosis. In terms of improving diplopia, TMB was most likely to be the best treatment, followed by TCZ and RTX.TCZ was the highest probability of safety, followed by RTX and TMB.

Conclusions: Based on the best available evidence,TCZ should be the preferred treatment for moderate to severe GO.In the absence of head-to-head trials, indirect comparisons of treatments are routinely used to estimate the effectiveness of the treatments of interest. In addition,the optimal dose and potential mechanism of action of monoclonal antibodies remain to be

established,and it is encouraging that the treatment paradigm for GO may change in the future.This study was designed in accordance with the Preferred Reporting Items for conducting Systematic Reviews and Meta-Analyses (PRISMA) (27).

Systematic Review Registration: http://www.crd.york.ac.uk/prospero, identifier CRD42023398170.

KEYWORDS

monoclonal antibodies, tocilizumab, teprotumumab, rituximab, Graves ophthalmopathy, treatment, meta-analysis

1 Introduction

Graves' ophthalmopathy (GO) is a complex autoimmune disease of the orbit caused by progressive inflammation and damage to the orbital and ocular tissues (1, 2). It is the most important and typical extrathyroidal manifestation of Graves' disease (3) and causes enlargement of the retro-orbital fat and extraocular muscles, thought to be mediated primarily by upregulation of the insulin-like growth factor 1 receptor on orbital fibroblasts (1). The prevalence of GO ranges from 0.1% to 0.3% (4) and is sight-threatening in 3-5% of patients and clinically relevant in 25-50% of patients with Graves' disease (5). It can cause ocular symptoms such as periorbital oedema and chemosis, lid retraction, diplopia, proptosis, exposure keratopathy and dysthyroid optic neuropathy (DON). Severe proptosis can lead to disfiguring facial changes, disabling diplopia and, in severe cases, visual impairment (6–8) and may occur before, after or concurrently with Graves' disease. These symptoms have a variable impact on patients' quality of life (9–12). In fact, two main processes are involved in GO, namely cellular and humoral immunity. T lymphocytes, to which antigen-presenting cells and B lymphocytes present anti-TSH receptor antibodies, are involved in cellular immunity. Activation of B lymphocytes results in the secretion of various cytokines, including tumour necrosis factor alpha (TNF-α), interferon gamma (IFN-γ), interleukin-1 (IL-1) and interleukin-6 (IL-6), which primarily target the orbital adipocyte, inducing its differentiation into a mature adipocyte and the synthesis of glycosaminoglycans (GAGs), particularly hyaluronan (HA). This results in orbital muscle and connective tissue oedema, orbital fat hypertrophy and signs of inflammation, making it crucial to find a safe and effective treatment for GO (13–15), the pathogenesis of which remains poorly understood and the treatment of which is controversial (7).

Depending on the activity and severity of GO, medications, radiotherapy and eye surgery have been used to improve symptoms. The European Group on Graves' Orbitopathy (EUGOGO) has reached a consensus that all but the mildest patients with GO should be referred to multidisciplinary clinicians for further evaluation and management, and that intravenous glucocorticoids (GCs) are used to treat active ophthalmopathy.Surgical decompression is considered in the stable phase or in an emergency (sight-threatening or corneal collapse) (16). Thus, GCs have been the mainstay of treatment for the past six decades, with oral, intravenous or topical injections being the most common and widely used immunosuppressive agents for active and moderate to severe GO (17–19), as further recommended by EUGOGO (14). The treatment of GO remains challenging and often unsatisfactory, although several approaches have been used (20). To prevent the progression of the autoimmune disease, GCs play a beneficial role in reducing inflammation and congestion in the orbital tissues.However, high doses of GCs are usually associated with adverse events, such as glycaemia, cushingoid features,weight gain, liver damage,peptic ulcer, and cardiovascular complications (21, 22). Morbidity and mortality were reported to be 6.5% and 0.6%, respectively, in patients undergoing intravenous GC therapy for GO (23). In addition, the non-response rate was approximately 20-25% and a further 10-20% of patients experienced disease relapse after discontinuation of GCs (24, 25). In the event of a lack of response, partial response or adverse reactions to first-line treatment, there is an urgent need for a rapid switch to an effective second-line therapy. Therefore, alternative treatment modalities are urgently needed.

In recent years, with advances in the pathophysiology of GO and monoclonal antibody technology, immunotherapy targeting different molecular pathways from Thyroid Stimulating Hormone Receptor (TSHR) to insulin-like growth factor 1 receptor (IGF-1R), from cytokine mechanisms such as TNF-alpha and IL-6R to Tregs and beyond has been investigated and shown to be a promising therapeutic alternative or adjunct to treatment (26). More recently, TCZ (targeting the IL-6 receptor), RTX (targeting CD20), TMB (a human anti-IGF-1R monoclonal antibody) have been shown to be effective and safe therapeutic options in the treatment of refractory GO. Effective early treatment of these patients is predictive of a favorable outcome (8) and reduces the need for surgery for second-stage disease sequelae. Therefore, the present systematic review aimed to investigate the relative efficacy and safety of intravenous monoclonal antibodies as a therapy for GO, as to our knowledge there are currently no comparative studies on the efficacy of monoclonal antibodies.

2 Methods

2.1 Protocol and registration

This study was designed in accordance with the Preferred Reporting Items for conducting Systematic Reviews and Meta-Analyses (PRISMA) (27). Consent for this analysis was registered with PROSPERO (http://www.crd.york.ac.uk/prospero), registration number CRD42023398170.

2.2 Data sources and search strategy

A comprehensive search strategy was used to identify relevant English-language literature in the following electronic databases: Web of Science, Pubmed, Embase, Cochrane Library, Chinese Biomedical Literature Database (CBM), China National Knowledge Internet (CNKI), Wan-Fang digital database and WHO International Clinical Trial Registration Platform (ICTRP). A manual search was performed when necessary. The electronic search covered the period from April 1966 to September 2022. The following search terms were used: "monoclonal antibody" or "rituximab" or "rituxan" or "teprotumumab" or "etanercept" or "K1-70" or "adalimumab", and "endocrine ophthalmopathy" or "Graves' ophthalmopathy" or "dysthyroid ophthalmopathy" or "thyroid ophthalmopathy" or "thyroid-associated ophthalmopathy" or "Graves' orbitopathy" or "endocrine orbitopathy" or "thyroid orbitopathy" or "Graves' eye disease" or "thyroid eye disease". We also screened the reference lists of all included trials, relevant systematic reviews and previous meta-analyses to identify additional trials not included in the primary search.

2.3 Selection and eligibility criteria

Two reviewers (YH, JHC) independently screened references and abstracts retrieved from the primary search for eligible studies. Discussion and a third reviewer (XJY) were used to resolve disagreements.This meta-analysis included published studies that met the following selection criteria:(i) study design (i.e. randomised controlled trial or cohort study including intravenous monoclonal antibody therapy, excluding other combination interventions for the treatment of GO);(ii) population (iii) intervention (i.e. monoclonal antibody or placebo); (iv) outcome variables (i.e. at least one of the following outcome variables: disease response rate, disease inactivation rate, CAS, proptosis and diplopia). Exclusion criteria were the following:(i) reviews, systematic reviews or meta-analyses, commentaries, letters, case reports, conference abstracts or *in vitro* studies;(ii) failure to meet the above-mentioned GO diagnostic criteria;(iii) failure to strictly follow the advice of the physician during the procedure or loss to follow-up during the procedure or acceptance of other special treatments that affect the observation indicators of this study;(iv) studies with insufficient data to extract or calculate results; and (v) studies with duplication of data or repeated analyses.

2.4 Data extraction and results

2.4.1 Data extraction

Data from the trials were extracted using a specially adapted form and then jointly reviewed by two independent reviewers (YH, JHC). The following information was extracted and databased:title, sample size, inclusion/exclusion criteria, baseline characteristics of participants,interventions, outcome measures,adverse events and follow-up. We estimated data from graphs using Plot Digitizer (version 2.6.8) when exact data were not available in the article.

2.4.2 Quality assessment

For randomized controlled trials (RCTs), the Cochrane Collaboration Risk of Bias tool was used to independently assess the methodological quality of eligible trials by two reviewers (28). Each term had three levels of difficulty on the basis of seven aspects, one of which was the generation of random sequences, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, integrity of the outcome data, selective reporting, and other biases. Risk of bias graphs were generated using RevMan5.3 software.For non-RCTs, two reviewers rated all included studies using the NOS, which consists of study group selection, comparability and exposure (29). The total score ranged from 5 to 9, with a higher score representing a higher quality assessment, and studies with ≥7 score were considered to be of high quality. Consensus discussion with a third author resolved any discrepancies or low levels of agreement.

2.4.3 Outcome measures

The primary outcome measure was each trials defined response rate (i.e. the ratio of responders to total patients),and the secondary outcome measures were disease inactivation rate, reduction in CAS, reduction in proptosis, and improvement in diplopia from baseline to the end of follow-up. Tolerability was assessed by calculating the proportion of patients with adverse events in each regimen. Where a response rate figure was available, it was used directly. Where these were not available, we used the following criteria (in the order given): CAS reduction ≥2, ophthalmoscopic index reduction ≥2, proptosis reduction ≥2 mm and no need for additional therapy.

2.5 Statistical analysis and quality assessment

2.5.1 Statistical analysis

R (version 4.2.0) was used for statistical analysis, and the Freeman-Tukey double inverse sine transformation was used to transform data for dichotomous variables that did not follow a normal distribution, otherwise the original data were used as effect sizes. Cochran's Q statistic and I^2 values were used to assess heterogeneity between studies. I^2 describes the percentage of the total change that is caused by heterogeneity between studies and not by chance. The random effects model with 95% CI was used as the combined method when heterogeneity was high (I^2 >50%).The discussion of possible sources of heterogeneity mainly used

subgroup analysis (by study design type: RCT and non-RCT), and sensitivity analysis (one by one method) was used to screen the studies with a large effect on heterogeneity. Funnel plots were used to assess publication bias when more than 10 studies were included, and sensitivity analysis was used to assess the stability of the results. The symmetry of the funnel plot was used to assess publication bias, and the Peters test (or Egger test) was applied, including the Peters test for bicategorical variables and the Egger test for continuous variables. All tests were two-tailed and $p<0.05$ was considered statistically significant.

3 Results

3.1 Identification and selection of studies

A total of 1076 records were initially identified after electronic searches of PubMed (n=408), Web of Science (n=400), Embase (n=230), Cochrane Library (n=59), CBM (n=8), CNKI (n=6), Central Register of Clinical Trials (CENTRAL) (n=6) and Wanfang digital database (n=2). All records were downloaded and imported into EndNote X9.A total of 613 duplicates were removed using the duplicate detection function. After excluding ineligible records (n=386) based on title and abstract screening, full text articles were assessed (n=65), a total of 12 eligible studies were included in the final meta-analysis. The process of identifying and selecting eligible studies is shown in Figure 1.

3.2 Included eligible study characteristics

All eligible studies had a publication date between 2001 and 2021.Of the 12 eligible studies, the sample size of each study ranged from 33 to 90, with a median sample size of 57 and a cumulative sample size of 593.12 trials enrolled patients with moderate-to-severe active GO, of which 5 trials were RCTs and 7 trials were observational studies. The baseline characteristics details of the 12 eligible trials are shown in Table 1.

3.3 Risk of bias

In this meta-analysis, the risk of bias of 5 RCTs was assessed using the Cochrane Risk of Bias Tool.A total of 5 trials reported details of the of random sequence generation, blinding of participants and personnel, outcome assessment, and selective reporting. 2 trials clearly described the methods used to conceal allocation.The details of assessing risk of bias are summarised (Figure 2). For 7 observational trials, 4 trials with NOS scores were considered to be of high quality (Table 1). 12 studies with complete data or use of appropriate statistical methods, and all studies reported expected outcomes. Funnel plots were used to assess publication bias.

3.4 Effectiveness

3.4.1 Response rate

All 12 included trials reported the response rate.The meta-analysis concluded that all the trials of the three drugs,obtained the combined value of the response rate (OR:0.82;95%CI=0.72-0.91, random effect model,I^2 = 80%,p<0.01; Figure 3A). The results of subgroup analysis based on different drugs showed significant differences between the combined effect values (χ^2 = 19.80;random effect; p <0.01; Figure 3A) with the RTX group(OR:0.68;95%CI=0.46-0.89,random-effect model,I^2 = 89%,p<0.01),the TCZ group (OR:0.95;95%CI=0.91-0.99;fixed effect model;I^2 = 11%,p=0.34),and the TMB group(OR:0.75;95%CI=0.66-0.83;fixed effect model;I^2 = 0%; p=0.60).The source of heterogeneity was further analysed in the RTX group (Figure 3B), the combined effect value of the RCT

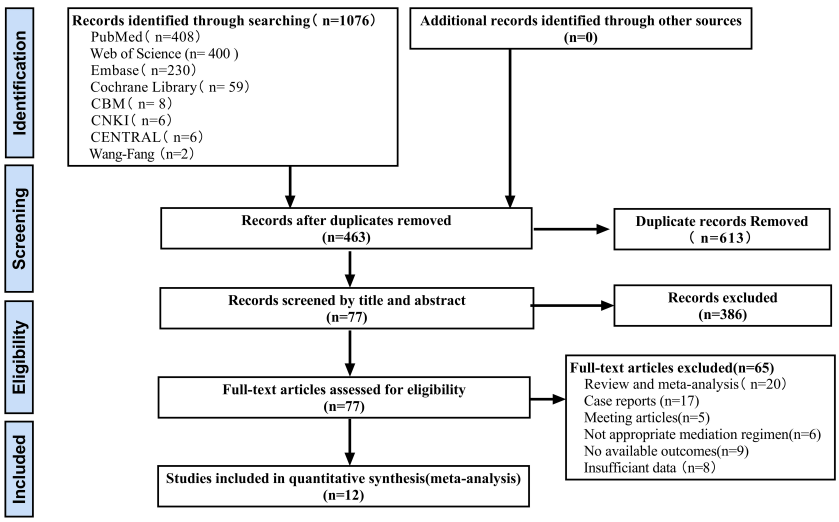

FIGURE 1
The process of identifying trials eligible for inclusion in the meta-analysis.

TABLE 1 Characteristics of included studies in the meta-analysis.

Study (author/ year)	Study Characteristics						Baseline Characteristics						
	Baseline simple size T(C)	Location	Treatments group (Control)	Study design	Single vs Multicenter	Main Out-comes	Mean Age,y	Female NO. (%)	CAS mean (SD)/ median (IQR)	Proptosis, mm mean (SD)/ median (IQR)	Diptopia NO. (%)	Follow-up	Study quality
Salvi 2015 (30)	15 (17)	Italy	RTX(IVGC)	RCT	Single	CAS	51.9	14 (93.3)	4.4 (0.7)	OS:23.5 (3.5) OD:23.2 (2.5)	9 (66.7)	52wks	–
Stan 2015 (26)	13 (12)	USA	RTX (placo)	RCT	Single	CAS	57.6	9 (69.2)	4.9 (1.0)	OS:24.2 (3.3) OD:24.6 (3.0)	NR	52wks	–
Deltour 2020 (31)	23	France	RTX(pre-post)	RC	Multicentric	CAS	51.2	15 (67)	4.09 (0.79)	21.84 (2.59)	NR	24wks	NOS: 6
Eid 2019 (32)	14	France	RTX(pre-post)	RC	Single	CAS	60	9 (60)	4.0 (3.0-4.0)	NR	NR	24wks	NOS: 5
Perez-Moreiras 2018 (33)	15 (17)	Spain	TCZ(placo)	RCT	Multicenter	CAS	45.07	11 (73.3)	5 (5.0-7.0)	21 (19.5-23)	NR	40wks	–
Pérez-Moreiras 2021 (34)	54	Spain	TCZ(pre-post)	RC	Single	CAS TRAb levels	53.8	41 (75.9)	6.7 (1.5)	21.8 (15–29)	40 (85.1)	16wks	NOS: 7
Sánchez-Bilbao 2020 (35)	45	Spain	TCZ(pre-post)	RC	Multicenter	BCVA, CAS, IOP	51	38 (79.2)	4.64 (1.5)	NR	NR	48wks	NOS: 6
Pérez-Moreiras 2014 (36)	18	Spain	TCZ(pre-post)	PC	Single	CAS	47.94	16 (88.9)	6.5 (1.29)	22.33 (3.16)	7 (38.9)	36wks	NOS: 7
Smith 2017 (37)	42 (45)	USA	TMB(placo)	RCT	Multicenter	CAS Proptosis response	51.6	28 (65)	5.1 (0.97)	23.4 (3.2)	38 (90)	24wks	–
Douglas 2020 (38)	41 (42)	USA&Europe	TMB(placo)	RCT	Multicenter	CAS Proptosis response	51.6	29 (71)	5.1 (0.9)	22.62 (3.32)	NR	24wks	–
Douglas 2021 (39)	14	USA&Europe	TMB(pre-post)	PC	Multicenter	Proptosis response	56.1	11 (78.6)	3.6 (1.7)	23.0 (3.1)	NR	28wks	NOS: 8
Bennedjaï 2020 (40)	21 (7)	France	RTX (TCZ)	RC	Multicenter	CAS	50.0	14 (66.7)	5(0.5)	NR	NR	44wks	NOS: 8

RTX, rituximab; TCZ,tocilizumab; TMB,teprotumumab; IVGC, intravenous glucocorticoids; RCT, randomized controlled trial; RC, retrospective cohort; PC, prospective cohort; CAS, clinical activity score; NR, not reported.

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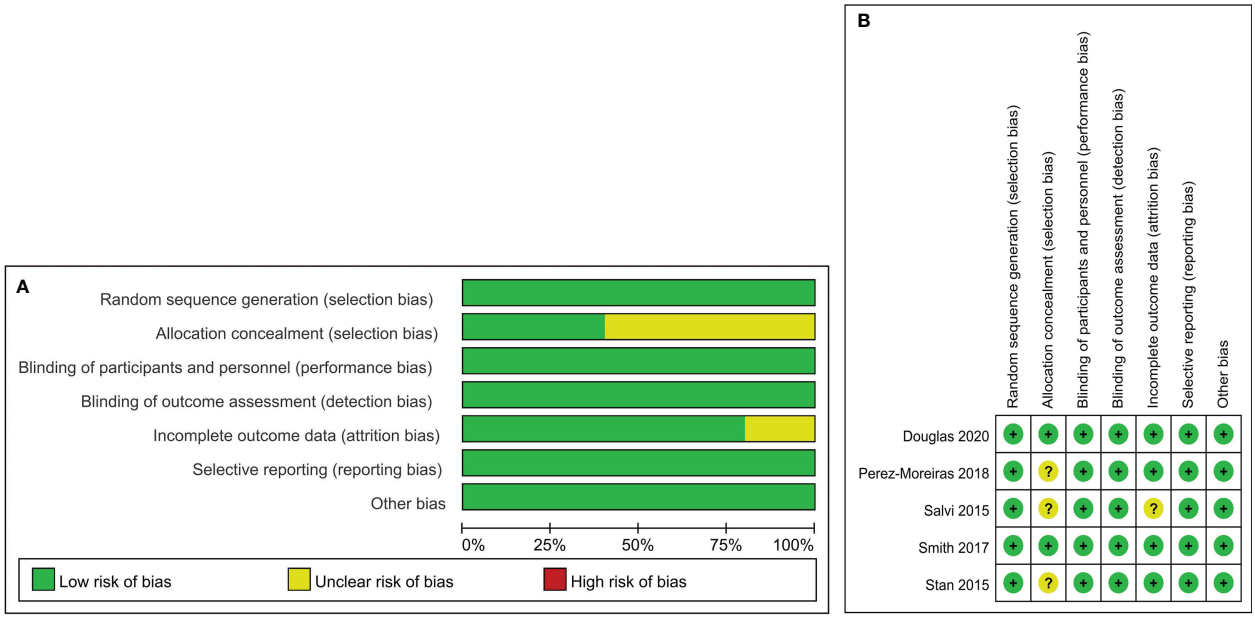

FIGURE 2
Risk of bias summary and Risk of bias graph. Risk of bias summary **(A)**: a review of authors' judgments about each risk of bias item for each included study. Risk of bias graph **(B)**: A review of authors' judgments about each risk of bias item presented as percentages across all included studies.

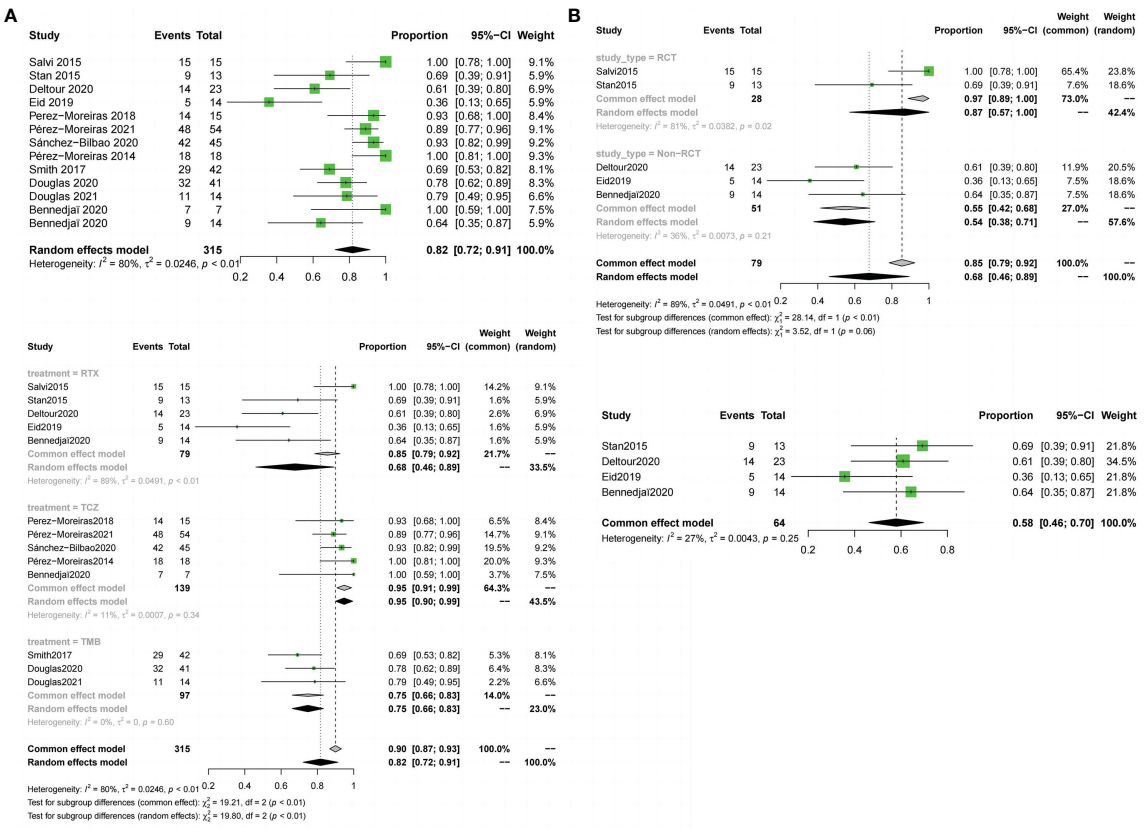

FIGURE 3
Forest plot and Funnel plots of response rate. **(A)** Forest plot of response rate (Combined analysis and Drugs subgroup). **(B)** Forest plot of response rate (RTX subgroup).

subgroup(OR:0. 87;95%CI=0.57-1.00;random effect model;I^2 = 81%; p=0.02). Non-RCT subgroup (OR:0.55;95%CI=0.42-0. 68;fixed effect model;I^2 = 36%;p=0.21).The results do not prove that different trial types (RCT and non-RCT) are the significant factors affecting heterogeneity. Furthermore, for the RTX group with one by one exclusion of literature, the results found that there is no heterogeneity excluding Salvi2015 (41) (I^2 = 27.2%;p=0.25; Figure 3B). The funnel map test of the test results (p=0.1135) could be considered as no publication bias (Figure 4A).

3.4.2 Disease inactivation rate

Meta-analysis concluded that 12 studies of the three drugs obtained the combined value of disease inactivation rate (OR:0.78;95%CI=0.68-0.88;random effect model;I^2 = 83%;p<0.01; Figure 5A).The results of subgroup analysis based on the different drugs showed, significant differences between the combined effect values(χ^2 = 14.18;p<0.01; Figure 5A), with the RTX group (OR:0.74;95%CI=0.52-0.96;random effect model;I^2 = 86%;p<0.01), the TCZ group (OR:0.89;95% CI=0.8-0.98;random effect model;I^2 = 70%;p<0.01),the TEP group (OR:0.64;95%CI=0.55-0.74;fixed effect model;I^2 = 0%;p=0.61).The source of heterogeneity was further analyzed in the RTX group and the TCZ group. For the RTX group, the subgroups by test type were unchanged after one by one (I^2 = 12%; p=0. 32; Figure 5B) that no heterogeneity was found; the TCZ group excluded one by one indicated that this document has a great impact on heterogeneity except Perez-Moreiras 2014 (I^2 = 0%, p=0.89; Figure 5B). The funnel map test of the test results (p=0.2777) could be considered as no publication bias (Figure 4B).

3.4.3 Reduction in CAS

Reduction in CAS from baseline to the end of follow-up was reported in 9 studies, including two drugs, RTX and TCZ. The literature examining the two drugs showed the CAS (SMD:-2.78; random effect model;95%CI:-3.89 to -1.66; I^2 = 91%;p<0.01; Figure 6) and high heterogeneity. The results of the subgroup analysis based on RTX and TCZ showed a significant difference between the combined effect value and SMD (χ^2 = 13.40;random effect;p<0.01; Figure 6) with the RTX group (SMD:-1.56;95%CI:-1.92 to -1.19;random effect model;I^2 = 41%; p=0.16), and the TCZ group (SMD:-4.42; 95%CI:-5.9 to -2.93;random effect model; I^2 = 92%; p <0.01). Exclusion analysis one by one indicated that this literature Sanchez-Bilbao 2020 (35) had a significant impact on heterogeneity (I^2 = 0%, p=0.94; Figure 6).

3.4.4 Reduction in proptosis

9 studies described the reduction of proptosis. The three drugs were analyzed together (OR:0.43;random effect model;95%CI:0.2 to 0.66; I^2 = 97%; p<0.01; Figure 7A) and there was high heterogeneity.

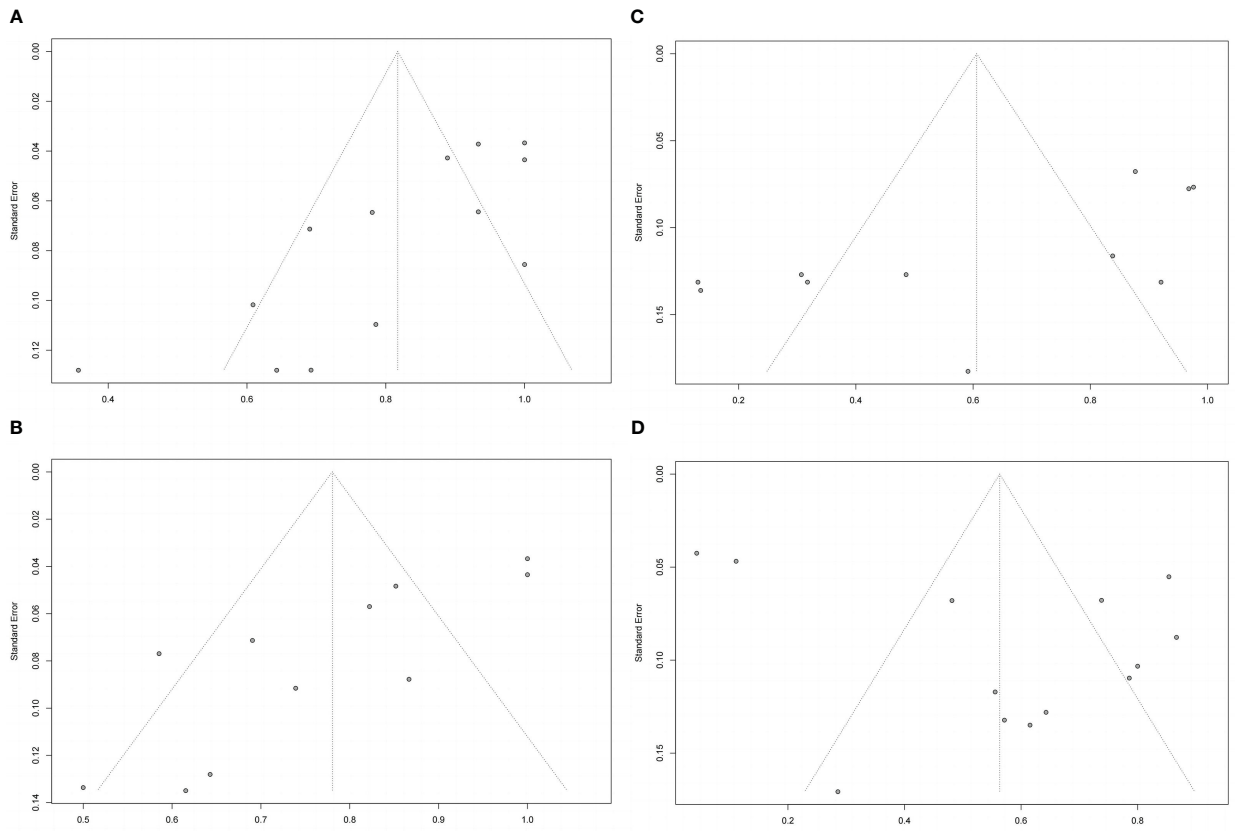

FIGURE 4
Funnel plots of response rate,disease inactivation rate, improvement in diplopia and adverse events rate. Funnel plots of response rate **(A)**, disease inactivation rate **(B)**, improvement in diplopia **(C)** and adverse events rate **(D)**.

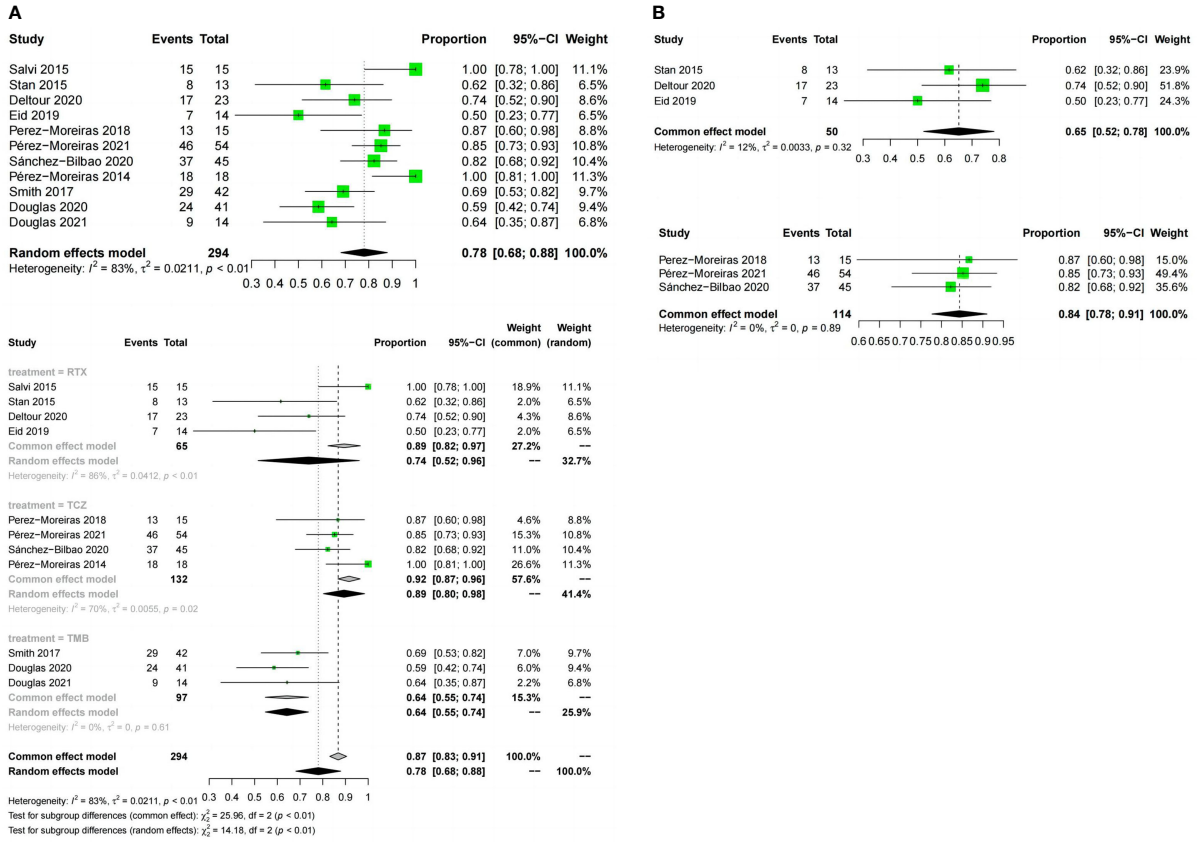

FIGURE 5
Forest plot and Funnel plots of disease inactivation rate. **(A)** Forest plot of disease inactivation rate (Combined analysis and Drugs subgroups). **(B)** Forest plot of disease inactivation rate (RTX subgroup and TCZ subgroup).

There was no significant difference between the combined effect scores of the three drugs in the subgroup analysis based on the three drugs (χ^2 = 6.29; random effect; p=0.04; Figure 7A), with the RTX group(OR:0.15;random effect model;95%CI:0 to 0.35; I^2 = 76%; p<0.01), the TCZ group (OR:0.61;random effect model;95%CI:0.3 to 0.91;I^2 = 93%;p<0.01), the TEP group (OR:0.47; random effect model;95% CI:0 to 1.00;I^2 = 98%, p<0.01). Sources of heterogeneity in the different drug groups were discussed. The RTX group, divided according to different types of trials, showed significant differences between the RCT and non-RCT combinations (χ^2 = 6.18;fixed effect;p=0.01; Figure 7B), the RCT group (OR:0.02;fixed effect model;95% CI:0 to 0.1;I^2 = 48%;p=0.17), and the overall heterogeneity (I^2 = 76%, p=0.01).The TCZ group (χ^2 = 44.03, stochastic effect, p<0.01; Figure 7B), the RCT group (OR:0.13;95% CI:0.02 to 0.4), the non-RCT group (OR:0. 77; random effect model;95%CI:0.69 to 0.85; I^2 = 0%; p=0.89), and the overall heterogeneity (I^2 = 93%, p<0.01). Grouping factors could be considered as significant factors leading to heterogeneity.

3.4.5 Improvement in diplopia

11 studies described the improvement of diplopia.The three drugs (OR:0.31;random effect model;95%CI=0.14 to 0.52;I^2 = 89%; p<0.01; Figure 8). The results of the subgroup analysis showed a significant difference between the combined effect values (χ^2 = 49.16;random effect; p<0.01; Figure 8),and the RTX group (OR:0.05;fixed effect model;95%CI:0 to 0.13;I^2 = 41%; p=0.16), the TCZ group (OR:0.38; random effect model;95%CI=0.13 to 0.66;I^2 = 82%;p<0.01), the TMB group (OR:0.68;fixed effect model;95%CI=0.58 to 0.77;I^2 = 0%; p=0.93).Sources of heterogeneity in the TCZ group were discussed.The results showed that the RCT group and non-RCT combinations (χ^2 = 31.53;stochastic effect;p<0.01; Figure 8), with the RCT group (OR:0.07;95%CI:0 to 0.32), the non-RCT group (OR:0.55; random effect model;95%CI:0.44 to 0.66;I^2 = 29%;p=0.25), the overall heterogeneity (I^2 = 92%, p<0.01). Therefore, the grouping factor could be considered as a significant factor leading to the heterogeneity.The result of the funnel plot asymmetry test could be considered without publication bias(t =-2.09;df =7;p=0.0754; Figure 4C).

3.5 Tolerability

Adverse events were evaluated in all studies. The three drugs of adverse event incidence (OR:0.56;random effect model;95%CI:0.41 to 0.72;I^2 = 95%;p <0.01; Figure 9A), and with high heterogeneity. Subgroup analysis showed a significant difference between the combined effect values of the three drugs (χ^2 = 9.71;random effect; p<0.01; Figure 9A), with the RTX group(OR:0.54;random effect model;95%CI:0.25 to 0.83;I^2 = 96%;p<0.01),the TCZ group (OR:0.44;

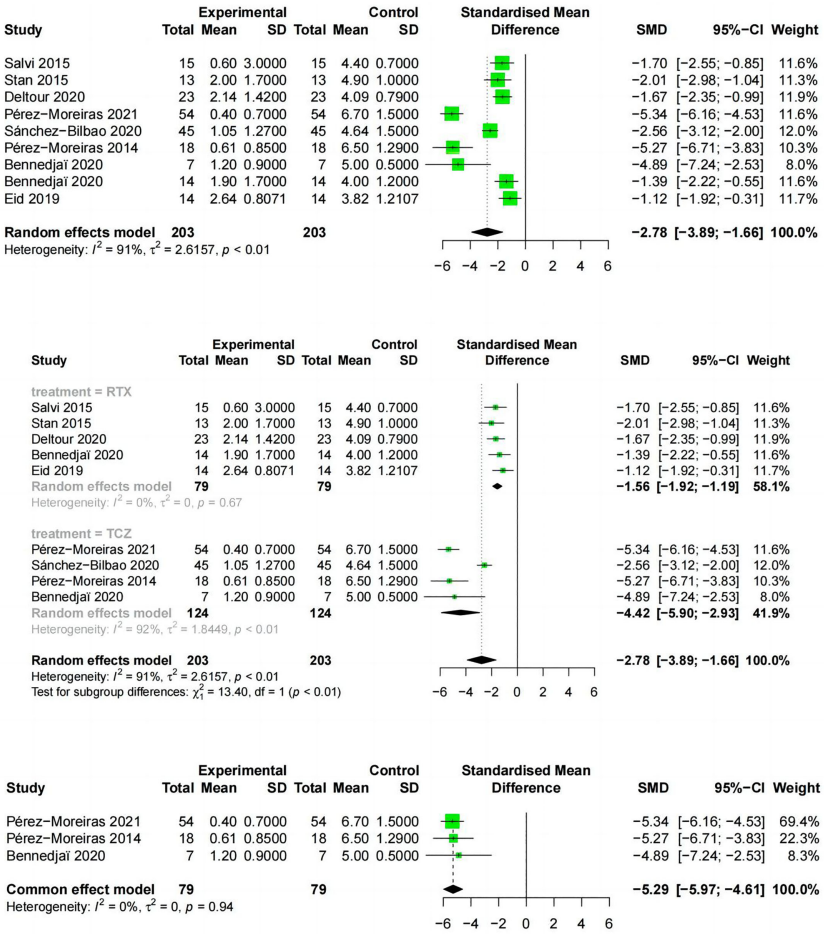

FIGURE 6
Forest plot of reduction in CAS. (Combined analysis, Drugs subgroups and TCZ subgroup).

random effect model;95%CI:0.2 to 0.68;I^2 = 92%;p<0.01), the TMB group (OR:0.8;fixed effect model;95%CI:0.723 to 0.88;I^2 = 0%; p=0.41).Sources of heterogeneity of the RTX and TCZ groups were further discussed as follows: the RTX group, CT and non-RCT groups were not significantly different (χ^2 = 2.39, random effect, p <0.12; Figure 9B). No heterogeneity was found after excluding the Deltour 2020 study (31). (I^2 = 17%, p=0.3; Figure 9B). The assessment of heterogeneity in the TCZ group needs further discussion from the perspective of clinical inclusion criteria. The result of the funnel plot asymmetry test could be considered without publication bias (t =0.29;df =11;p=0.7786; Figure 4D).

4 Discussion

Intravenous GCs treatment is still the preferred method for active moderate to severe GO, and published studies have extensively reported the effects on improving clinical activity and markers of graphene oxide severity (42, 43). Recent EUGOGO recommendations include a cumulative dose of 4.5-5 g for most patients with moderate to severe active GO and a recommended dose of 7.5 g for patients with more severe or persistent/unstable diplopia (19). However, recurrence after treatment was been reported in about 20% and compressive optic neuropathy in 7.5%.This suggests that the primary role of GCs is anti-inflammatory rather than pathogenic (44). Furthermorehe efficacy of GCs treatment is restricted to moderate-to-severe GO because higher doses are associated with a higher incidence of adverse effects,and there have been reports of acute, fatal hepatotoxicity in patients treated with high doses of Intravenous GCs (45). Therefore, novel pharmacotherapy is of vital importance to improve the physical health and quality of life of patients with GO.After the initial attempt at biological therapies for GO (46), one of the most prominent types of new drug treatment for GO more recently has been monoclonal antibodies, mainly including RTX (which acts against CD20), TCZ (which acts against the IL-6 receptor) and TMB (a human monoclonal anti-IGF-1R blocking antibody), which have shown promising results in reducing symptoms and signs in moderate to severe patients. Our review also found that these three monoclonal antibodies had reliable clinical trial data from literature searches. Comparison of new therapeutic approaches is essential and requires a better understanding of each drug's place in the treatment armamentarium for TED. To our knowledge, this is the first analysis of the efficacy of monoclonal antibodies.

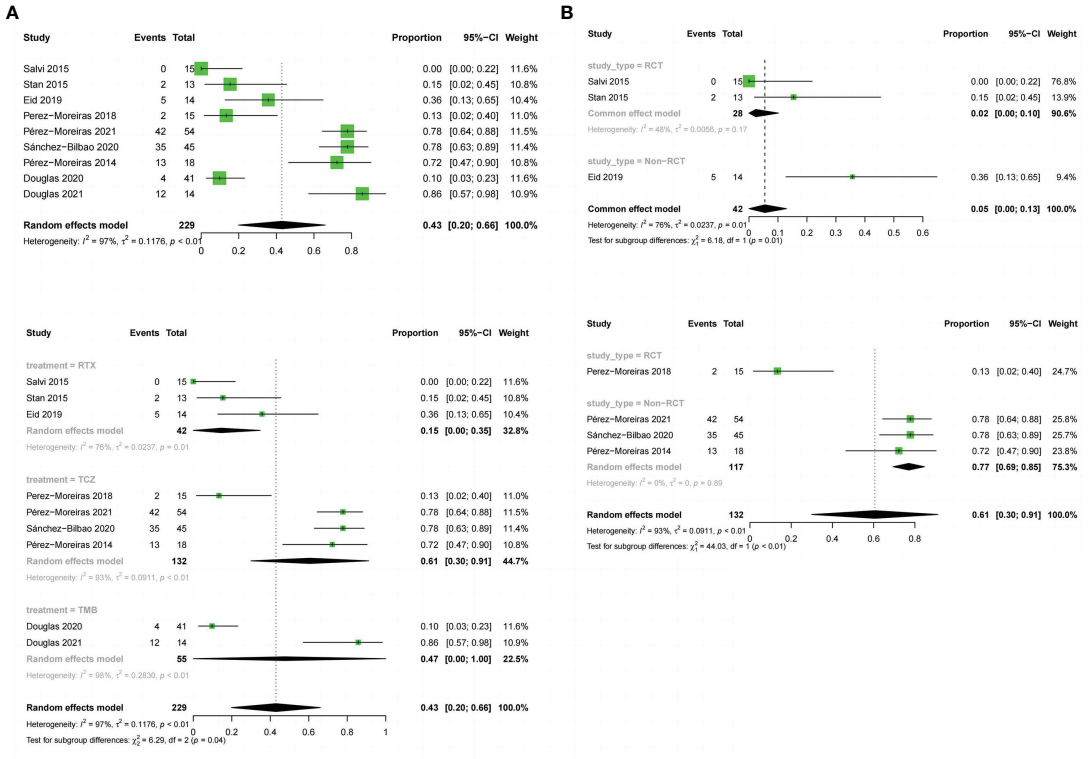

FIGURE 7
Forest plot and Funnel plots of reduction in proptosis. **(A)** Forest plot of reduction in proptosis (Combined analysis and Drugs subgroups). **(B)** Forest plot of reduction in proptosis (RTX subgroup and TCZ subgroup).

This review compared different monoclonal antibodies for the treatment of GO, including the most recent trials. In this meta-analysis, we reviewed five RCTs and seven observational studies comparing RTX, TCZ and TMB as monotherapies for patients with active and moderate-to-severe GO, and provided a hierarchy of both efficacy and tolerability for GO interventions. Although the precise pathogenesis of GO continues to be investigated, the current evidence clearly indicates that autoimmune mechanisms clearly play an important role (Figure 10). Activation of B lymphocytes induces the secretion of numerous cytokines, including IFN-γ, TNF-α,IL-1 and IL-6,etc.The release of cytokines induces the synthesis and release of large amounts of glycosaminoglycans such as hyaluronan by orbital fibroblasts, causing swelling of the orbital tissues and extraocular muscles. Humoral immunity brings anti-TSH receptor antibodies into play. TSH receptor expression on orbital fibroblast membranes is increased, and binding to IGF-1 also stimulates hyaluronic acid and lipogenesis during the active phase of the disease (47).

RTX is a monoclonal antibody that targets the CD20 protein present on pre-B cells through to mature and memory B cells (48). and depletes the B cell population, leading to a reduction in the ability of B cells to present antigens, thereby reducing T cell activation and halting ongoing inflammation (49, 50). The US Food and Drug Administration (FDA) has approved RTX for the treatment of RA, Wegener's granulomatosis, non-Hodgkin's lymphoma and chronic lymphocytic leukaemia,as well as off-label use in other autoimmune diseases (51), and has been suggested for the treatment of GO (52). TCZ is a humanised monoclonal antibody directed against IL-6 soluble and membrane receptors, and is approved for rheumatoid arthritis (53), Castleman's disease and systemic juvenile idiopathic arthritis (54). IL-6 is a pro-inflammatory cytokine secreted by T cells and macrophages to stimulate the immune response. It has been reported that IL-6 and its soluble receptor are activated, and high serum IL-6 receptor levels have been found in patients with active GO (55). IL-6 is also involved in the synthesis of GAGs in orbital fibroblasts and is also involved in the increase in surface TSH of these cells, and orbital volume has also been shown to be proportional to IL-6 mRNA expression levels (56–58). TMB is a recombinant, fully human, anti-IGF-1R monoclonal antibody, the first immunomodulatory agent approved by the FDA for the treatment of GO.The IGF-1R was found to be over-expressed in orbital connective tissue, T and B cells in GO patients, which produce autoantibodies capable of binding to the IGF-1R and initiating signalling from the TSHR/IGF-1R physical and functional protein complex.Autoimmune activation of orbital fibroblasts by autoantibodies with receptor agonist properties triggers and drives active (inflammatory) GO, which stimulates the release of chemoattractant cytokines, leading to fibroblast proliferation and differentiation, extracellular matrix increase, tissue expansion, oedema and extensive orbital tissue remodelling (41, 59–63). Therefore, using mAbs against IGF-1R can attenuate signaling from either TSHR or IGF-1R (64). TMB binds with high affinity to IGF1R as a pharmacological, functional inhibitor *via* its endogenous ligands (IGF1 and IGF2), blocking

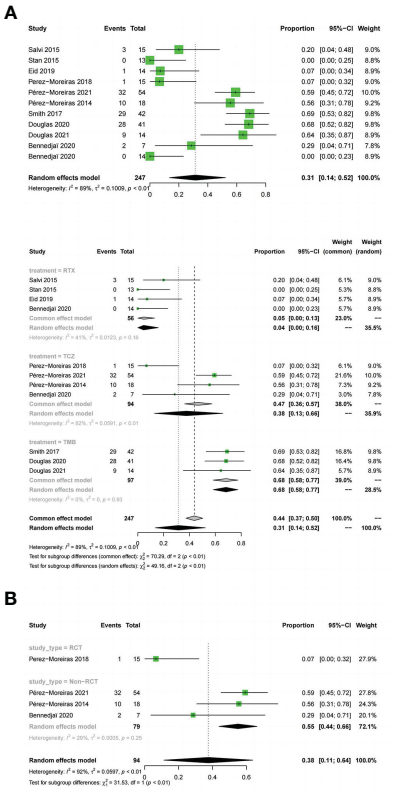

FIGURE 8
Forest plot and Funnel plots of improvement in diplopia. Forest plot of improvement in diplopia (Combined analysis, Drugs subgroups and TCZ subgroup).

IGF1R activation and leading to receptor internalisation.An *in vitro* study demonstrated its efficacy in reducing fibrocyte expression of IGF-1R and TSH-R and their downstream signals, thereby blocking the induction of pro-inflammatory cytokines (65, 66).

CAS significantly predicts response to anti-inflammatory therapies, and the efficacy response rate is the main basis for determining efficacy.In our study, as monotherapy for moderate-to-severe active GO,TCZ, TMB and RTX showed significant efficacy in the main analysis.Meanwhile, we compared meanwhile three indicators, mainly based on CAS, including efficacy response rate, disease inactivation rate and CAS. According to the results of the indirect contrast, TCZ was most likely to become the best regimen based on response, followed by TMB and RTX. TCZ was also most likely to become the best treatment for reducing proptosis, followed by TMB and RTX.TMB was most likely to become the best treatment for improving diplopia, followed by TCZ and RTX.TCZ was most likely to become the best treatment for safety, followed by RTX and TMB.

The promising results of RTX in GO were first reported in 2006 (25), and since then several studies have shown significant improvement in CAS with low relapse rates after RTX infusion (67, 68). However, in 2015, two RCTs of 25 and 32 patients with GO showed conflicting results, raising concerns about the benefit of RTX in GO (26, 30, 32, 69, 70). More recently, a multi-centre retrospective study of 40 GO patients and another study of 14 patients with active and moderate to severe GO investigating the efficacy of RTX have shown that CAS is significantly improved and GO inactivation is remarkably observed, especially in the early phase of the disease. In addition, its effect on proptosis is inconsistent and has been refuted by many studies (26, 30), which is consistent with our findings that RTX was the least effective in improving proptosis. A double-blind, randomised controlled trial in Spain investigated the effects of intravenous TCZ in moderate-to-severe corticosteroid-resistant GO (33). Significant reductions in CAS and exophthalmos were observed in patients treated with TCZ after 16 weeks of treatment, and no effect on diplopia was observed. TCZ was evaluated in a prospective, non-randomised study in 18 patients with GO (previously resistant to CS) and showed a statistically significant reduction in CAS, improvement in proptosis, improvement in extraocular motility, but resolution of diplopia (71). A prospective, randomised, open-label study in patients with bilateral active steroid-resistant GO (33 TCZ group) showed the same results. Diplopia improvement remained the worst, which is consistent with our analysis that TCZ was not optimal for diplopia improvement (64, 72–78). The first multicentre, double-masked, randomised, placebo-controlled trial enrolled 88 patients, and a subsequent phase 3 trial enrolled 83 patients to investigate the efficacy of TMB in patients with active moderate to severe GO (37). The majority of patients in the TMB group had a response at week 24, resulting in better outcomes than placebo in terms of CAS,diplopia, proptosis and quality of life, and non-responders were included in an open-label extension. The plus

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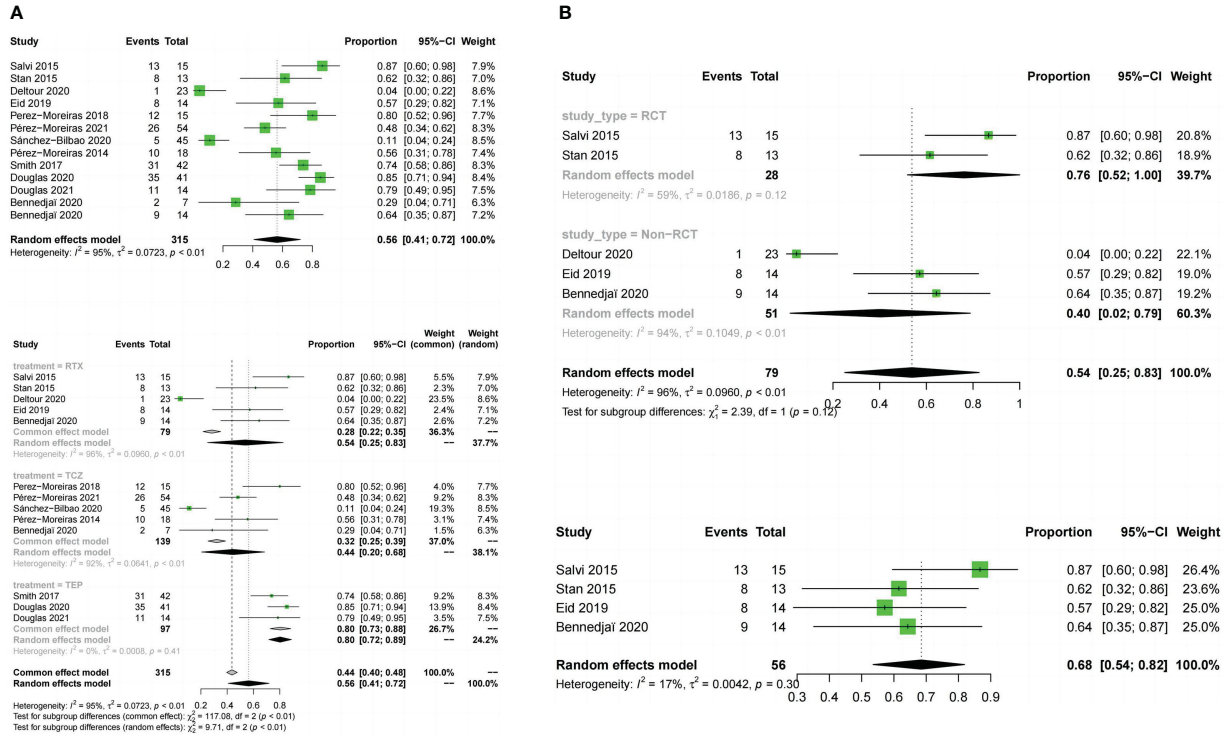

FIGURE 9
Forest plot and Funnel plots of adverse events rate. **(A)** Forest plot of adverse events rate (Combined analysis and Drugs subgroups). **(B)** Forest plot of adverse events rate (RTX subgroup).

extension study showed that the majority of patients who responded with improvement in proptosis and diplopia at week 24 continued to respond (79). The potential benefit of treatment with TMB is based on its beneficial effects on all of the symptoms of GO, especially in cases of diplopia and exophthalmos,which is consistent with our analysis. Few controlled trials of mAbs and GCs have been reported. In a 32-patient, double-blind, randomized trial of RTX vs intravenous methylprednisolone (IVMP), 100% of patients in the RTX group improved at 24 weeks compared with 69% in the IVMP group. At 52 weeks, TX was better than IVMP (in clinical activity score, lid aperture, proptosis, and diplopia score), and there were no relapses in the RTX group compared to 31% in the IVMP group. The study showed that RTX was superior to IVMP in terms of efficacy, durability and control of recurrence (30). More recently, a match-adjusted indirect comparison of TMB vs IVMP vs placebo including 12 trials by Raymond S et al (80). This meta-analysis suggested that TMB was favored over IVMP (odds ratio,2.32; 95% CI,1.07-5.03) in odds of proptosis (95% CI,-3.45 to -1.17 mm) and diplopia response (odds ratio,2.32; 95% CI,1.07-5.03),and may be twice as likely to achieve a 1 grade or higher reduction in diplopia.

However, safety is a necessary consideration in determining whether a drug is suitable for clinical use. In our included trials, the majority of patients receiving their first RTX infusion experienced mild adverse events, including mild fever, nasal congestion, infusion reaction, throat itching, and nausea. Slowing down the RTX infusion or giving intravenous hydrocortisone resolved these symptoms spontaneously (32, 81). TCZ adverse events that occurred during the trial were mainly pulmonary, gastrointestinal and renal infections, similar to those reported in rheumatoid arthritis trials (82, 83). However, there is a risk of serious adverse events exists, such as opportunistic infections, which have been reported during treatment and therefore monitoring for these during treatment is essential (33, 82, 84). Nevertheless, TCZ remains an interesting treatment option and is currently used as a second-line treatment in France.TMB was relatively poorly tolerated, with 11.9% of patients receiving it withdraw from the trials in our review due to adverse events.The adverse events were mild to moderate in severity, with hyperglycemia being the most common, which can easily attributed to therapy adjustments. Other AEs included hearing abnormalities, diarrhea, muscle cramps, alopecia and dysgeusia (31, 85). TMB has been approved by the US FDA for the treatment of GO and is currently used in clinical practice in North America (79).

Unlike previous trials, we compared different monoclonal antibodies for GO patients.The outcome measured was not just response rate, multiple databases and websites were searched for publication bias prevention.To detect potential bias, we also used funnel plots, and fortunately there was little evidence of bias.Howeverur current meta-analysis had its own limitations. Firstly, we included observational studies in addition to randomised controlled trials, which is a particular problem for monoclonal antibodies for GO, because there are very few RCTs.

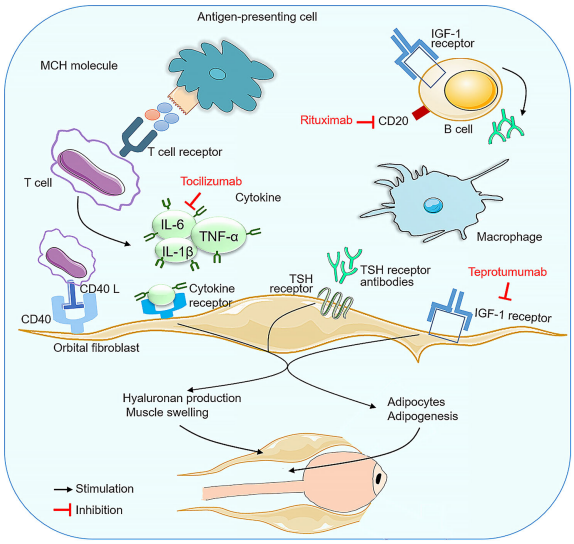

FIGURE 10
Immunopathogenesis of Graves'ophthalmopathy and therapeutic targets of mAbs.

This issue has not been sufficiently studied due to the limited number of trials available to us.

5 Conclusion

In the absence of RCTs, which are the best source of evidence on the balance of risks and benefits of different treatments. These comparative efficacy results may be useful as a basis for clinical decisions and future studies. In addition, the optimal dose and potential mechanism of action of monoclonal antibodies remains to be established. There appears to be a long way to go to better understand the biological mechanism of RTX and to develop a rational therapeutic regimen. If these results are confirmed, it is likely that the treatment paradigm will change in the future. Overall, there are many encouraging advances in the treatment of Graves' ophthalmopathy that make the future more promising for patients with this disease.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

Author contributions

YH designed the research process. YH and JHC searched the database for corresponding articles, extracted the data, performed the statistical analyses, and wrote the manuscript with support from other. KL and XJY performed the supervision and project administration. All authors contributed to the article and approved the submitted version.

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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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References

1. Bahn RS. Graves' ophthalmopathy. *N Engl J Med* (2010) 362(8):726–38. doi: 10.1056/NEJMra0905750

2. Ugradar S, Goldberg RA, Rootman DB. Bony orbital volume expansion in thyroid eye disease. *Ophthalmic Plast Reconstr Surg* (2019) 35(5):434–7. doi: 10.1097/IOP.0000000000001292

3. Gerding MN, Terwee CB, Dekker FW, Koornneef L, Prummel MF, Wiersinga WM. Quality of life in patients with graves' ophthalmopathy is markedly decreased: measurement by the medical outcomes study instrument. *Thyroid* (1997) 7(6):885–9. doi: 10.1089/thy.1997.7.885

4. Hiromatsu Y, Eguchi H, Tani J, Kasaoka M, Teshima Y. Graves' ophthalmopathy: epidemiology and natural history. *Intern Med* (2014) 53(5):353–60. doi: 10.2169/internalmedicine.53.1518

5. Tanda ML, Piantanida E, Liparulo L, Veronesi G, Lai A, Sassi L, et al. Prevalence and natural history of graves' orbitopathy in a large series of patients with newly diagnosed graves' hyperthyroidism seen at a single center. *J Clin Endocrinol Metab* (2013) 98(4):1443–9. doi: 10.1210/jc.2012-3873

6. Bartalena L, Tanda ML. Clinical practice. *Graves' ophthalmopathy N Engl J Med* (2009) 360:994–1001. doi: 10.1056/NEJMcp0806317

7. Bartalena L, Pinchera A, Marcocci C. Management of graves'ophthalmopathy: reality and perspectives. *Endocr Rev* (2000) 21:168–99. doi: 10.1210/edrv.21.2.0393

8. Lazarus JH. Epidemiology of graves' orbitopathy (GO) and relationship with thyroid disease. *Best Pract Res Clin Endocrinol Metab* (2012) 26:273–9. doi: 10.1016/j.beem.2011.10.005

9. Son BJ, Lee SY, Yoon JS. Evaluation of thyroid eye disease: quality-of-life questionnaire (TED-QOL) in Korean patients. *Can J Ophthalmol* (2014) 49(2):167–73. doi: 10.1016/j.jcjo.2013.12.007

10. Lin IC, Lee CC, Liao SL. Assessing quality of life in Taiwanese patients with graves' ophthalmopathy. *J Formos Med Assoc* (2015) 114(11):1047–54. doi: 10.1016/j.jfma.2013.12.002

11. Cockerham KP, Padnick-Silver L, Stuertz N, Francis-Sedlak M, Holt RJ. Quality of life in patients with chronic thyroid eye disease in the United States. *Ophthalmol Ther* (2021) 10(4):975–87. doi: 10.1007/s40123-021-00385-8

12. Chin YH, Ng CH, Lee MH, Koh JWH, Kiew J, Yang SP, et al. Prevalence of thyroid eye disease in graves' disease: a meta-analysis and systematic review. *Clin Endocrinol (Oxf)* (2020) 93(4):363–74. doi: 10.1111/cen.14296

13. Taylor PN, Albrecht D, Scholz A, Gutierrez-Buey G, Lazarus JH, Dayan CM, et al. Global epidemiology of hyperthyroidism and hypothyroidism. *Nat Rev Endocrinol* (2018) 14(5):301–16. doi: 10.1038/nrendo.2018.18

14. Bartalena L, Baldeschi L, Boboridis K, Eckstein A, Kahaly GJ, Marcocci C, et al. The 2016 European thyroid Association/European group on graves' orbitopathy guidelines for the management of graves' orbitopathy. *Eur Thyroid J* (2016) 5:9–26. doi: 10.1159/000443828

15. Prummel MF, Bakker A, Wiersinga WM, Baldeschi L, Mourits MP, Kendall-Taylor P, et al. Multi-center study on the characteristics and treatment strategies of patients with graves' orbitopathy: the first European group on graves' orbitopathy experience. *Eur J Endocrinol* (2003) 148(5):491–5. doi: 10.1530/eje.0.1480491

16. Bartalena L, Baldeschi L, Dickinson AJ, Eckstein A, Kendall-Taylor P, et al. Consensus statement of the European Group on Graves' orbitopathy (EUGOGO) on management of GO. *Eur J Endocrinol* (2008) 158(3):273-85. doi: 10.1530/EJE-07-0666

17. Kinsell LW, Partridge JW, Foreman N. The use of ACTH and cortisone in the treatment and in the differential diagnosis of malignant exophthalmos. *Ann Intern Med* (1953) 38(5):913–7. doi: 10.7326/0003-4819-38-5-913

18. Brent GA. Clinical practice. graves' disease. *N Engl J Med* (2008) 358(24):2594–605. doi: 10.1056/NEJMcp0801880

19. Bartalena L, Kahaly GJ, Baldeschi L, Dayan CM, Eckstein A, Marcocci C, et al. The 2021 European group on graves' orbitopathy (EUGOGO) clinical practice guidelines for the medical management of graves' orbitopathy. *Eur J Endocrinol* (2021) 185(4):G43–67. doi: 10.1530/EJE-21-0479

20. Kahaly G, Pitz S, Müller-Forell W, Hommel G. Randomized trial of intravenous immunoglobulins versus prednisolone in graves' ophthalmopathy. *Clin Exp Immunol* (1996) 106(2):197–202. doi: 10.1046/j.1365-2249.1996.d01-854.x

21. Wichary H, Gasińska T. Methylprednisolone and hepatotoxicity in graves' ophthalmopathy. *Thyroid* (2012) 22(1):64–9. doi: 10.1089/thy.2010.0158

22. Le Moli R, Baldeschi L, Saeed P, Regensburg N, Mourits MP, Wiersinga WM. Determinants of liver damage associated with intravenous methylprednisolone pulse therapy in graves' ophthalmopathy. *Thyroid* (2007) 17(4):357–62. doi: 10.1089/thy.2006.0267

23. Kauppinen-Mäkelin R, Karma A, Leinonen E, Löyttyniemi E, Salonen O, Sane T, et al. High dose intravenous methylprednisolone pulse therapy versus oral prednisone for thyroid-associated ophthalmopathy. *Acta Ophthalmol Scand* (2002) 80(3):316–21. doi: 10.1034/j.1600-0420.2002.800316.x

24. El Fassi D, Nielsen CH, Hasselbalch HC, Hegedüs L. Treatment-resistant severe, active graves' ophthalmopathy successfully treated with b lymphocyte depletion. *Thyroid* (2006) 16(7):709–10. doi: 10.1089/thy.2006.16.709

25. Salvi M, Vannucchi G, Campi I, Rossi S, Bonara P, Sbrozzi F, et al. Efficacy of rituximab treatment for thyroid-associated ophthalmopathy as a result of intraorbital b-cell depletion in one patient unresponsive to steroid immunosuppression. *Eur J Endocrinol* (2006) 154(4):511–7. doi: 10.1530/eje.1.02119

26. Stan MN, Garrity JA, Carranza Leon BG, Prabin T, Bradley EA, Bahn RS. Randomized controlled trial of rituximab in patients with graves' orbitopathy. *J Clin Endocrinol Metab* (2015) 100(2):432–41. doi: 10.1210/jc.2014-2572

27. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* (2009) 339:b2700. doi: 10.1136/bmj.b2700

28. Cumpston M, Li T, Page MJ, Chandler J, Welch VA, Higgins JP, et al. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. *Cochrane Database Syst Rev* (2019) 10:ED000142. doi: 10.1002/14651858.ED000142

29. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. (2014). *The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses - 2008*. Available at: http:// www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

30. Salvi M, Vannucchi G, Currò N, Campi I, Covelli D, Dazzi D, et al. Efficacy of b-cell targeted therapy with rituximab in patients with active moderate to severe graves' orbitopathy: a randomized controlled study. *J Clin Endocrinol Metab* (2015) 100(2):422–31. doi: 10.1210/jc.2014-3014

31. Deltour JB, d'Assigny Flamen M, Ladsous M, Giovansili L, Cariou B, Caron P, et al. Efficacy of rituximab in patients with graves' orbitopathy: a retrospective multicenter nationwide study. *Graefes Arch Clin Exp Ophthalmol* (2020) 258(9):2013–21. doi: 10.1007/s00417-020-04651-6

32. Eid L, Coste-Verdier V, Longueville E, Ribeiro E, Nicolescu-Catargi B, Korobelnik JF. The effects of rituximab on graves'orbitopathy: a retrospective study of 14 patients. *Eur J Ophthalmol* (2020) 30(5):1008–13. doi: 10.1177/1120672119845224

33. Perez-Moreiras JV, Gomez-Reino JJ, Maneiro JR, Perez-Pampin E, Romo Lopez A, et al. Efficacy of tocilizumab in patients with moderate-to-Severe corticosteroid-resistant graves orbitopathy: a randomized clinical trial. *Am J Ophthalmol* (2018) 195:181–90. doi: 10.1016/j.ajo.2018.07.038

34. Pérez-Moreiras JV, Varela-Agra M, Prada-Sánchez MC, Prada-Ramallal G. Steroid-resistant graves' orbitopathy treated with tocilizumab in real-world clinical practice: a 9-year single-center experience. *J Clin Med* (2021) 10(4):706. doi: 10.3390/jcm10040706

35. Sánchez-Bilbao L, Martínez-López D, Revenga M, López-Vázquez Á, Valls-Pascual E, Atienza-Mateo B, et al. Anti-IL-6 receptor tocilizumab in refractory graves' orbitopathy: national multicenter observational study of 48 patients. *J Clin Med* (2020) 9(9):2816. doi: 10.3390/jcm9092816

36. Pérez-Moreiras JV, Alvarez-López A, Gómez EC. Treatment of active corticosteroid-resistant graves' orbitopathy. *Ophthalmic Plast Reconstr Surg* (2014) 30(2):162–7. doi: 10.1097/IOP.0000000000000037

37. Smith TJ, Kahaly GJ, Ezra DG, Fleming JC, Dailey RA, Tang RA, et al. Teprotumumab for thyroid-associated ophthalmopathy. *N Engl J Med* (2017) 376(18):1748–61. doi: 10.1056/NEJMoa1614949

38. Douglas RS, Kahaly GJ, Patel A, Sile S, Thompson EHZ, Perdok R, et al. Teprotumumab for the treatment of active thyroid eye disease. *N Engl J Med* (2020) 382(4):341–52. doi: 10.1056/NEJMoa1910434

39. Douglas RS, Kahaly GJ, Ugradar S, Elflein H, Ponto KA, Fowler BT, et al. Teprotumumab efficacy, safety, and durability in longer-duration thyroid eye disease and re-treatment: OPTIC-X study. *Ophthalmology* (2022) 129(4):438–49. doi: 10.1016/j.ophtha.2021.10.017

40. Bennedjaï A, Bouheraoua N, Gatfossé M, Dupasquier-Fediaevsky L, Errera MH, Tazartes M, et al. Tocilizumab versus rituximab in patients with moderate to severe steroid-resistant graves' orbitopathy. *Ocul Immunol Inflamm* (2022) 30(2):500–5. doi: 10.1080/09273948.2020.1808688

41. Smith TJ. The insulin-like growth factor-I receptor and its role in thyroid-associated ophthalmopathy. *Eye (Lond)* (2019) 33(2):200–5. doi: 10.1038/s41433-018-0265-2

42. Gao G, Dai J, Qian Y, Ma F. Meta-analysis of methylprednisolone pulse therapy for graves' ophthalmopathy. *Clin Exp Ophthalmol* (2014) 42(8):769–77. doi: 10.1111/ceo.12317

43. Stiebel-Kalish H, Robenshtok E, Hasanreisoglu M, Ezrachi D, Shimon I, Leibovici L. Treatment modalities for graves' ophthalmopathy: systematic review and metaanalysis. *J Clin Endocrinol Metab* (2009) 94(8):2708–16. doi: 10.1210/jc.2009-0376

44. Bartalena L, Krassas GE, Wiersinga W, Marcocci C, Salvi M, Daumerie C, et al. Efficacy and safety of three different cumulative doses of intravenous methylprednisolone for moderate to severe and active graves' orbitopathy. *J Clin Endocrinol Metab* (2012) 97(12):4454–63. doi: 10.1210/jc.2012-2389

45. Marcocci C, Watt T, Altea MA, Rasmussen AK, Feldt-Rasmussen U, Orgiazzi J, et al. Fatal and non-fatal adverse events of glucocorticoid therapy for graves' orbitopathy: a questionnaire survey among members of the European thyroid association. *Eur J Endocrinol* (2012) 166(2):247–53. doi: 10.1530/EJE-11-0779

46. Baschieri L, Antonelli A, Nardi S, Alberti B, Lepri A, Canapicchi R, et al. Intravenous immunoglobulin versus corticosteroid in treatment of graves' ophthalmopathy. *Thyroid* (1997) 7(4):579–85. doi: 10.1089/thy.1997.7.579

47. Krieger CC, Place RF, Bevilacqua C, Marcus-Samuels B, Abel BS, Skarulis MC, et al. TSH/IGF-1 receptor cross talk in graves' ophthalmopathy pathogenesis. *J Clin Endocrinol Metab* (2016) 101(6):2340–7. doi: 10.1210/jc.2016-1315

48. Du Pasquier-Fediaevsky L, Andrei S, Berche M, Leenhardt L, Héron E, Rivière S. Low-dose rituximab for active moderate to severe graves' orbitopathy resistant to conventional treatment. *Ocul Immunol Inflamm* (2019) 27(5):844–50. doi: 10.1080/09273948.2018.1453078

49. Gürcan HM, Keskin DB, Stern JN, Nitzberg MA, Shekhani H, Ahmed AR. A review of the current use of rituximab in autoimmune diseases. *Int Immunopharmacol* (2009) 9(1):10–25. doi: 10.1016/j.intimp.2008.10.004

50. Ahuja A, Anderson SM, Khalil A, Shlomchik MJ. Maintenance of the plasma cell pool is independent of memory b cells. *Proc Natl Acad Sci U S A.* (2008) 105(12):4802–7. doi: 10.1073/pnas.0800555105

51. Atienza-Mateo B, Remuzgo-Martínez S, Prieto-Peña D, Mora Cuesta VM, Iturbe-Fernández D, Llorca J, et al. Rituximab in the treatment of interstitial lung disease associated with autoimmune diseases: experience from a single referral center and literature review. *J Clin Med* (2020) 9(10):3070. doi: 10.3390/jcm9103070

52. Salvi M, Vannucchi G, Currò N, Introna M, Rossi S, Bonara P, et al. Small dose of rituximab for graves orbitopathy: new insights into the mechanism of action. *Arch Ophthalmol* (2012) 130(1):122–4. doi: 10.1001/archopthalmol.2011.1215

53. Emery P, Keystone E, Tony HP, Cantagrel A, van Vollenhoven R, Sanchez A, et al. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. *Ann Rheum Dis* (2008) 67(11):1516–23. doi: 10.1136/ard.2008.092932

54. Yokota S, Imagawa T, Mori M, Miyamae T, Aihara Y, Takei S, et al. Efficacy and safety of tocilizumab in patients with systemic-onset juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled, withdrawal phase III trial. *Lancet* (2008) 371(9617):998–1006. doi: 10.1016/S0140-6736(08)60454-7

55. Salvi M, Girasole G, Pedrazzoni M, Passeri M, Giuliani N, Minelli R, et al. Increased serum concentrations of interleukin-6 (IL-6) and soluble IL-6 receptor in patients with graves' disease. *J Clin Endocrinol Metab* (1996) 81(8):2976–9. doi: 10.1210/jcem.81.8.8768861

56. Hunter CA, Jones SA. Corrigendum: IL-6 as a keystone cytokine in health and disease. *Nat Immunol* (2017) 18(11):1271. doi: 10.1038/ni1117-1271b

57. Chen B, Tsui S, Smith TJ. IL-1 beta induces IL-6 expression in human orbital fibroblasts: identification of an anatomic-site specific phenotypic attribute relevant to thyroid-associated ophthalmopathy. *J Immunol* (2005) 175(2):1310–9. doi: 10.4049/jimmunol.175.2.1310

58. Douglas RS, Gupta S. The pathophysiology of thyroid eye disease: implications for immunotherapy. *Curr Opin Ophthalmol* (2011) 22(5):385–90. doi: 10.1097/ICU.0b013e3283499446

59. Smith TJ. Insulin-like growth factor-I regulation of immune function: a potential therapeutic target in autoimmune diseases? *Pharmacol Rev* (2010) 62 (2):199–236. doi: 10.1124/pr.109.002469

60. Pritchard J, Han R, Horst N, Cruikshank WW, Smith TJ. Immunoglobulin activation of T cell chemoattractant expression in fibroblasts from patients with graves' disease is mediated through the insulin-like growth factor I receptor pathway. *J Immunol* (2003) 170(12):6348–54. doi: 10.4049/jimmunol.170.12.6348

61. Smith TJ, Hoa N. Immunoglobulins from patients with graves' disease induce hyaluronan synthesis in their orbital fibroblasts through the self-antigen, insulin-like growth factor-I receptor. *J Clin Endocrinol Metab* (2004) 89(10):5076–80. doi: 10.1210/jc.2004-0716

62. Tsui S, Naik V, Hoa N, Hwang CJ, Afifiyan NF, Sinha Hikim A, et al. Evidence for an association between thyroid-stimulating hormone and insulin-like growth factor 1 receptors: a tale of two antigens implicated in graves' disease. *J Immunol* (2008) 181 (6):4397–405. doi: 10.4049/jimmunol.181.6.4397

63. Wang Y, Smith TJ. Current concepts in the molecular pathogenesis of thyroid-associated ophthalmopathy. *Invest Ophthalmol Vis Sci* (2014) 55(3):1735–48. doi: 10.1167/iovs.14-14002

64. Wémeau JL, Klein M, Sadoul JL, Briet C, Vélayoudom-Céphise FL. Graves' disease: introduction, epidemiology, endogenous and environmental pathogenic factors. *Ann Endocrinol (Paris)* (2018) 79(6):599–607. doi: 10.1016/j.ando.2018.09.002

65. Smith TJ, Janssen JA. Building the case for insulin-like growth factor receptor-I involvement in thyroid-associated ophthalmopathy. *Front Endocrinol (Lausanne)* (2017) 7:167. doi: 10.3389/fendo.2016.00167

66. Paik JS, Kim SE, Kim JH, Lee JY, Yang SW, Lee SB. Insulin-like growth factor-1 enhances the expression of functional TSH receptor in orbital fibroblasts from thyroid-associated ophthalmopathy. *Immunobiology* (2020) 225(2):151902. doi: 10.1016/j.imbio.2019.151902

67. Supronik J, Szelachowska M, Kretowski A, Siewko K. Rituximab in the treatment of graves' orbitopathy: latest updates and perspectives. *Endocr Connect* (2022) 11(12): e220303. doi: 10.1530/EC-22-0303

68. Salvi M, Vannucchi G, Beck-Peccoz P. Potential utility of rituximab for graves' orbitopathy. *J Clin Endocrinol Metab* (2013) 98(11):4291–9. doi: 10.1210/jc.2013-1804

69. Shen WC, Lee CH, Loh EW, Hsieh AT, Chen L, Tam KW. Efficacy and safety of rituximab for the treatment of graves' orbitopathy: a meta-analysis of randomized controlled trials. *Pharmacotherapy* (2018) 38(5):503–10. doi: 10.1002/phar.2111

70. Insull EA, Sipkova Z, David J, Turner HE, Norris JH. Early low-dose rituximab for active thyroid eye disease: an effective and well-tolerated treatment. *Clin Endocrinol (Oxf)* (2019) 91(1):179–86. doi: 10.1111/cen.13970

71. Brownell J, Polyak SJ. Molecular pathways: hepatitis c virus, CXCL10, and the inflammatory road to liver cancer. *Clin Canc Res: Offl J Am Assoc Cancer Res* (2013) 19:1347e52. doi: 10.1158/1078-0432.CCR-12-0928

72. Antonelli A, Ferrari SM, Frascerra S, Galetta F, Franzoni F, Corrado A, et al. Circulating chemokine (CXC motif) ligand (CXCL)9 is increased in aggressive chronic autoimmune thyroiditis, in association with CXCL10. *Cytokine* (2011) 55(2):288–93. doi: 10.1016/j.cyto.2011.04.022

73. Spinelli C, Bertocchini A, Antonelli A, Miccoli P. Surgical therapy of the thyroid papillary carcinoma in children: experience with 56 patients < or =16 years old. *J Pediatr Surg* (2004) 39(10):1500–5. doi: 10.1016/j.jpedsurg.2004.06.016

74. Perricone C, Versini M, Ben-Ami D, Gertel S, Watad A, Segel MJ, et al. Smoke and autoimmunity: the fire behind the disease. *Autoimmun Rev* (2016) 15(4):354–74. doi: 10.1016/j.autrev.2016.01.001

75. Fallahi P, Ferrari SM, Ragusa F, Ruffilli I, Elia G, Paparo SR, et al. Th1 chemokines in autoimmune endocrine disorders. *J Clin Endocrinol Metab* (2020) 105 (4):dgz289. doi: 10.1210/clinem/dgz289

76. Rapoport B, McLachlan SM. Graves' hyperthyroidism is antibody-mediated but is predominantly a Th1-type cytokine disease. *J Clin Endocrinol Metab* (2014) 99 (11):4060–1. doi: 10.1210/jc.2014-3011

77. Rapoport B, McLachlan SM. Reflections on thyroid autoimmunity: a personal overview from the past into the future. *Horm Metab Res* (2018) 50(12):840–52. doi: 10.1055/a-0725-9297

78. Kotwal A, Stan M. Thyrotropin receptor antibodies-an overview. *Ophthalmic Plast Reconstr Surg* (2018) 34(4S Suppl 1):S20–7. doi: 10.1097/IOP.0000000000001052

79. Smith TJ. Insulin-like growth factor pathway and the thyroid. *Front Endocrinol (Lausanne)* (2021) 12:653627. doi: 10.3389/fendo.2021.653627

80. Douglas RS, Dailey R, Subramanian PS, Barbesino G, Ugradar S, Batten R, et al. Proptosis and diplopia response with teprotumumab and placebo vs the recommended treatment regimen with intravenous methylprednisolone in moderate to severe thyroid eye disease: a meta-analysis and matching-adjusted indirect comparison. *JAMA Ophthalmol* (2022) 140(4):328–35. doi: 10.1001/jamaophthalmol.2021.6284

81. Savino G, Mandarà E, Gari M, Battendieri R, Corsello SM, Pontecorvi A. Intraorbital injection of rituximab versus high dose of systemic glucocorticoids in the treatment of thyroid-associated orbitopathy. *Endocrine* (2015) 48(1):241–7. doi: 10.1007/s12020-014-0283-1

82. Yamamoto K, Goto H, Hirao K, Nakajima A, Origasa H, Tanaka K, et al. Longterm safety of tocilizumab: results from 3 years of followup postmarketing surveillance of 5573 patients with rheumatoid arthritis in Japan. *J Rheumatol* (2015) 42(8):1368–75. doi: 10.3899/jrheum.141210

83. Komura T, Ohta H, Nakai R, Seishima J, Yamato M, Miyazawa M, et al. Cytomegalovirus reactivation induced acute hepatitis and gastric erosions in a patient with rheumatoid arthritis under treatment with an anti-IL-6 receptor antibody, tocilizumab. *Intern Med* (2016) 55(14):1923–7. doi: 10.2169/internalmedicine.55.5981

84. Teitsma XM, Marijnissen AK, Bijlsma JW, Lafeber FP, Jacobs JW. Tocilizumab as monotherapy or combination therapy for treating active rheumatoid arthritis: a meta-analysis of efficacy and safety reported in randomized controlled trials. *Arthritis Res Ther* (2016) 18(1):211. doi: 10.1186/s13075-016-1108-9

85. Markham A. Teprotumumab: first approval. *Drugs* (2020) 80(5):509–12. doi: 10.1007/s40265-020-01287-y

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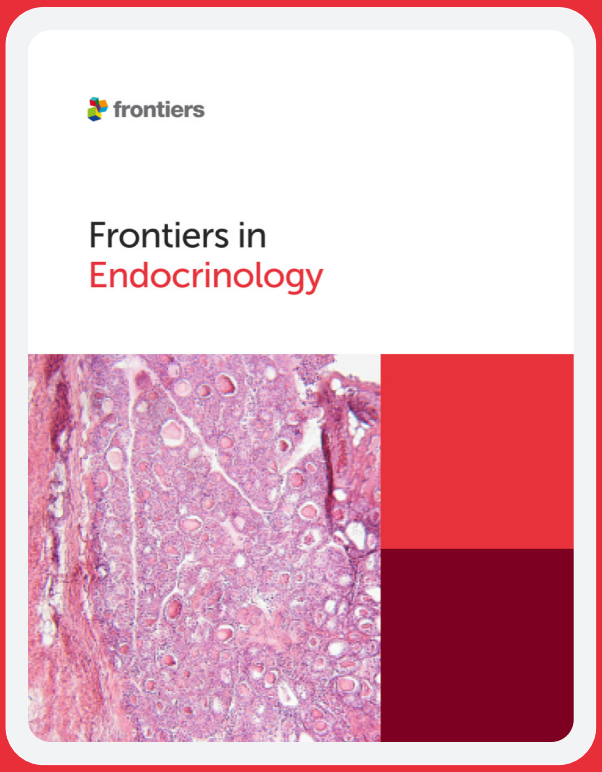

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