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Triglycerides as a predictor of activity and severity in thyroid eye disease: a multicentre study

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ABSTRACT

Background This study investigated the association between dyslipidaemia and thyroid eye disease (TED) activity and severity using a multicentre dataset from South Korea.

Methods A retrospective, multicentre study included adult patients (aged ≥19 years) with TED and elevated thyroid autoantibody levels, including thyroid-stimulating immunoglobulin >140% and thyroid-stimulating hormone-binding inhibitory immunoglobulin >1.5 IU/L. Patients previously treated with systemic steroids were excluded. TED activity was defined by a Clinical Activity Score, and severity was categorised as mild or marked based on the NOSPECS classification. Logistic regression analyses identified associations between lipid profiles and TED activity/severity. Subgroup analysis excluded statin users. Receiver operating characteristic curves determined optimal triglyceride (TG) cut-off values.

Results Of 330 patients (71.2% women; mean age, 45.7±13.2 years), elevated TG levels were independently associated with TED activity (OR=1.005, 95% CI 1.001 to 1.008, p=0.011) and severity (OR=1.004, 95% CI 1.001 to 1.007, p=0.014). Optimal TG cut-off values were 104 mg/dL for active TED and 108 mg/dL for marked severity. These associations remained consistent in non-statin users with similar cut-off values. Elevated intraocular pressure and smoking were significantly associated with increased disease severity. Subgroup analysis excluding statin users revealed significant associations of total cholesterol and low-density lipoprotein cholesterol with TED activity.

Conclusions Elevated TG levels are significantly associated with TED activity and severity, highlighting the potential clinical value of measuring TG for risk stratification and disease management. Further studies should explore whether TG-lowering interventions improve TED outcomes.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Statin use and elevated cholesterol levels (total cholesterol and low-density lipoprotein cholesterol) have previously been linked to the presence and activity of thyroid eye disease (TED), but the underlying mechanisms remain unclear, and uncertainty persists regarding their precise roles in TED severity.

WHAT THIS STUDY ADDS

⇒ Elevated triglyceride (TG) levels were independently associated with increased TED activity and severity, regardless of statin use.
⇒ Optimal TG cut-off values (104 mg/dL for active TED and 108 mg/dL for severe TED) were identified, supporting the utility of TG as a biomarker in clinical assessments.
⇒ TG may be involved in shared inflammatory and immunometabolic pathways contributing to TED progression.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Measuring TG levels is expected to be beneficial for clinical decision-making and risk stratification in managing TED.
⇒ Future studies are warranted to investigate whether TG-lowering interventions can improve clinical outcomes in TED, potentially informing new therapeutic strategies.

INTRODUCTION

Thyroid eye disease (TED), also known as Graves' orbitopathy, is a complex autoimmune disorder primarily associated with Graves' disease (GD), although it can occasionally occur in euthyroid or hypothyroid individuals. It is characterised by orbital inflammation and tissue remodelling, resulting in symptoms such as proptosis, eyelid retraction and diplopia. In severe cases, optic nerve compression may lead to vision loss. The pathogenesis of TED involves autoantibodies targeting the thyrotropin and insulin-like growth factor-1 receptors on the orbital fibroblasts, triggering inflammation and adipogenesis. Several risk factors, including smoking, thyroid dysfunction and genetic predisposition, have been identified to contribute to the variability in clinical presentation and severity among patients.[1]

Recent studies have suggested a potential link between lipid metabolism and TED. Dyslipidaemia, which is characterised by altered cholesterol and triglyceride (TG) levels, has been implicated in the pathogenesis of various autoimmune and inflammatory conditions. Elevated cholesterol levels may contribute to immune cell activation and inflammatory signalling pathways, which are critical in the progression of TED. A previous longitudinal cohort study demonstrated that statin use for >60 days in the past year was associated with a 40% decreased hazard for TED development.[2] Additionally, a correlation between TED and both

total and low-density lipoprotein (LDL) cholesterol has been observed.[3] This correlation persisted even after adjusting for TED duration. The cut-off values indicating an increased risk of TED were 191 mg/dL for total cholesterol and 118.4 mg/dL for LDL cholesterol. However, while elevated cholesterol levels were associated with TED presence, no correlation was found with TED severity or activity.[4] Recently, the triglyceride glucose index (TGI) was found to be significantly higher in both inactive and active patients with TED than in controls, indicating that the TGI may serve as a useful marker for predicting and monitoring TED activity in clinical practice. Understanding this relationship could provide novel insights into TED's pathophysiology and identify potential therapeutic targets.[5]

Therefore, this multicentre retrospective cross-sectional study conducted in South Korea aimed to investigate the relationship between lipid parameters, including TG and cholesterol levels, and TED activity and severity.

MATERIAL AND METHODS

Study design

This retrospective, cross-sectional, multicentre study involved 29 institutions across South Korea. The Institutional Review Board (IRB) of Seoul St. Mary's Hospital (IRB No. KC24RCDI0777) provided central ethical approval for this study. We analysed the clinical and laboratory data of patients diagnosed with TED between 1 September 2023 and 31 August 2024.

Patient recruitment

Patients were eligible if they met the following inclusion criteria: (1) levels exceeding diagnostic thresholds for thyroid autoantibodies—thyroid-stimulating immunoglobulin (TSI) (>140%) or thyroid-stimulating hormone-binding inhibitory immunoglobulin (TBII) (>1.5 IU/L); (2) clinical and imaging findings consistent with TED as determined by an oculoplastic specialist ophthalmologist; (3) age ≥19 years; (4) onset of TED symptoms within the past 12 months; and (5) availability of relevant ophthalmologic and laboratory test results within 1 month of the initial visit. Patients with a history of steroid treatment before TED diagnosis or those using steroids for other conditions were excluded.

Of the 360 patients initially identified, 30 were excluded because of missing essential data or inability to meet the inclusion criteria, leaving 330 for the final analysis.

Clinical and laboratory assessment

Demographic data (sex, age, height, weight, smoking history and family history), comorbidities (eg, diabetes mellitus and hypertension) and other systemic conditions (eg, dyslipidaemia, asthma and rheumatological disorders) were documented. Statin use was recorded to assess potential confounding effects on lipid profiles.

Disease-specific variables included intraocular pressure (IOP), glaucoma medication use and key time intervals such as GD duration, TED duration and the interval between GD diagnosis and TED onset. For cases in which TED onset preceded GD diagnosis, the interval was recorded as a negative value to maintain chronological consistency. Treatments for thyroid disease were categorised as anti-thyroid medication, hormone replacement, combination therapy or no treatment. Additionally, records of radioactive iodine (RAI) ablation and thyroidectomy were examined.

Subjective TED symptoms, such as soft tissue swelling, proptosis, eyelid retraction, ocular pain, tearing, diplopia and decreased vision, were assessed. The eyelid position, including palpebral fissure height and margin reflex distance 1 (MRD1), was measured. Proptosis was assessed using Hertel exophthalmometry and stratified into four groups (<17 mm, 17–18 mm, 19–22 mm and >22 mm). Differences in inter-eye proptosis (≤2 mm or >2 mm) were noted. Diplopia severity was graded using the Gorman score (no, intermittent, inconstant or constant). Extraocular muscle (EOM) limitation was evaluated using the Hess screen test, and EOM involvement was determined using orbital imaging with CT or MRI.

Dysthyroid optic neuropathy (DON) was defined as the presence of apical crowding on imaging, in addition to one or more of the following: reduced visual acuity, abnormal colour vision, a positive relative afferent pupillary defect, optic disc swelling on fundus examination, and characteristic visual field defects.

TED activity was assessed using the Clinical Activity Score (CAS), with a threshold of ≥4 indicating active disease, as per established criteria. TED severity was assessed using the NOSPECS classification, with scores of 0–5 categorised as 'mild' and 6–12 as 'marked''[6] Additionally, severity was categorised according to the European Group on Graves' Orbitopathy (EUGOGO) guidelines into mild, moderate-to-severe or sight-threatening stages.[7]

Laboratory evaluations included thyroid function tests (free thyroxine (Free T4), triiodothyronine (T3) and thyroid-stimulating hormone (TSH)) and thyroid autoantibody levels (TSI and TBII). The lipid profiles included total cholesterol, LDL cholesterol, high-density lipoprotein (HDL) cholesterol and TG levels. Lipid profiles were obtained after overnight fasting of at least 8 hours (water only), following standard practice at participating Korean centres.

Our primary analysis focused on the association between dyslipidaemia and both the activity and severity of TED, as well as potential correlations with other clinical findings. To address the potential confounding effects of statin therapy, a subgroup analysis was conducted among non-statin users. We further examined the relationship between TG levels and the presence of active moderate-to-severe TED and determined the optimal TG cut-off value for clinical prediction.

Statistical analysis

All statistical analyses were performed using SPSS Statistics version 28.0 (IBM Corp., Armonk, New York, USA) and Python (V. 3.9), leveraging libraries such as statsmodels, scikit-learn and pandas. Continuous variables were expressed as mean±SD and compared using independent sample t-tests. Categorical variables were presented as frequencies and percentages and analysed using χ^2 tests.

Univariate logistic regression identified statistically significant predictors of TED activity and severity ($p<0.05$). Factors meeting this criterion were included in multivariate logistic regression models to control for potential confounders. Variables with high multicollinearity were excluded from the analysis. For logistic regression analyses of severity, proptosis (including inter-eye difference), Gorman score, EOM limitation and radiologic muscle involvement were excluded to minimise bias from confounding and collinearity. Statistical significance was set at $p<0.05$. Cases with missing data were excluded from the analysis.

Receiver operating characteristic (ROC) curve analyses assessed the predictive accuracy of TG levels for TED activity (active vs inactive) and severity (mild vs marked). An additional combined ROC analysis assessed the predictive performance of

TG for both TED activity and moderate-to-severe disease. The area under the curve (AUC) was calculated for each analysis. The optimal cut-off values were identified using Youden's index, which maximises the sum of sensitivity and specificity.

RESULTS

Baseline Characteristics and Laboratory Findings

A total of 330 patients with TED were included in the study, and 15.2% were on statin therapy. The mean CAS was 2.23±1.47, with 20% of patients classified as having active TED (CAS≥4). Soft tissue swelling (66.4%) and proptosis (58.8%) were the most common clinical signs, and DON was observed in 3.6% of patients.

Regarding the interval from GD diagnosis to TED onset, the mean time was 12.9±38.0 months. Notably, 95 patients (28.8%) presented with negative intervals (ie, <0 months), suggesting that TED was clinically identified prior to GD diagnosis. In patients with active TED, the mean interval was 4.61±12.3 months, which was significantly shorter than that in the inactive group at 15.0±41.9 months (p<0.001). The mean GD duration was 17.4±38.1 months in the entire cohort.

The mean MRD1 was 4.61±1.57 mm and was significantly greater in the active group (5.28±2.11 mm) than in the inactive group (4.44±1.35 mm, p<0.001). Although the mean proptosis was 18.1±3.9 mm, no significant difference was observed between active and inactive TED (p=0.11). Elevated IOP was more frequent in the active TED group (22.7%) than in the inactive TED group (4.2%, p<0.001).

Biochemical and immunological parameters

No significant differences were observed between the active and inactive TED groups in total cholesterol, LDL cholesterol or HDL cholesterol levels. However, TG levels were significantly higher in the active group (165.2±163.6 mg/dL) than in the inactive group (114.5±64.3 mg/dL, p<0.001). Moreover, patients with marked TED had higher TG levels (143.1±98.2 mg/dL) than did those with mild disease (112.9±59.2 mg/dL, p<0.001).

No significant difference in TBII levels was detected between active and inactive TED (p=0.768). In contrast, TSI levels were significantly higher in the active group than in the inactive group (p=0.031). The detailed baseline characteristics and laboratory findings are presented in online supplemental table 1.

Factors associated with activity and severity of TED

The key factors associated with TED activity and severity are shown in tables 1 and 2. Among the lipid parameters, only TG level was significantly associated with both TED activity (p=0.011) and marked severity (p=0.014). The total cholesterol, LDL cholesterol and HDL cholesterol levels were not significantly associated with TED outcomes.

Marked NOSPECS severity was independently associated with active TED (p=0.001). Higher MRD1 values were correlated with greater TED activity (p=0.007). Elevated IOP was associated with both activity (p=0.002) and severity (p<0.001), and smoking was associated with increased severity (p=0.028). In contrast, palpebral fissures and proptosis were not significantly associated with activity or severity. TBII levels were not significantly associated with disease activity. In contrast, TSI levels were significantly associated with disease activity.

Subgroup analysis for activity and severity in non-statin users

To assess whether statin therapy influenced these relationships, the analyses were repeated in patients who did not receive statins (n=279) (table 3). In this subgroup, higher TG levels remained significantly associated with increased TED activity (p=0.005) and severity (p=0.020). Notably, in non-statin users, elevated total cholesterol and LDL cholesterol levels were also significantly associated with greater TED activity (p=0.008) but not with TED severity.

Subgroup analysis for predicting active and moderate-to-severe TED

Higher TG levels were independently associated with both active and moderate-to-severe disease (table 4; p=0.003). Although higher HDL cholesterol (p=0.015) and higher BMI (p=0.021) were associated with these outcomes in the univariate analyses, their significance did not persist after multivariate adjustment.

Analysis with binary classification of lipid parameters

For TG, 150 mg/dL served as the threshold between the normal and elevated levels. In this dichotomised model, TG was the only lipid parameter that remained significantly associated with both TED activity (OR=2.113, 95% CI 1.107 to 4.035; p=0.023) and marked severity (OR=1.803, 95% CI 1.070 to 3.040; p=0.027). Notably, for active and moderate-to-severe TED in this binary approach, TG showed a borderline significance (OR=2.160, 95% CI 0.994 to 4.694; p=0.051). These binary classification results are not included in the current tables.

Optimal TG cut-off values for TED activity and severity

Figure 1 shows the ROC curves for determining the optimal TG cut-off values. The optimal cut-off values for TED activity and severity were 104 mg/dL (AUC=0.611; p=0.005) and 108 mg/dL (AUC=0.621; p=0.001), respectively. Among non–statin users, the activity cut-off was slightly lower at 100.5 mg/dL (AUC=0.609; p=0.001), while the severity cut-off remained 101.5 mg/dL (AUC=0.615; p=0.003). For predicting both active and moderate-to-severe TED, 107.5 mg/dL was the optimal cut-off value (AUC=0.685; p<0.001).

DISCUSSION

Our study demonstrates that elevated TG levels significantly influence TED activity and severity. Specifically, we identified cut-offs of 104 mg/dL for active TED, 108 mg/dL for severe TED and 107.5 mg/dL for active, moderate-to-severe disease, underscoring the consistency of TG as a biomarker across varying disease statuses. Previous studies primarily focused on cholesterol subfractions (eg, LDL and HDL) and statin therapy, our findings highlight the more pronounced role of TG, suggesting that hypertriglyceridaemia may drive orbital inflammation and tissue remodelling via immunometabolic pathways.[2 3]

In our cohort, TG levels were markedly higher among patients exhibiting active versus inactive TED and in those with severe disease compared with mild disease. This trend challenges the conventional notion that hyperthyroidism inherently lowers TG levels through enhanced lipolysis and metabolic turnover.[8] Instead, the inflammatory milieu characteristic of TED appears to override thyroid hormone–driven lipid-lowering effects, pointing to a complex interplay between endocrine and immune processes. Mediators such as interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α) can reshape lipid metabolism, promoting TG accumulation rather than its expected depletion. Similar patterns have been documented in autoimmune conditions such as rheumatoid arthritis, where systemic inflammation correlates with paradoxical increases in TG.[9 10] Moreover, antithyroid medications such as methimazole (MMI) or propylthiouracil (PTU) may upregulate lipogenic gene expression, thus further increasing TG levels in vulnerable individuals.[11]

Table 1 Logistic regression analysis of factors associated with activity in TED patients

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Sex	0.764 (0.429 to 1.363)	0.363	—	NS
Age group (≤50)	1.355 (0.782 to 2.347)	0.279	—	NS
BMI (kg/m^2)	1.010 (0.934 to 1.091)	0.806	—	NS
Past history				
DM	0.689 (0.250 to 1.899)	0.471	—	NS
HTN	0.675 (0.328 to 1.391)	0.287	—	NS
Family history	1.292 (0.571 to 2.920)	0.539	—	NS
Smoking habit	1.374 (0.750 to 2.519)	0.303	—	NS
Statin use	0.851 (0.409 to 1.769)	0.666	—	NS
IIOP	**6.791 (2.946 to 15.655)**	**<0.001**	**4.264 (1.684 to 10.799)**	**0.002**
Glaucoma medication	0.224 (0.081 to 0.621)	0.004	—	NS
TED duration	0.983 (0.903 to 1.070)	0.692	—	NS
GD duration	0.986 (0.972 to 1.001)	0.063	—	NS
Time from GD to TED onset	0.987 (0.972 to 1.001)	0.066	—	NS
Eyelid status				
Palpebral fissure	1.082 (0.933 to 1.256)	0.297	—	NS
MRD1	**1.407 (1.157 to 1.711)**	**0.001**	**1.328 (1.084 to 1.627)**	**0.007**
Proptosis				
<17 mm	Ref		Ref	
17–18 mm	1.791 (0.888 to 3.623)	0.103	0.686 (0.316 to 1.492)	0.157
19–22 mm	**2.188 (1.100 to 4.351)**	**0.026**	1.020 (0.415 to 2.510)	0.965
>22 mm	2.415 (0.768 to 7.588)	0.131	0.601 (0.123 to 2.943)	0.530
Difference in proptosis				
≤2 mm	Ref			
>2 mm	1.246 (0.393 to 3.952)	0.709	—	NS
Gorman score				
1	Ref			
2	**2.908 (1.300 to 6.504)**	**0.009**	—	NS
3	**4.137 (1.955 to 8.756)**	**<0.001**	—	NS
4	**3.625 (1.409 to 9.329)**	**0.008**	—	NS
EOM limitation*	**0.336 (0.187 to 0.605)**	**<0.001**	—	NS
EOM involvement				
No	Ref			
>20° upgaze, >35° abduction	**2.504 (1.223 to 5.127)**	**0.012**	—	NS
≤20° upgaze, ≤35° abduction, diplopia at PP	**4.216 (1.789 to 9.935)**	**0.001**	—	NS
Muscle involvement (radiologic)	**4.087 (2.251 to 7.421)**	**<0.001**	**2.160 (1.076 to 4.336)**	**0.030**
DON	**2.077 (1.377 to 3.134)**	**<0.001**	1.257 (0.774 to 2.040)	0.269
NOSPECS, score	**1.517 (1.330 to 1.731)**	**<0.001**	—	NS
NOSPECS severity				
Mild	Ref		Ref	
Marked	**4.614 (2.618 to 8.132)**	**<0.001**	**2.285 (1.165 to 4.481)**	**0.001**
EUGOGO severity				
Mild	Ref			
Moderate-severe	**5.701 (3.051 to 10.650)**	**<0.001**	—	NS
Sight-threatening	**21.412 (5.841 to 89.494)**	**<0.001**	—	NS
Thyroid function test				
Free T4 (ng/dL)	0.994 (0.855 to 1.157)	0.943	—	NS
T3 (ng/dL)	1.000 (0.997 to 1.003)	0.950	—	NS
TSH (mIU/L)	0.944 (0.856 to 1.042)	0.252	—	NS
TBII (IU/L)	1.002 (0.990 to 1.014)	0.768	—	NS
TSI (SRR%)	**1.001 (1.000 to 1.002)**	**0.048**	1.000 (0.999 to 1.002)	0.329
Lipid profile (mg/dL)				
Total cholesterol	1.000 (0.993 to 1.007)	0.968	—	NS
LDL cholesterol	1.003 (0.996 to 1.010)	0.380	—	NS
HDL cholesterol	0.983 (0.965 to 1.002)	0.084	—	NS
Triglycerides	**1.005 (1.002 to 1.009)**	**0.001**	**1.005 (1.001 to 1.008)**	**0.011**

*EOM limitation was assessed using the Hess or Lancaster test.
NS, no significant in multivariate analysisBMI, body mass index; DM, diabetes mellitus; DON, dysthyroid optic neuropathy; EOM, extraocular muscle; EUGOGO, European Group on Graves' Orbitopathy; GD, Graves' disease; HDL, high-density lipoprotein; HTN, hypertension; IIOP, increased intraocular pressure; LDL, low-density lipoprotein; MRD, margin reflex distance; PP, primary position; TBII, TSH-binding inhibitory immunoglobulin; TED, thyroid eye disease; TSH, thyroid-stimulating hormone; TSI, thyroid-stimulating immunoglobulin.

Table 2 Logistic regression analysis of factors associated with severity in TED patients

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Sex	1.011 (0.993 to 1.030)	0.239	—	NS
Age group (≤50)	1.137 (0.699 to 1.850)	0.605	—	NS
BMI (kg/m^2)	**1.075 (1.003 to 1.152)**	**0.041**	1.047 (0.972 to 1.127)	0.225
Past history				
DM	0.541 (0.217 to 1.347)	0.187	—	NS
HTN	1.094 (0.554 to 2.161)	0.796	—	NS
Family history	1.617 (0.760 to 3.439)	0.212	—	NS
Smoking habit	**2.132 (1.229 to 3.701)**	**0.007**	**1.893 (1.073 to 3.342)**	**0.028**
Statin use	1.226 (0.620 to 2.424)	0.558	—	NS
IIOP	**6.199 (2.566 to 14.973)**	**<0.001**	**5.970 (2.456 to 14.512)**	**<0.001**
Glaucoma medication	**0.156 (0.053 to 0.456)**	**0.001**	—	NS
TED duration	1.056 (0.982 to 1.134)	0.142	—	NS
GD duration	0.999 (0.993 to 1.006)	0.771	—	NS
Time from GD to TED onset	1.000 (0.993 to 1.006)	0.903	—	NS
Thyroid function test				
Free T4 (ng/dL)	1.149 (0.976 to 1.351)	0.094	—	NS
T3 (ng/dL)	1.001 (0.999 to 1.003)	0.471	—	NS
TSH (mIU/L)	1.004 (0.974 to 1.035)	0.787	—	NS
TBII (IU/L)	0.991 (0.978 to 1.006)	0.234	—	NS
TSI (SRR%)	1.001 (1.000 to 1.001)	0.165	—	NS
Lipid profile (mg/dL)				
Total cholesterol	1.004 (0.998 to 1.011)	0.172	—	NS
LDL cholesterol	1.001 (0.995 to 1.007)	0.740	—	NS
HDL cholesterol	0.996 (0.985 to 1.008)	0.530	—	NS
Triglycerides	**1.005 (1.002 to 1.008)**	**0.003**	**1.004 (1.001 to 1.007)**	**0.014**

Severity-related variables (proptosis with inter-eye difference, Gorman diplopia score, EOM limitation and radiologic muscle involvement) were excluded from the primary severity models to prevent overadjustment and collinearity.
NS, no significant in multivariate analysisBMI, body mass index; DM, diabetes mellitus; GD, Graves' disease; HDL, high-density lipoprotein; HTN, hypertension; IIOP, increased intraocular pressure; LDL, low-density lipoprotein; TBII, TSH-binding inhibitory immunoglobulin; TED, thyroid eye disease; TSH, thyroid-stimulating hormone; TSI, thyroid-stimulating immunoglobulin.

Our findings also highlight a potential mechanistic link between elevated TG and the inflammatory pathways in TED. TG, composed of three fatty acids bound to a glycerol backbone, is primarily metabolised through exogenous (diet-derived chylomicrons) and endogenous (hepatic-derived VLDL) pathways. Elevated TG levels can exacerbate inflammatory processes through multiple pathways,

Table 3 Subgroup analysis for predicting activity and severity in non-statin using TED patients using multivariate logistic regression analysis

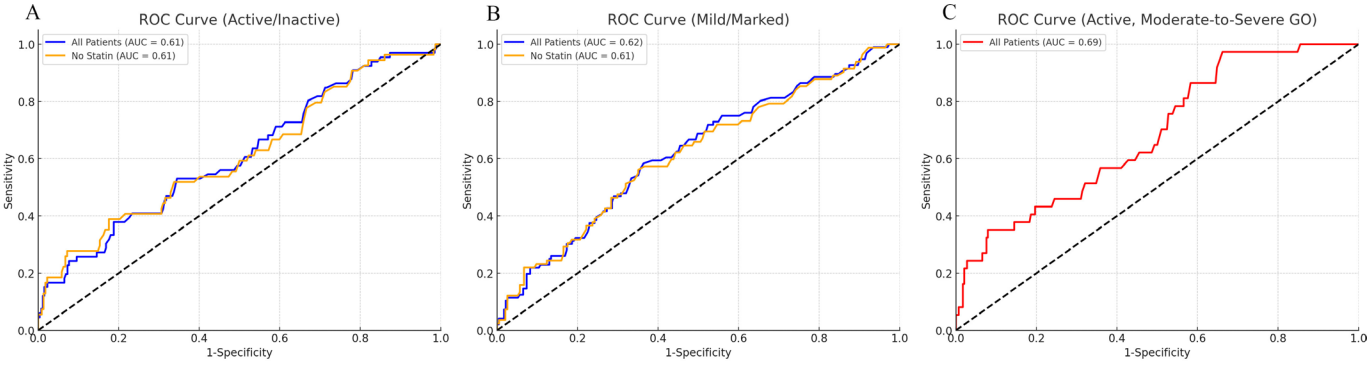
Variables	Activity OR (95% CI)	P value	Severity OR (95% CI)	P value
IIOP	**3.847 (1.376 to 10.751)**	**0.019**	**5.460 (2.097 to 14.214)**	**0.001**
Smoking	1.392 (0.697 to 2.781)	0.348	1.838 (0.955 to 3.396)	0.052
MRD1	**1.447 (1.103 to 1.900)**	**0.008**	—	NS
Muscle involvement (Radiologic)	0.370 (0.164 to 0.834)	0.016	—	NS
NOSPECS severity			N/A	N/A
Mild	Ref			
Marked	2.786 (1.109 to 6.999)	0.029		
Thyroid function test				
TBII (IU/L)	1.004 (0.989 to 1.018)	0.603	—	NS
TSI (SRR%)	1.001 (1.000 to 1.002)	0.139	—	NS
Lipid profile (mg/dL)				
Total cholesterol	**0.979 (0.965 to 0.993)**	**0.003**	—	NS
LDL cholesterol	**1.016 (1.004 to 1.029)**	**0.008**	—	NS
HDL cholesterol	NS	NS	—	NS
Triglycerides	**1.007 (1.002 to 1.011)**	**0.005**	**1.004 (1.001 to 1.007)**	**0.02**

*Of the 330 patients, 50 were on statins and one had an unknown statin usage status, resulting in 279 patients being included in this non-statin subgroup analysis.
N/A, Not applicableDON, dysthyroid optic neuropathy; HDL, high-density lipoprotein; IIOP, increased intraocular pressure; LDL, low-density lipoprotein; MRD, margin reflex distance; NS, no significant in multivariate analysis; TBII, TSH-binding inhibitory immunoglobulin; TED, thyroid eye disease; TSI, thyroid-stimulating immunoglobulin.

Table 4 Subgroup analysis for predicting active, moderate-to-severe TED patients

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Sex				
Woman	Ref		—	NS
Man	**2.343 (1.168 to 4.702)**	**0.019**	0.800 (0.303 to 2.117)	0.654
Age group (≤50)	1.498 (0.747 to 3.005)	0.255	—	NS
BMI (kg/m^2)	**1.117 (1.017 to 1.226)**	**0.021**	—	NS
Past history				
DM	0.854 (0.246 to 2.956)	0.803	—	NS
HTN	0.646 (0.266 to 1.568)	0.334	—	NS
Family history	2.069 (0.605 to 7.075)	0.247	—	NS
Smoking habit	**2.263 (1.030 to 4.976)**	**0.030**	2.004 (0.879 to 4.572)	0.293
Statin use	0.719 (0.293 to 1.764)	0.472	—	NS
IIOP	**11.945 (4.888 to 29.191)**	**<0.001**	**12.064 (4.857 to 29.964)**	**<0.001**
Glaucoma medication	0.819 (0.186 to 3.608)	0.792	—	NS
Thyroid function test				
Free T4 (ng/dL)	1.008 (0.836 to 1.214)	0.936	—	NS
T3 (ng/dL)	0.999 (0.995 to 1.003)	0.630	—	NS
TSH (mIU/L)	0.824 (0.624 to 1.089)	0.174	—	NS
TBII (IU/L)	0.993 (0.970 to 1.017)	0.567	—	NS
TSI (SRR%)	1.001 (1.000 to 1.002)	0.063	—	NS
Lipid profile (mg/dL)				
Total cholesterol	1.001 (0.992 to 1.010)	0.791	—	NS
LDL cholesterol	1.002 (0.993 to 1.011)	0.626	—	NS
HDL cholesterol	**0.968 (0.944 to 0.994)**	**0.015**	0.996 (0.983 to 1.009)	0.533
Triglycerides	**1.006 (1.003 to 1.010)**	**0.001**	**1.006 (1.002 to 1.010)**	**0.003**

NS, no significant in multivariate analysisBMI, body mass index; DM, diabetes mellitus; HDL, high-density lipoprotein; HTN, hypertension; IIOP, increased intraocular pressure; LDL, low-density lipoprotein; TBII, TSH-binding inhibitory immunoglobulin; TED, thyroid eye disease; TSI, thyroid-stimulating immunoglobulin.



		AUC	95% confidence intervals		Se	Sp	P-value	Cutoff value
			Inferior	Superior				
Activity	TG	0.611	0.533	0.689	0.378	0.812	0.005	104
	TG (No-statin)	0.609	0.521	0.697	0.388	0.824	0.001	100.5
Severity	TG	0.621	0.554	0.688	0.583	0.636	0.001	108
	TG (No-statin)	0.615	0.542	0.688	0.561	0.649	0.003	101.5
Active, moderate-to-severe	TG	0.685	0.598	0.771	56.5	59	<0.000	107.5

CAS, clinical activity score; TG, triglyceride; AUC, area under curve

Figure 1 Receiver operating characteristic (ROC) curves for predicting TED activity, severity and active or moderate-to-severe TED using triglyceride (TG) levels.(A) The optimal TG cut-off for predicting TED activity was 104 mg/dL (area under the curve (AUC) = 0.611, p=0.005). (B) For predicting TED severity, the optimal TG cut-off was 108 mg/dL (AUC=0.621, p=0.001). (C) Using combined criteria for predicting active and moderate-to-severe TED, the optimal TG cut-off was 107.5 mg/dL (AUC=0.685, p<0.001). These curves demonstrate the ability of TG levels to serve as a biomarker for TED activity, severity and progression to active or moderate-to-severe TED, potentially guiding earlier intervention.

including adipocyte-induced hypoxia, endoplasmic reticulum stress triggering the NF-κB pathway leading to TNF-α and IL-6 secretion, activation of Toll-like receptor 4 (TLR4) by increased free fatty acids (FFA), oxidative stress via elevated reactive oxygen species (ROS), and activation of the NLRP3 inflammasome complex.[12–14] Notably, these inflammatory mechanisms closely parallel the well-documented inflammatory pathways in TED, suggesting TG might act as an amplifier of inflammation in TED, influencing disease progression, activity and severity.[1 15–17]

From a statistical perspective, our logistic regression analysis showed that even small increases in TG levels (just 1 mg/dL) were associated with a higher likelihood of active or severe TED. Although a 0.5% or 0.4% increase in the risk per mg/dL may seem small, these effects accumulate over time. For example, a rise of 50 mg/dL above baseline could lead to an approximately 20–28% higher risk of developing active or severe TED.[18 19] We also examined a simple threshold of 150 mg/dL. Patients with TG levels above this cut-off had much higher odds of active and severe TED.

Notably, total and LDL cholesterol showed limited association with TED activity and severity in our cohort, diverging from earlier studies linking higher LDL and total cholesterol levels to TED presence and activity.[3] However, a subgroup analysis excluding statin users revealed that total and LDL cholesterol were associated with TED activity but not severity, a finding consistent with the study from Sabini *et al*,[3] whereas TG remained significant for both outcomes. This suggests that statin therapy may mask the role of cholesterol in TED by lowering LDL levels while having a more modest effect on TG.[2 20]

Statins modulate lipid levels and immune activity via mechanisms involving the mevalonate pathway. Beyond their lipid-lowering effects, they may inhibit inflammatory cytokine production, TGF-β-induced fibroblast activation and myofibroblast differentiation in orbital tissues.[21] These immunomodulatory properties may explain their protective effects, where statin use reduced GO risk by up to 80% in patients with Graves' disease.[8] However, our data reveal that TG—unaffected by statin status—remains powerfully linked to both TED activity and severity, pointing to a distinct immunometabolic mechanism beyond cholesterol-driven pathways.[22 23] These findings highlight the unique role of TG in TED pathophysiology, distinct from cholesterol-driven pathways.[24 25]

Notably, TC had an OR below one for predicting active TED, which contrasts with earlier studies that linked high TC with disease onset or activity. Methodological discrepancies may account for these discrepancies. For instance, Sabini *et al*[3] analysed a broader population of patients with Graves' disease, including those with and without TED, who were undergoing RAI treatment. In contrast, our cohort exclusively included patients with confirmed TED, encompassed a wider range of Graves' durations and used more comprehensive multivariable models. Furthermore, TC is a composite measure of various lipid fractions, including very-low-density lipoprotein cholesterol (VLDL-C), LDL-C and HDL-C, which could reduce its specificity. As such, TG and LDL-C can provide more precise insights into immunometabolic shifts, whereas TC may fail to capture nuanced disease-specific inflammation.[26–28]

In addition to lipid considerations, we identified other important correlates, including elevated IOP, which was strongly related to both TED activity and severity. This suggests that orbital inflammation may impede ocular venous outflow or directly affect the trabecular meshwork, thereby increasing IOP.[29] Similarly, a higher MRD1 was linked to active TED, reflecting more pronounced eyelid retraction.[30] Smoking, a well-established risk factor in Graves orbitopathy, also maintained its significance for increased severity, consistent with prior literature demonstrating that smoking exacerbates autoimmune and vascular components in TED.[31] Immunologically, TSI showed a stronger connection to TED outcomes than did TBII, reinforcing previous suggestions that TSI-driven TSH receptor activation in orbital fibroblasts escalates local inflammation and tissue expansion.[32–34]

Nevertheless, several limitations should be considered when interpreting our findings. First, the retrospective design limited control of confounding. Although lipid measurements followed routine fasting protocols (overnight fast ≥8 hours, water only) per standard Korean clinical practice and analyses were restricted to fasting lipid profiles, we did not systematically capture detailed dietary habits or recent alcohol intake that may influence baseline TG levels. Second, TG was assessed at a single time point, precluding evaluation of within-person variability and temporal concordance with disease activity. Third, limiting the study to a Korean population may restrict the generalisability of these cut-offs to other ethnic groups with different genetic or dietary backgrounds. Finally, while plausible immunometabolic mechanisms linking TG to TED were proposed, direct experimental evidence is still lacking. Future prospective, multicentre trials are needed to clarify causal relationships and determine whether TG modulation can alter the course of TED.

In conclusion, elevated TG levels were independently associated with activity and severity in TED, expanding the pathophysiological framework beyond thyroid hormone and LDL-centric paradigms. By delineating clear TG cut-offs for disease stratification, we provide clinicians with actionable benchmarks that persist regardless of statin status. Moreover, the paradoxical TG elevation in a nominally hyperthyroid context underscores the complexity of TED's immunometabolic axis, necessitating a reevaluation of standard lipid thresholds. Future investigations into whether TG-lowering interventions can mitigate TED activity could reveal new therapeutic pathways that merge metabolic regulation with immunomodulation. Ultimately, such an approach may help reduce disease morbidity, improve patients' quality of life and strengthen our understanding of how metabolic and autoimmune factors converge to drive orbital pathology in TED.

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