Prognostic Factors of Restrictive Myopathy in Thyroid Eye Disease

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Abstract

To investigate the prognostic factors of extraocular muscle restriction in patients with thyroid eye disease (TED), sixty-five patients with TED and restrictive myopathy were evaluated. Demographics, clinical activity score (CAS), smoking status, thyroid disease status, thyroid hormone status, thyroid autoantibody status, orbital computed tomography (CT) scan at initial presentation, and treatment regimens were assessed. The movements of the most severely affected extraocular muscles were categorized into five grades. The patients were divided into the improved and the not-improved group based on the improvement in the limitation of the extraocular muscle excursion (LOM) throughout the follow-up, and the groups were compared using clinical factors. The mean LOM significantly improved from 2.3 ± 1.1 to 1.7 ± 1.2 after 1 year of follow-up. The excursion of the most restricted muscle improved in 32 patients but not in 33 patients during the follow-up. The initial concentration of the thyroid-stimulating antibody (TSAb) was significantly lower in the improved than in the not-improved group. Age, sex, smoking status, CAS, thyroid status, and muscle thickness on the CT scan did not significantly differ in the groups. This study showed that the initial concentration of TSAb is a factor affecting the recovery of restrictive myopathy.

Introduction

Thyroid eye disease (TED) is a condition characterized by the inflammation of all periocular tissues, and it may result in proptosis, eyelid retraction, strabismus, or compressive optic neuropathy. The degree of clinical manifestations varies from asymptomatic or mild inflammation of the eye and eyelid to severe visual dysfunction. In addition, the clinical course of TED is occasionally chronic and relapsing; therefore, long-term care and follow-up are required.

During the active phase of TED in general, orbital fibroblasts located in the orbital fat and rectus muscles, are activated by autoactivated T-cells and autoantibodies. When activated, they interact with autoreactive T-cells and differentiate into myofibroblasts or mature adipocytes, depending on their cell subtypes and types of cytokines. Both myofibroblasts and adipocytes can produce hyaluronan, leading to edematous swelling of soft tissues of the orbit. Proinflammatory T-helper type 1 cytokines are predominant during this phase; an inflammatory reaction is also dominant during this phase.[1] Therefore, immunosuppressive measures, including the administration of systemic steroids, immunosuppressants, and low-dose radiotherapy, have been used to suppress and shorten the active phase. [2,3] During the chronic fibrotic phase, T-helper type 2 cytokines are predominant. They induce fibrotic changes in orbital soft tissues and rectus muscles.[4] Rehabilitation surgeries can be considered to correct structural changes resulting from the disease process.

Restrictive myopathy of the extraocular muscle occurs in approximately 20% of patients with TED.[5] It can be caused by rectus muscle swelling during an active phase and by fibrotic changes of the rectus muscles during a chronic phase. The most distressing symptom caused by restrictive myopathy is diplopia. It not only worsens the quality of life, but also causes work disability.[6] According to Nunery's

classification of extraocular movements, patients with TED having normal ocular motility and predominant lipogenic change were classified as type I, whereas patients with significant restrictive myopathy and diplopia within 20° of the primary position were classified as type II.[7] The type II disease, which also be called TED with significant restrictive myopathy, showed a higher peak age of onset, lower female-to-male ratio, and higher smoking prevalence than the type I disease. The clinical outcome was worse in patients with type II disease with a high incidence of compressive optic neuropathy and a poorer outcome after orbital decompression[7,8] Although the epidemiology and natural history of type II disease have been well elucidated, the clinical course of restrictive myopathy in patients with TED undergoing immunosuppressive treatment has not been well-described. Clinical factors affecting the restoration of the muscle and the strabismus angle during long-term follow-up have not been established.

In this study, we analyzed the clinical and laboratory features to identify the prognostic factors of TED-associated restrictive myopathy.

Methods

The medical records of patients who were diagnosed with TED and had diplopia within 20 degrees from the primary position at the Samsung Medical Center between January 2011 and March 2016 were retrospectively reviewed. The study adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of Samsung Medical Center, Seoul, South Korea (IRB number 2017-02-090). The board waived the need for informed consent based on the retrospective design of this study. All the enrolled patients were ethnically Korean. The patients with diplopia for more than 6 months before presentation or those who had undergone treatment for TED were excluded. The patients with compressive optic neuropathy or those who had been followed-up less than 6 months were also excluded.

The patient data, including demographics, thyroid status (triiodothyronine (T3), free thyroxine (fT4), and thyroid-stimulating hormone (TSH) levels), thyroid autoantibody status (thyrotropin receptor antibody (TSHR-Ab) and thyroid-stimulating antibody (TSAb) levels), and orbital computed tomography (CT) scans at the time of presentation, clinical activity score (CAS), limitation of extraocular muscle excursion (LOM), and diplopia grades and clinical features at the initial visit and 3, 6, 9, and 12 months of follow-up were assessed. The patients were divided into the improved or not-improved groups, based on the improvement of LOM of the most severely restricted rectus muscle at the last follow-up.

The TSHR-Ab titer was measured using a radioreceptor assay and the TRAK human kit (Brahms GmbH, Hennigsdorf, Germany). The TSAb concentrations were measured using the Thyretain™ (Diagnostic Hybrids Inc., Athens, OH, USA) bioreporter assay, according to the manufacturer's instructions.

The clinical findings of LOM, diplopia grade, and CAS were evaluated by a single oculoplastic specialist (KIW). The range of CAS was 0–7 points, based on the presence of seven signs of orbital inflammation: conjunctival injection, chemosis, eyelid redness, eyelid swelling, pain on eye movement, and retrobulbar

pain.[3] The LOM was classified into five grades: grade 0, no restriction of muscle excursion; grade 1, mild restriction of muscle excursion (limitation of motion at extreme gaze); grade 2, moderate restriction (evident restriction, less than half of normal range); grade 3, severe restriction (evident restriction, more than half of normal range); grade 4, complete restriction (fixation of the globe). In addition, diplopia was also categorized using the Gorman grading: grade 0, no diplopia, grade 1, intermittent diplopia; grade 2, inconstant diplopia; grade 3, constant diplopia.[9]

Patients who presented with TED and normal thyroid function without any history of thyroid dysfunction were allocated to the euthyroid orbitopathy group in this study. The diagnostic criteria for this group included the elevation the concentration TSHR-Ab and/or TSAb, and clinical ocular features related to TED.

The maximum rectus muscle diameters were measured on the orbital CT scan by two investigators (JHC and HN). The maximum diameters of the superior and inferior rectus muscles were measured using a coronal scan, and those of the lateral and medial rectus muscles were measured using an axial scan.[10] The muscle was categorized as “enlarged” when the maximum diameter of the rectus muscle was higher than two standard deviations from the mean of the normal population in *Orgen & Ariyurek*’s study.[11]

The treatment modalities for the patients were not controlled and they underwent various treatments for TED: daily oral prednisolone (1 mg/kg/day) with tapering for 2–3 months, weekly intravenous (IV) methylprednisolone (500 mg/week for six times followed by 250 mg/week for six times), and/or orbital radiotherapy of 20 Gy. A group of patients underwent conservative treatment, and they were classified as the conservative group.

The Chi-squared test or Fisher’s exact test was used to analyze the categorical variables, such as age group, gender, smoking status, and treatment method. The student’s t-test or Mann-Whitney test was used to compare the numerical variables of the improved and not-improved groups. To investigate the factors associated with the prognosis of restrictive myopathy associated with TED, univariate and multivariate logistic regression analyses were performed. The parameters with a P-value of less than 0.2 in the univariate analysis, age, and sex ratio were included for the multivariate logistic analysis. To evaluate interobserver (measured by JHC and HN) reproducibility for the measurement of the maximum rectus muscle diameters, the intraclass correlation coefficients (ICCs) were calculated. All statistical analyses were performed using R software version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria). A *P*-value of < 0.05 was considered statistically significant.

Results

Of the 652 patients diagnosed with TED during the study period, 65 met the inclusion criteria for restrictive myopathy. Their mean age was 54.0 ± 10.0 (range, 29–76) years. For these 65 patients, the female-to-male ratio was 0.85:1, whereas it was 3.88:1 for all 652 patients with TED. The mean duration

of diplopia before presentation was 4.3 ± 3.8 months. Regarding smoking status, 48 patients (73.8%) had never smoked, 3 (4.6%) were past smokers, and 14 (21.6%) were current smokers during the first visit.

Thyroid status at presentation included euthyroid in 47 patients (72.3%), hypothyroid in 5 patients (7.7%), and hyperthyroid in 13 patients (20.0%).

The following treatments were administered: IV methylprednisolone in 52 (80.0%) cases, oral prednisolone in 23 (35.4%) cases, and orbital radiotherapy in 23 (35.4%) cases. Seven patients (10.8%) had to undergo strabismus surgery after the stabilization of the clinical activity and degree of deviation angle. The mean follow-up duration was 11.4 ± 2.4 (range, 6–15) months. (Table 1)

Table 1
Comparisons of demographic and clinical characteristics in the improved and not-improved groups at initial presentation

Characteristics	All patients	Improved (N = 32)	Not-improved (N = 33)	*P*-value
N (%)	65 (100%)	32 (49.2%)	33 (50.8%)	NA
Mean age, y (SD)	54.0 (10.0)	54.6 (8.1)	53.3 (8.1)	0.62†
Age group, n (%)				
≤ 50 y	18 (27.7 %)	7 (21.9%)	11 (33.3%)	0.30‡
> 50 y	47 (72.3 %)	25 (78.1%)	22 (66.7%)	
Sex, M : F	35 : 30	17 : 15	18 : 15	0.91‡
Mean symptom onset, mo (SD)	4.3 (3.8)	3.6 (2.0)	4.9 (4.8)	0.16†
Smoking status, n (%)				
- Non smoker	48 (73.8 %)	21 (65.6%)	27 (81.8%)	0.37‡
- Past smoker	3 (4.6 %)	2 (6.3%)	1 (3.0%)	
- Current smoker	14 (21.6 %)	9 (28.1%)	5 (15.2%)	
Mean LOM (SD)	2.3 (1.1)	2.5 (1.0)	2.2 (1.1)	0.25†
Diplopia grade, N (%)				
Grade 0	0 (0.0 %)	0 (0.0%)	0 (0.0%)	0.59‡
Grade 1	27 (41.5 %)	15 (46.9%)	12 (36.4%)	
Grade 2	13 (20.0 %)	5 (15.6%)	8 (24.2%)	
Grade 3	25 (38.5 %)	12 (37.5%)	13 (39.4%)	
Mean CAS (SD)	2.9 (1.7)	3.0 (1.9)	2.7 (1.6)	0.55†
Mean thyroid hormone, autoAb				

n: number, SD: standard deviation, y: year, Mo: month, M: male, F: female, LOM: limitation of muscle excursion, CAS: clinical activity score, TSH : thyroid stimulating hormone, T3: triiodothyronine, fT4: free thyroxine, TSAb: thyroid-stimulating antibody, TSHR-Ab: thyroid stimulating hormone receptor antibody, IV methylPD: intravenous methylprednisolone, NA: not available,

†Student's t-test or Mann–Whitney test, ‡Chi-square test or Fisher's exact test

*If the patient underwent multiple treatment modalities, all modalities were included.

Characteristics	All patients	Improved (N = 32)	Not-improved (N = 33)	*P*-value
TSH, μIU/mL (SD)	2.6 (6.5)	2.7 (7.4)	2.5 (5.6)	0.89†
T3, ng/dL (SD)	125.7 (39.8)	121.2 (40.6)	129.5 (39.6)	0.49†
fT4, ng/dL (SD)	1.5 (1.2)	1.7 (1.6)	1.3 (0.6)	0.18†
TSAb, % (SD)	288.6 (159.9)	229.3 (114.1)	345.0 (178.6)	0.02†
TSHR-Ab, IU/L (SD)	24.5 (43.0)	24.3 (54.7)	24.7 (29.9)	0.98†
Presence of thyroidopathy, n (%)				
euthyroid orbitopathy	10 (15.4 %)	5 (15.6%)	5 (15.2%)	1.00‡
Orbitopathy with thyroidopathy	55 (84.6 %)	27 (84.4%)	28 (84.8%)	
Thyroid status at visit, n (%)				
Euthyroid	47 (72.3 %)	25 (78.1%)	22 (66.7%)	0.45‡
Hypothyroid	5 (7.7 %)	1 (3.1%)	4(12.1%)	
Hyperthyroid	13 (20.0 %)	6 (18.8%)	7(21.2%)	
Treatment, n (%)*				
Conservative	4 (6.2 %)	2 (6.3%)	2 (6.1%)	1.00‡
Oral prednisolone	22 (33.8 %)	11 (34.4%)	11 (33.3%)	0.27‡
IV methylPD	52 (80.0 %)	27 (84.4%)	23 (69.7%)	0.16‡
Orbital radiotherapy	23 (35.4 %)	11 (34.4%)	12 (36.4%)	0.87‡
Strabismus operation	7 (10.8 %)	0 (0.0%)	7 (21.2%)	NA

n: number, SD: standard deviation, y: year, Mo: month, M: male, F: female, LOM: limitation of muscle excursion, CAS: clinical activity score, TSH : thyroid stimulating hormone, T3: triiodothyronine, fT4: free thyroxine, TSAb: thyroid-stimulating antibody, TSHR-Ab: thyroid stimulating hormone receptor antibody, IV methylPD: intravenous methylprednisolone, NA: not available,

†Student's t-test or Mann–Whitney test, ‡Chi-square test or Fisher's exact test

*If the patient underwent multiple treatment modalities, all modalities were included.

After 1 year of treatment and follow-up, the mean CAS value improved from 2.9 ± 1.7 to 1.2 ± 1.5 ($P < 0.01$). The mean LOM also improved from 2.3 ± 1.1 to 1.7 ± 1.2, which was statistically significant ($P <$

0.01). The mean diplopia grade decreased from 2.0 ± 0.9 to 1.6 ± 1.1, but it was not significant (P = 0.07). The mean fT4 and TSH concentrations did not change significantly (P = 0.55 and 1.00, respectively). The mean TSAb concentration decreased from 288.8 ± 157.9% to 256.2 ± 103.5%, but it was not statistically significant (P = 0.56).

Although the average value of LOM decreased throughout the follow-up period, there was a group of patients (33 patients, 50.8%) who showed no improvement in LOM. The clinical factors of the improved (32 patients, 49.2%) and not-improved (33 patients, 50.8%) groups were compared to identify the factors affecting the improvement in LOM. There were no significant differences in the demographics, smoking status, mean CAS, thyroid status at visit, and presence of thyroidopathy. The time to symptom onset was shorter in the improved group, but this was not statistically significant (P = 0.16). The laboratory findings of the improved and non-improved groups were compared. The mean fT4 concentration was slightly lower in the not-improved group (1.7 ± 1.6 in the improved group and 1.3 ± 0.6 in the not-improved group), but the difference was not statistically significant (P = 0.18). The mean initial TSAb concentration was 229.3 ± 114.1% in the improved group and 345.0 ± 178.6 in the not-improved group; the not-improved group showed a 66.4% higher initial TSAb concentration than the improved group. The initial TSAb concentration was significantly higher in the not-improved group than in the improved group (P = 0.02). The analysis of the treatment modalities showed that there was no significant difference between the treatment regimens used in the two groups. The proportion of patients receiving IV methylprednisolone treatment was slightly higher (84.4%) in the improved group than in the not-improved group (69.7%); however, the difference was not statistically significant (P = 0.16).

The extraocular rectus muscle diameter analysis using the orbital CT scan showed that the most frequently involved muscle was the inferior recuts muscle (42/130), followed by the medial rectus muscle (38/130) (Table 2). There was no significant difference between the initial mean maximum diameters of the rectus muscles in the improved and not-improved groups (Fig. 1). The mean number of enlarged rectus muscles was 2.5 ± 1.6 in the improved group and 2.7 ± 1.9 in the not-improved group (P = 0.62). The mean total maximum diameter of the 8 rectus muscles was 35.2 ± 7.0 mm in the improved group and 35.0 ± 7.8 mm in the not-improved group (P = 0.93). The orbital CT analysis showed that the intraobserver and interobserver intraclass correlation coefficient (ICC) showed good agreement of the assessments of the maximum diameters of the rectus muscles. The intraobserver ICC ranged from 0.91 to 0.95, and the interobserver ICC ranged from 0.90 to 0.92.

Table 2
Mean maximum EOM, diplopia grade, and number of involved muscles at initial presentation

Characteristics	OD	OS
The mean maximum rectus muscle diameter, mm (SD)		
SR	4.1 (1.5)	4.3 (1.7)
IR	5.5 (2.1)	5.1 (1.7)
LR	4.0 (1.4)	3.8 (1.0)
MR	4.3 (1.6)	4.2 (1.6)
Number of orbits with enlarged EOM		
SR	5 (7.7%)	8 (12.3%)
IR	24 (36.9%)	18 (27.7%)
LR	13 (20.0%)	5 (7.7%)
MR	19 (29.2%)	19 (29.2%)
OD, oculus dexter; OS, oculus sinister; SD, standard deviation; EOM, extraocular muscle;		
SR, superior rectus muscle; IR, inferior rectus muscle; LR, lateral rectus muscle; MR, medial rectus muscle		

In the univariate logistic regression analysis, a higher initial TSAb concentration was associated with poor prognosis in the improvement of LOM throughout the follow-up period ($P = 0.03$). The multivariate logistic regression analysis showed that higher TSAb levels were also associated with poor recovery of LOM throughout the follow-up period ($P = 0.04$). The fT4 concentration tended to be lower in the not-improved group, but the difference was not statistically significant ($P = 0.08$) (Table 3).

Table 3
Logistic regression analysis of the pre-treatment variables associated with poor prognosis of extraocular muscle movement limitation in the restrictive myopathy associated with thyroid eye disease

	Univariate analysis			Multivariate analysis		
Parameters	OR	95% CI	*P*	OR	95% CI	*P**
Age, y	0.99	0.94–1.04	0.614	0.91	0.81–1.03	0.138
Sex, M : F	0.94	0.36–2.51	0.909	0.55	0.30–9.94	0.546
Disease onset, mo	1.11	0.95–1.31	0.191	1.01	0.74–1.37	0.953
CAS	0.91	0.68–1.22	0.540			
Diplopia grade	1.12	0.66–1.90	0.681			
TSH, μIU/mL	0.99	0.91–1.08	0.89			
T3, ng/dL	1.01	0.99–1.02	0.483			
fT4, ng/dL	0.61	0.25–1.45	0.259	0.19	0.03–1.18	0.075
TSAb, 10%	1.06	1.01–1.11	**0.028**	1.09	1.00–1.18	**0.044**
TSHR-Ab, 10 IU/L	1.00	0.89–1.14	0.975			
Treatment, n						
Conservative	0.97	0.13–7.32	0.975			
Oral PD	0.96	0.34–2.67	0.929			
IV methylPD	0.43	0.13–1.43	0.166	0.80	0.11–5.81	0.827
Radiotherapy	1.09	0.39–3.02	0.867			

y: year, mo: month, M: male, F: female, CAS: clinical activity score, TSH : thyroid stimulating hormone, T3: triiodothyronine, fT4: free thyroxine, TSAb: thyroid-stimulating antibody, TSHR-Ab: thyroid stimulating hormone receptor antibody, n: number, IV methylPD: intravenous methylprednisolone

CI: confidence interval, OR: odds ratio

* Variables with $P < 0.20$ in the univariate analysis, age, and sex were included in the multivariate analysis.

For the longitudinal analysis, the mean LOM at initial presentation did not differ in the improved and the not-improved groups; however, the difference became obvious after 9 months of follow-up. The mean diplopia grade began to improve significantly in the improved group after 3 months of follow-up (Table 4). The mean TSAb at 12 months was lower in the improved group, but the difference was not significant ($P = 0.13$). The mean CAS, fT4, TSH, and TSHR-Ab concentrations were not significantly different in the two groups during follow-up.

Table 4
Comparisons of longitudinal changes in the limitation of extraocular movement, diplopia, clinical activity score, and thyroid status in the improved and not-improved groups

		Pre-treatment	3 months	6 months	9 months	12 months
LOM (SD)	Improved	2.5 (1.0)	2.2 (1.0)	1.9 (1.1)	1.2 (1.1)†	1.2 (1.0)†
	Not-improved	2.2 (1.1)	2.4 (0.9)	2.2 (1.1)	2.4 (1.0)†	2.3 (1.1)†
Diplopia grade (SD)	Improved	1.9 (0.9)	1.3 (0.8)†	1.3 (0.7)†	1.3 (1.0)†	1.1 (1.0)†
	Not-improved	2.0 (0.9)	2.2 (0.9)†	2.1 (0.9)†	2.2 (0.8)†	2.1 (1.0)†
CAS (SD)	Improved	3.0 (1.9)	1.3 (1.6)	1.5 (1.5)	1.2 (1.2)	1.4 (1.7)
	Not-improved	2.7 (1.6)	1.6 (1.4)	1.7 (1.2)	1.7 (1.5)	1.1 (1.4)
TSH, μIU/mL (SD)	Improved	2.7 (7.4)	2.7 (7.0)	1.8 (3.0)	0.6 (1.0)	3.3 (4.4)
	Not-improved	2.5 (5.6)	5.7 (11.6)	4.3 (7.0)	0.6 (0.9)	3.6 (5.9)
T3, ng/dL (SD)	Improved	121.2 (40.6)	146.1 (70.3)	106.6 (22.8)	111.6 (28.5)	97.1 (19.4)†
	Not-improved	129.5 (39.6)	111.1 (27.7)	120.0 (32.6)	130.8 (38.2)	127.1 (30.2)†
fT4, ng/dL (SD)	Improved	1.7 (1.6)	1.3 (0.3)	1.3 (0.3)	1.3 (0.3)	1.3 (0.6)
	Not-improved	1.3 (0.6)	1.1 (0.2)	1.1 (0.2)	2.3 (1.9)	1.5 (0.7)
TSAb, % (SD)	Improved	229.3 (114.1)	NA	NA	NA	162.5 (116.6)
	Not-improved	345.0 (178.6)	NA	NA	NA	266.4 (118.2)
TSHR-Ab, IU/L (SD)	Improved	24.3 (54.7)	14.6 (22.9)	6.5 (12.5)	9.6 (12.8)	3.2 (3.1)
	Not-improved	24.7 (29.9)	15.3 (26.9)	4.7 (5.3)	2.1 (2.0)	7.0 (11.6)

LOM: limitation of muscle excursion, CAS: clinical activity score, TSH : thyroid stimulating hormone, T3: triiodothyronine, fT4: free thyroxine, TSAb: thyroid-stimulating antibody, TSHR-Ab: thyroid stimulating hormone receptor antibody

†: the difference between the two groups was significant ($P < 0.05$, Student's t-test or Mann Whitney U-test)

Discussion

In this study, the mean LOM in patients with TED significantly improved throughout the follow-up after treatment; however, a group of patients showed no improvement in LOM. A higher initial titer of TSAb was associated with a poor prognosis for the recovery of LOM. The mean initial TSAb concentration of the not-improved group was 66.4% higher than that of the improved group. In addition, the diplopia grade at 1 year after treatment was significantly lower in the improved group than in the not-improved group, while the pre-treatment diplopia grade, pre-treatment LOM, and mean rectus muscle thickness did not significantly differ in the two groups.

The mean age at the initial visit was 54.6 years in male patients and 53.3 years in female patients in this study. It was much higher than the mean age (42.8 years in men and 41.7 years in women) of Korean patients with dysthyroid TED from the multicentral epidemiological study involving patients in 24 centers.[12] This was consistent with other studies that reported a significantly higher mean age in patients with restrictive myopathy.[7,13] The female-to-male ratio was 0.85:1 for restrictive myopathy in this study. This contrasted with the female-to-male ratio of all 652 patients with TED during the study period (3.88:1). In Woo et al.'s Korean multicenter study, the female-to-male ratio (3.9:1) was compatible with that of all the 652 patients. The female-to-male ratio of patients with restrictive myopathy has been reported to be lower (1-1.74:1) than that of all patients with TED. [14-16]

According to several studies, smoking is strongly associated with the development of TED and unfavorable clinical outcomes. Current smokers had more than twice the odds ratio or relative risk of TED development than those who had never smoked or past smokers. Current smokers also showed a higher incidence of proptosis, diplopia, and total ophthalmopathy, but no differences in clinical manifestations and clinical outcomes in some reports.[17] In our study, the smoking factor was not related to the prognosis of restrictive myopathy, which contrasted with other studies reporting worse ocular motility prognosis in smokers.[18,19] The limitations of our study were the small sample size and the inclusion of only the initial smoking status.

Of note, the proportion of patients with euthyroid orbitopathy was 15.4%. This was higher than that of other epidemiologic studies conducted more than a decade ago: 5.0–7.3% of euthyroid orbitopathy patients with TED of all the stages.[20-22] According to a study by Yoon et al. the proportion of euthyroid orbitopathy was 14.7%, and euthyroid orbitopathy was known to take a milder form of TED, although the prevalence of restrictive myopathy was not significantly different from that of hyperthyroid TED.[23] Euthyroid orbitopathy was diagnosed when typical clinical signs of TED and high autoantibody titers of TSHR-Ab or TSAb were observed without any evidence of preceded dysthyroid disease. The higher proportion of euthyroid orbitopathy in our study may be related to the recent trend of routine autoantibody testing for the diagnosis of TED. Further studies are needed to establish the relationship between euthyroid orbitopathy and restrictive myopathy.

Muscle thickness is known to be related to the degree of extraocular muscle motility restriction in patients with active-phase TED.[10] The correlation between the cross-sectional area of the vertical rectus muscles in the CT scan and the vertical angle of deviation of the eye was previously reported.[24] However, in search of prognostic factors of restrictive myopathy on the pre-treatment CT scans, we could not find any significant factors. The type and number of involved muscles and the muscle thickness at initial presentation did not affect the recovery of the limitation of muscle movement. Since initial pre-treatment CT scans were only used in this study, imaging studies compatible with the 1-year clinical status could not be evaluated in this study.

Since all the patients in this study met the moderate-to-severe TED classification by EUGOGO, the treatment recommendations of EUGOGO were adopted.[3] Eighty percent of patients received IV methylprednisolone as a first-line treatment after a thorough discussion of the treatment course and side effects. Patients who could not follow the treatment schedule took oral steroid treatment as the first treatment. Orbital radiotherapy and oral prednisolone treatments were administered to 35.4% and 33.8% of the patients, respectively (Table 1). The proportion of patients who received IV methylprednisolone was higher in the improved group, but the difference was not significant (P = 0.16). Although there are debates on the efficacy of orbital radiotherapy for TED, it has been accepted as an effective treatment option for restrictive myopathy related to TED.[3] However, in our study, the proportion of patients who underwent radiotherapy in the improved and not-improved groups were not different. A limitation of our study is that a few patients received radiation therapy, and there may have been a selection bias for treatment decisions.

During the longitudinal analysis, the treatment outcomes were evaluated chronologically (Table 4). Notably, the LOM of the improved group did not show any improvement until after 9 months of follow-up, whereas the CAS in both groups decreased after 3 months of follow-up. This implies that the restoration of LOM takes time after treatment even though the inflammatory signs decrease during the early post-treatment period. Therefore, we need to follow-up on patients with restrictive myopathy for a long time after immunosuppressive treatment to determine the effect of treatment. Interestingly, the diplopia grade decreased in the improved group after 3 months of follow-up: quality of vision can improve from the early post-treatment period even if LOM does not recover at all.

Some studies have categorized the severe TED subtypes and demonstrated the association of TSHR-Ab and TSAb with the severity of restrictive myopathy in TED.[13,25] Our study is worthwhile because it focused solely on the prognosis of restrictive myopathy. A high titer of TSAb may be predictive of a poor prognosis for restrictive myopathy, as our study shows; moreover, if the titer of TSAb does not diminish through the follow-up, it may also contribute to a poor prognosis in restrictive myopathy. Therefore, checking the concentration of TSAb during follow-up may be important for prognosticating restrictive myopathy.[26] Our study is worthwhile because it focused solely on the prognosis of restrictive myopathy. A high titer of TSAb may be predictive of a poor prognosis for restrictive myopathy, as our study shows; moreover, if the titer of TSAb does not diminish through the follow-up, it may also contribute to a poor

prognosis in restrictive myopathy. Therefore, checking the concentration of TSAb during follow-up may be important for prognosticating restrictive myopathy.

TSHR-Ab, including TSAb and TSHR binding inhibitory immunoglobulins and other autoantibodies, activate helper T-cells, which, in turn, activate B-cells to express autoantibodies or become autoactivated T-cells.[27,28] High TSAb concentrations are related to severe inflammatory responses; therefore, conventional systemic steroid treatment or radiotherapy may not be sufficient to control the status with high pre-treatment TSAb concentrations. Subsequent studies focusing on the treatment response of patients with high TSAb restrictive myopathy using other immunosuppressants and novel biologic agents are required.[3,29]

This study was designed as a retrospective study and performed at a single tertiary care center in Korea. The limitations of this study are referral bias, uncontrolled treatment options, and the small sample. Further multicenter studies with larger sample sizes may be required to confirm our findings.

In conclusion, patients with TED and restrictive myopathy who had higher pre-treatment TSAb titers showed poorer responses to treatment. Pre-treatment and regular TSAb follow-up may be beneficial for predicting the prognosis of restrictive myopathy in patients with TED.

Declarations

Competing interests:

The authors have no proprietary or commercial interest in any material discussed in this article.

Author contributions:

K.I.W and J.H.C conceived and designed the study. J.H.C wrote the manuscript. J.H.C and H.N performed the data collection, J.H.C and K.I.W analyzed the data. K.I.W and Y.D.K critically revised the manuscript. All authors approved the final version of the manuscript.

References

1. Shan, S. J. & Douglas, R. S. The pathophysiology of thyroid eye disease. *J Neuroophthalmol* **34**, 177-185, http://doi.org/10.1097/WNO.0000000000000132 (2014).
2. Bhatti, M. T. & Dutton, J. J. Thyroid eye disease: therapy in the active phase. *J Neuroophthalmol* **34**, 186-197, http://doi.org/10.1097/wno.0000000000000128 (2014).
3. Bartalena, L. *et al.* The 2016 European Thyroid Association/European Group on Graves' Orbitopathy Guidelines for the Management of Graves' Orbitopathy. *Eur Thyroid J* **5**, 9-26, http://doi.org/10.1159/000443828 (2016).

4. Aniszewski, J. P., Valyasevi, R. W. & Bahn, R. S. Relationship between disease duration and predominant orbital T cell subset in Graves' ophthalmopathy. *The Journal of clinical endocrinology and metabolism* **85**, 776-780, http://doi.org/10.1210/jcem.85.2.6333 (2000).
5. Hiromatsu, Y., Eguchi, H., Tani, J., Kasaoka, M. & Teshima, Y. Graves' ophthalmopathy: epidemiology and natural history. *Internal medicine (Tokyo, Japan)* **53**, 353-360 (2014).
6. Ponto, K. A. *et al.* Public health relevance of Graves' orbitopathy. *The Journal of clinical endocrinology and metabolism* **98**, 145-152, http://doi.org/10.1210/jc.2012-3119 (2013).
7. Nunery, W. R. Ophthalmic Graves' disease : a dual theory of pathogenesis. *Ophthalmol Clin North Am* **4**, 73-87 (1991).
8. Nunery, W. R., Nunery, C. W., Martin, R. T., Truong, T. V. & Osborn, D. R. The risk of diplopia following orbital floor and medial wall decompression in subtypes of ophthalmic Graves' disease. *Ophthalmic Plast Reconstr Surg* **13**, 153-160, http://doi.org/10.1097/00002341-199709000-00001 (1997).
9. Gorman, C. A. The measurement of change in Graves' ophthalmopathy. *Thyroid : official journal of the American Thyroid Association* **8**, 539-543, http://doi.org/10.1089/thy.1998.8.539 (1998).
10. Dagi, L. R., Zoumalan, C. I., Konrad, H., Trokel, S. L. & Kazim, M. Correlation between extraocular muscle size and motility restriction in thyroid eye disease. *Ophthalmic plastic and reconstructive surgery* **27**, 102-110, http://doi.org/10.1097/IOP.0b013e3181e9a063 (2011).
11. Ozgen, A. & Ariyurek, M. Normative measurements of orbital structures using CT. *AJR. American journal of roentgenology* **170**, 1093-1096, http://doi.org/10.2214/ajr.170.4.9530066 (1998).
12. Woo, K. I., Kim, Y. D. & Lee, S. Y. Prevalence and risk factors for thyroid eye disease among Korean dysthyroid patients. *Korean J Ophthalmol* **27**, 397-404, http://doi.org/10.3341/kjo.2013.27.6.397 (2013).
13. Regensburg, N. I., Wiersinga, W. M., Berendschot, T. T., Potgieser, P. & Mourits, M. P. Do subtypes of graves' orbitopathy exist? *Ophthalmology* **118**, 191-196, http://doi.org/10.1016/j.ophtha.2010.04.004 (2011).
14. Gharib, S., Moazezi, Z. & Bayani, M. A. Prevalence and severity of ocular involvement in Graves' disease according to sex and age: A clinical study from Babol, Iran. *Caspian J Intern Med* **9**, 178-183, http://doi.org/10.22088/cjim.9.2.178 (2018).
15. Kim, J. W., Woo, Y. J. & Yoon, J. S. Is modified clinical activity score an accurate indicator of diplopia progression in Graves' orbitopathy patients? *Endocr J* **63**, 1133-1140, http://doi.org/10.1507/endocrj.EJ16-0165 (2016).
16. Li, Q. *et al.* Clinical characteristics of moderate-to-severe thyroid associated ophthalmopathy in 354 Chinese cases. *PLoS One* **12**, e0176064-e0176064, http://doi.org/10.1371/journal.pone.0176064 (2017).
17. Thornton, J., Kelly, S. P., Harrison, R. A. & Edwards, R. Cigarette smoking and thyroid eye disease: a systematic review. *Eye (Lond)* **21**, 1135-1145, http://doi.org/10.1038/sj.eye.6702603 (2007).
18. Eckstein, A. *et al.* Impact of smoking on the response to treatment of thyroid associated ophthalmopathy. *British Journal of Ophthalmology* **87**, 773, http://doi.org/10.1136/bjo.87.6.773

(2003).

19. Pfeilschifter, J. & Ziegler, R. Smoking and endocrine ophthalmopathy: impact of smoking severity and current vs lifetime cigarette consumption. *Clinical endocrinology* **45**, 477-481, http://doi.org/10.1046/j.1365-2265.1996.8220832.x (1996).
20. Cozma, I. *et al.* Variation in thyroid status in patients with Graves' orbitopathy. *Choroid Plexus - Pineal Gland Correlations Medical Anthropology - Computed Tomography Studies Intracranial Physiological Calcification* **5**, 191-198, http://doi.org/10.4183/aeb.2009.191 (2009).
21. Bartley, G. B. The epidemiologic characteristics and clinical course of ophthalmopathy associated with autoimmune thyroid disease in Olmsted County, Minnesota. *Trans Am Ophthalmol Soc* **92**, 477-588 (1994).
22. Bartley, G. B. *et al.* Clinical Features of Graves' Ophthalmopathy in an Incidence Cohort. *American journal of ophthalmology* **121**, 284-290, http://doi.org/https://doi.org/10.1016/S0002-9394(14)70276-4 (1996).
23. Jang, S. Y., Lee, S. Y., Lee, E. J. & Yoon, J. S. Clinical features of thyroid-associated ophthalmopathy in clinically euthyroid Korean patients. *Eye (London, England)* **26**, 1263-1269, http://doi.org/10.1038/eye.2012.132 (2012).
24. Lee, J.-Y., Bae, K., Park, K.-A., Lyu, I. J. & Oh, S. Y. Correlation between Extraocular Muscle Size Measured by Computed Tomography and the Vertical Angle of Deviation in Thyroid Eye Disease. *PLoS One* **11**, e0148167, http://doi.org/10.1371/journal.pone.0148167 (2016).
25. Lytton, S. D. *et al.* A Novel Thyroid Stimulating Immunoglobulin Bioassay Is a Functional Indicator of Activity and Severity of Graves' Orbitopathy. *The Journal of Clinical Endocrinology & Metabolism* **95**, 2123-2131, http://doi.org/10.1210/jc.2009-2470 (2010).
26. Dragan, L. R., Seiff, S. R. & Lee, D. C. Longitudinal Correlation of Thyroid-Stimulating Immunoglobulin With Clinical Activity of Disease in Thyroid-Associated Orbitopathy. *Ophthalmic Plastic & Reconstructive Surgery* **22**, 13-19, http://doi.org/10.1097/01.iop.0000192649.23508.f7 (2006).
27. Bahn, R. S. & Heufelder, A. E. Pathogenesis of Graves' Ophthalmopathy. *New England Journal of Medicine* **329**, 1468-1475, http://doi.org/10.1056/nejm199311113292007 (1993).
28. Bahn, R. S. Graves' Ophthalmopathy. *New England Journal of Medicine* **362**, 726-738, http://doi.org/10.1056/NEJMra0905750 (2010).
29. Smith, T. J. *et al.* Teprotumumab for Thyroid-Associated Ophthalmopathy. *N Engl J Med* **376**, 1748-1761, http://doi.org/10.1056/NEJMoa1614949 (2017).

Figures

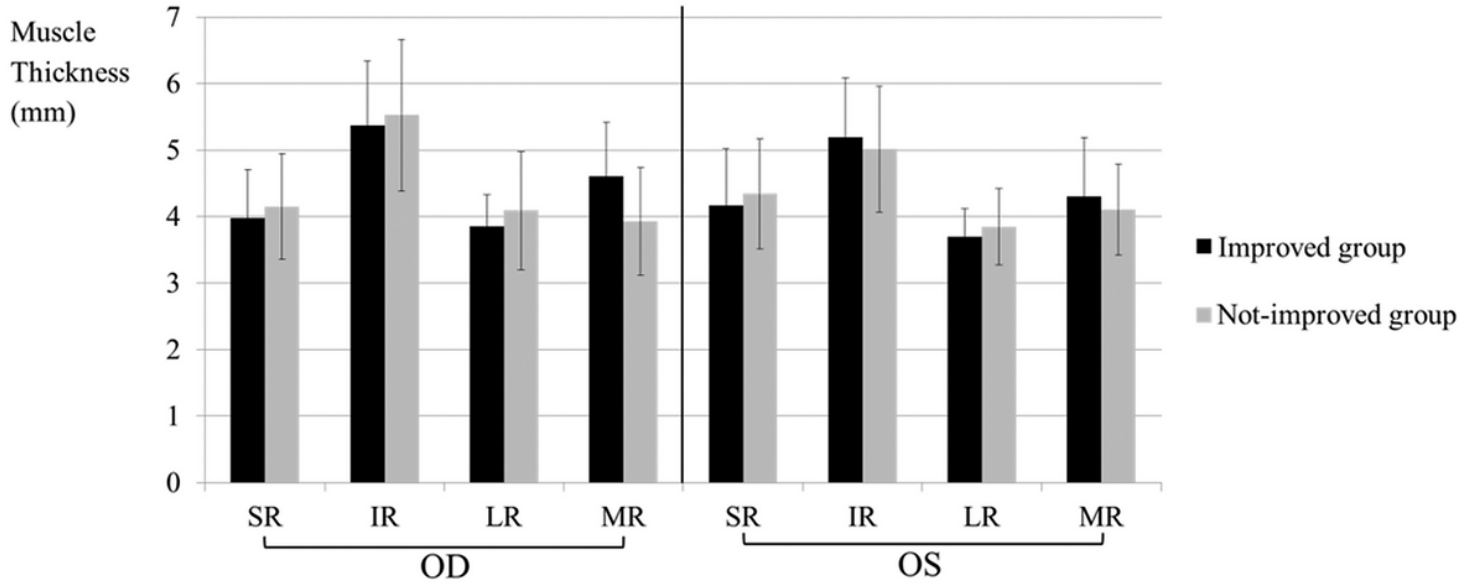

Figure 1

Comparisons of the pre-treatment mean maximal extraocular muscle thickness of patients in improved and not-improved groups. There was no significant difference of the pre-treatment mean maximal extraocular muscle thickness between the improved group and the not-improved group.