Is modified clinical activity score an accurate indicator of diplopia progression in Graves’ orbitopathy patients?

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Abstract. The aim of this study is to describe characteristics of Graves’ orbitopathy (GO) patients with progressive diplopia and to consider whether modified clinical activity score (CAS) is a useful indicator for prediction of diplopia progression. Medical records and images of GO patients with progressive diplopia were retrospectively reviewed. Clinical parameters (e.g., modified CAS, modified NOSPECS score, exophthalmometry results, score of diplopia, and prevalence of optic neuropathy) were evaluated. Thyroid stimulating hormone receptor autoantibody (TRAb) values were determined. Maximum recti muscle diameters and extraocular muscle (EOM) indices were evaluated. Sixty-three of the 435 GO patients had progressive diplopia; 44.4% (28/63) of these patients had a low CAS (<3). The subgroup analysis (by modified CAS, group 1: CAS<3, group 2: CAS≥3) revealed that the mean modified NOSPECS score and exophthalmos value were significantly higher in group 2 (7.2, 19.1 mm) compared with group 1 patients (5.5, 17.7 mm) (p<0.001, p=0.037, respectively). Score of diplopia, prevalence of optic neuropathy and the positive rate and level of TRAb were not significantly different between groups. There were no differences in maximum recti muscle diameters or EOM indices between the two groups. Diplopia may progress even in patients with a low modified CAS. CAS may not reflect the inflammatory activity of myopathy, especially in mild to moderate GO with low NOSPECS and exophthalmos values. Careful patient follow-up using subjective and objective measures for diplopia should be performed.

Key words: CAS, Graves’ orbitopathy, Diplopia, Extraocular muscle

EXTRAOCULAR MUSCLE (EOM) dysfunction occurs in approximately 40%–60% of Graves’ orbitopathy (GO) patients [1, 2]. EOM dysfunction increases GO severity and causes diplopia, which has significant negative effects on the patient’s quality of life [3]. An important treatment goal of GO is to prevent the development of EOM dysfunction, and subsequent deterioration. GO-associated EOM dysfunction is caused by lymphocytic infiltration and edematous swelling during the acute phase; it can be prevented via effective regulation of inflammation during the acute phase [4].

The modified clinical activity score (CAS) is the system most widely used to determine that the active phase of inflammation is present [5]. However, some patients treated in our clinical practice have shown rapidly worsening EOM dysfunction with the absence of the acute inflammatory signs indicated by elevated modified CAS. We evaluated clinical and laboratory characteristics in GO patients showing progressive diplopia to determine whether a modified CAS is a useful index to forecast progression and occurrence of progressive diplopia.

Patients and Method

Patients

Ethnically Korean GO patients who first visited Severance Hospital (Yonsei University College of Medicine, Seoul, Korea) between January 2010 and December 2014 were consecutively recruited for this retrospective study. The GO diagnosis was made by an oculoplastic specialist based on clinical ophthalmic examination (i.e., patient history, slit-lamp examination, visual acuity, intra-ocular pressure, exophthalmometry measured with a Hertel exophthalmometer, Hess chart test, binocular single vision test, and computed tomography [CT] scan) results. The presence of
progressive diplopia was evaluated comprehensively, using orbital CT as an objective method, whenever deterioration was observed with subjective methods including grade of diplopia symptoms and limiting eye movement on Hess charts. Deterioration in subjective diplopia included only cases with recent onset or deteriorating diplopia within <3 months. Deterioration of limiting eye movement was defined as a worsening of underaction ≥ one square (5°), observed by using two consecutive Hess chart tests within a 1-month period (Fig. 1). To distinguish between examination error and worsening of underaction in Hess charts, we consider together other clinical parameters of ocular motility impairment, including subjective diplopia, the binocular single vision test, and orbital CT. Deterioration of objective EOM involvement was evaluated using two consecutive orbital CT scans. Of a total of 435 patients with GO, data from 63 patients were available for analysis. Data on medical history, family history, smoking history, Graves’ disease (GD) and GO duration, and type of current GD treatment were also included in the analysis.

**Ophthalmic manifestations of Graves’ orbitopathy**

The clinical activity of the disease was assessed using a modified CAS based on seven signs of orbital inflammation [5]. The assessment items were spontaneous retrobulbar pain, pain on eye movement, eyelid redness, conjunctival injection, chemosis, caruncle swelling, and eyelid swelling. Each of these symptoms or clinical signs was assigned one point if it was present (score, 0–7 points). GO severity was described using the modified NOSPECS score obtained by adding the NOSPECS grades for lid retraction, soft tissue involvement, exophthalmos, EOM involvement, corneal defect, and optic nerve compression [6]. Patient

![Fig. 1 Representative case of progressive diplopia](image)

Patient with low CAS (i.e., CAS<3; CAS=1, left eyelid swelling) (A); CT scans at diplopia progression showing extraocular muscle enlargement in the both orbits (B); patient had deterioration of diplopia on binocular single vision test and had an increase of motility restriction degree in the both eyes, evaluated using a Hess chart (C: Biocular single vision tests, Hess charts were examined at 1-month intervals).
CAS and NOSPECS scores were evaluated by a single examiner (JSY). Subjective symptoms of diplopia were assessed using the modified Bahn–Gorman grading scheme (grade 0 [no diplopia]), grade 1 [diplopia with horizontal or vertical gaze], grade 2 [intermittent diplopia in straight gaze], or grade 3 [constant diplopia in straight gaze]) [7].

**Laboratory analysis**

Peripheral thyroid function tests (Total T3, free T4, and TSH levels), and thyroid stimulating hormone receptor autoantibody (TRAb) assays were included in our analysis. The measurement of TRAb was performed using two assays (i.e., TSH-binding inhibition assay (M22-TRAb) and thyroid stimulating immunoglobulin (TSI) assay (MC4-TSI)). M22-TRAb was measured using a third-generation thyrogropin-binding inhibitory immunoglobulin assay using the automated Cobas electrochemiluminescence immunoassay (Elecsys, Roche Diagnostics GmbH, Penzberg, Germany) according to the manufacturer’s instructions. The cut-off value for a positive result was 1.75 IU/L. Serum MC4-TSI was measured using the Thyretain™ TSI Reporter BioAssay (Diagnostic Hybrids, Inc., Athens, OH, USA) according to the manufacturer’s instructions. Results were considered positive with specimen-to-reference ratio >140% of the reference control.

**EOM analysis using computed tomography**

Each patient was imaged using CT scans to carefully and objectively define EOM involvement. The morphological diagnosis of EOM enlargement was defined as spindle-like spreading of the rectus muscles without tendon involvement [8]. Maximum rectus muscle diameters were determined using coronal scans of the inferior and superior rectus muscles and axial scans of the medial and lateral rectus muscles [9]. The extraocular muscle index (MI) was calculated according to the method proposed by Barrett et al., using a coronal image halfway between the orbital apex and the posterior aspect of the globe [10]. The vertical dimensions of the superior rectus and inferior rectus muscles, and orbital height, were calculated along a vertical line intersecting the midpoint of the optic nerve. The vertical MI was the percent of the orbital height occupied by the superior and inferior rectus muscles. Horizontal MI was calculated using the same method, and extraocular muscle index was expressed by the highest value rather than an average of vertical and horizontal indices. Apical crowding was graded as 0 (no perineural fat plane effacement present), 1 (mild, 1%–25% effacement), 2 (moderate, 26%–50% effacement), or 3 (severe, >50% effacement) by Nugent’s score (Supplementary Fig. 1) [11].

**Statistical analysis**

The assumption of a normal distribution was tested for all variables using the Kolmogorov–Smirnov test. We used independent t-tests and the Chi-square test to compare the clinical and laboratory characteristics and the CT findings between the two groups. The Mann-Whitney test was used to compare the median values for GD and GO duration.

**Results**

**Clinical and laboratory characteristics of patients with diplopia progression**

A total of 63 of 435 patients with GO had diplopia progression and had complete datasets available for analysis. The mean age was 52.1±11.4 years; 40 (63.5%) patients were women (Table 1). The median GD and GO durations were 8 months and 4 months, respectively. The mean CAS value was 3.0±1.8 (0-6), and the mean modified NOSPECS score was 6.4±2.1. Thirty patients (47.6%) were diagnosed with hyperthyroidism, twelve (19.0%) with hypothyroidism, and twenty-one (33.3%) with euthyroidism. Twenty-three patients (38.7%) had a history of smoking. Of the 63 patients with GO, 73% had been treated with antithyroid drugs, 4.8% underwent radioiodine treatment, and 4.8% underwent thyroidectomy. Twenty-two (34.9%) patients received previous or current treatment with steroids, and 1 (1.6%) patient received orbital radiotherapy. The prevalence of M22-TRAb-positive patients was 85.7% and the prevalence of Mc4-TSI-positive patients was 92.1%.

**Clinical and laboratory comparison between patients grouped by modified CAS**

The modified CAS is mostly used as an indicator of inflammatory activity in GO patients. However, 28 patients (44.4%) had a low modified CAS (i.e., <3) (Fig. 2). We occasionally find patients with compressive optic neuropathy who have a low modified CAS and no prominent inflammation symptoms. We analyzed and compared patients, grouped by modified
Table 1  Comparison of characteristics of patients showing progressive diplopia according to CAS

|                      | Total  | Group 1 (CAS<3) | Group 2 (CAS≥3) | P value |
|----------------------|--------|-----------------|-----------------|---------|
| N (% )               | 63 (100%) | 28 (44.4%)      | 35 (55.5%)      |         |
| Age, mean±SD, years  | 52.1 ± 11.4 | 52.4 ± 12.4      | 51.8 ± 10.7     | 0.831 * |
| Sex, female, n (%)   | 40 (63.5%) | 17 (60.7%)       | 23 (65.7%)      |         |
| Duration of GD, median (IQR), months | 8 (4-16) | 7.5 (4-15.5) | 8 (4-18) | 0.760 † |
| Duration of GO, median (IQR), months | 4 (2-8) | 4 (2-6.8) | 3 (2-8) | 0.906 † |
| CAS, mean±SD (range) | 3.0 ± 1.8 (0-6) | 1.2 ± 0.7 (0-2) | 4.4 ± 1.0 (3-6) | <0.001 * |
| Modified NOSPECS, mean±SD (range) | 6.4 ± 2.1 (3-12) | 5.5 ± 1.8 (3-10) | 7.2 ± 1.9 (4-12) | <0.001 * |
| Thyroid function (hyper/hypo/euthyroidism, %) | 47.6/19.0/33.3 | 50.0/10.7/39.3 | 45.7/25.7/28.6 | 0.296 |
| Smokers, n (%)       | 25 (39.6%) | 11 (39.3%)       | 14 (40%)        | 0.844 † |
| Current/Previous, %  | 19.0/20.6 | 17.9/21.4        | 22.9/17.1       |         |
| Family history of hyperthyroidism, n (%) | 12 (19.0%) | 5 (17.9%) | 7 (20%) | 0.830 |
| Thyroid treat modalities (none/ATD/RAI/surgery, %) | 17.5/73.4/8.4/8.8 | 21.4/67.9/3.6/7.1 | 14.3/77.1/5.7/2.9 | 0.708 |
| Previous or current steroid use history, n (%) | 22 (34.9%) | 10 (35.7%) | 12 (34.3%) | 0.906 † |
| Previous or current orbital radiation history, n (%) | 1 (1.6%) | 0 (0%) | 1 (2.9%) | 0.367 |
| Total T3 (0.58 - 1.59 ng/mL), mean±SD | 1.3 ± 0.9 | 1.2 ± 0.4 | 1.4 ± 1.2 | 0.336 * |
| fT4 (0.70 – 1.48 ng/dL), mean±SD | 1.3 ± 1.0 | 1.3 ± 0.4 | 1.4 ± 1.3 | 0.557 * |
| TSH (0.35-4.94 μIU/mL), mean±SD | 0.8 ± 1.2 | 1.5 ± 2.4 | 4.3 ± 8.7 | 0.110 |
| M22-TRAb (≤1.75 IU/L), mean±SD (positive %) | 14.2 ± 13.9 (85.7%) | 12.5 ± 13.0 (82.1%) | 15.6 ± 14.6 (88.6%) | 0.393 * |
| Mc4-TSI (≥140 SRR%), mean±SD (positive %) | 442.6 ± 160.9 (92.1%) | 463.1 ± 149.6 (92.8%) | 426.9 ± 169.6 (97.1%) | 0.391 * |
| Diplopia score, mean±SD | 1.8 ± 0.9 | 2.0 ± 0.9 | 1.6 ± 0.9 | 0.051 * |
| Exophthalmos, mean±SD (range, mm) | 18.6 ± 2.6 (12-26) | 17.7 ± 2.4 | 19.1 ± 2.6 | 0.037 * |
| Optic nerve involvement, n (%) | 8 (12.7%) | 2 (71.4%) | 5 (17.1%) | 0.577 † |
| Lid retraction, n (%) | 37 (58.7%) | 16 (57.1%) | 20 (60.0%) | 0.673 † |
| Asymmetric involvement, n (%) | 16 (25.4%) | 7 (25.0%) | 8 (22.9%) | 0.755 † |

CAS, clinical activity score; SD, standard deviation; GD, Graves’ disease; GO, Graves’ orbitopathy; hyper, hyperthyroidism; hypo, hypothyroidism; TSH, thyroid stimulating hormone; ATD, antithyroid drug; RAI, radioiodine therapy; TRAB, TSH receptor antibody; TSI, thyroid-stimulating immunoglobulin; SRR, specimen-to-reference ratio. * Independent t test, † Chi-squared test, ‡ Mann-Whitney test, P value compared between two groups, bold values denote statistical significance, p<0.05.

Fig. 2  Distribution of CAS based on findings at diplopia progression
Twenty-eight of 63 patients (44.4%) had low CAS (i.e., CAS<3).
Diplopia progression in GO

CAS. Results of a demographic comparison of the two groups revealed that there were no statistical differences in age, sex, duration of ocular symptoms, or smoking status (Table 1). The NOSPECS scores comparison revealed that group 1 experienced a less severe clinical course compared with group 2 (5.5 vs 7.2, \( p < 0.001 \)). Results of a comparison of peripheral thyroid function tests (Total T3, fT4, TSH) indicated that there were no statistical differences. The prevalence of M22-TRAb-positive patients in each group was 82.1% and 88.6%, respectively, and these values were not significantly different (\( p = 0.393 \)). The values for the TSI assay results were high in both group 1 (92.8%) and group 2 (97.1%), but the differences were not statistically significant (\( p = 0.391 \)).

The results for the analysis of ophthalmic manifestations indicated that the mean subjective diplopia scores were not different between groups 1 and 2. There were no differences in optic nerve involvement, lid retraction, or asymmetric involvement between the two groups. However, proptosis evaluated using mean exophthalmos (mm) was greater in group 2 (19.1±2.6) compared with group 1 (17.7±2.4, \( p = 0.037 \)).

Comparison of CT findings between patients, grouped by modified CAS

The difference between the mean numbers of involved extraocular muscles was not statistically significant between the two groups (2.5±1.0 vs. 2.6±1.1, \( p = 0.620 \)) (Table 2). Inferior rectus muscle enlargement occurred most frequently in both groups. In group 1, the types of EOMs involved (in descending order) were the inferior rectus, medial rectus, lateral rectus, and superior rectus muscles. For group 2, the involved muscles (in descending order) were the inferior rectus, medial rectus, superior rectus, and lateral rectus muscles. The mean maximum diameter of the four rectus muscles was not significantly different between the two groups (all \( p > 0.05 \)). The inferior rectus muscle was the thickest, and the lateral rectus muscle was the thinnest rectus muscle in both groups. The mean EOM index was >50% in both groups, and was not significantly different (54.6% vs. 54.6%, \( p = 0.987 \)). The percent values for patients with severe apical crowding were not statistically different (17.9% in group 1, 34.3% in group 2, \( p = 0.758 \)).

Table 2 Comparison of imaging characteristics in computed tomography in patients showing progressive diplopia according to CAS

|                                | Group 1 (CAS<3) | Group 2 (CAS≥3) | \( P \) value |
|--------------------------------|----------------|-----------------|--------------|
| Number of EOM involved, mean±SD| 2.5 ± 1.0       | 2.6 ± 1.1       | 0.620 *      |
| 1/2/3/4, n (%)                  | 4/11/8/5       | 6/10/10/9       |              |
| Type of EOM involved, n (%)     |                |                 |              |
| SR                             | 13 (46.4%)     | 20 (57.1%)      | 0.212 †      |
| LR                             | 15 (53.6%)     | 16 (45.7%)      | 0.535 †      |
| IR                             | 26 (92.9%)     | 30 (85.7%)      | 0.370 †      |
| MR                             | 18 (64.3%)     | 23 (65.7%)      | 0.906 †      |
| EOM max diameter, mm, mean±SD  |                |                 |              |
| SR                             | 5.6 ± 1.8      | 5.8 ± 1.9       | 0.585 *      |
| LR                             | 4.3 ± 1.2      | 4.5 ± 1.1       | 0.411 *      |
| IR                             | 7.6 ± 2.6      | 7.0 ± 1.8       | 0.265 *      |
| MR                             | 6.4 ± 2.2      | 6.7 ± 1.8       | 0.584 *      |
| Extraocular muscle index, mean±SD| 54.6 ± 9.3    | 54.6 ± 8.5      | 0.987 *      |
| Apical crowding, absent/mild/moderate/severe, n (%)| 4/8/11/5| 3/9/11/12| 0.758 †|

EOM, extraocular muscle; CAS, clinical activity score; SD, standard deviation; SR, superior rectus muscle; LR, lateral rectus muscle; IR, inferior rectus muscle; MR, medial rectus muscle. * Independent t test, † Chi-squared test, \( P \) value compared between two groups, bold values denote statistical significance, \( p < 0.05 \).
Dagi et al. reported that in the active phase, the muscle area of GO patients is larger than that of GO patients in the inactive phase, and that there are corresponding differences in levels of motility restriction [9]. Le Moli et al. found that as GO patients’ modified CAS decrease, the ratio of EOM coronal area to total orbit coronal area decreases [8]. Kvetny et al. similarly reported that rectus muscle thickness and CAS values are related [12]. In the patients with progressive diplopia, however, both groups had EOM enlargement regardless of modified CAS; the EOM index also increased >50%. There were also no differences between the two groups in maximum muscle diameters.

These results were affected by limitations in the modified CAS scoring system and differences in GO subtype. Because the symptoms (e.g., hyperemia and edema) that result from acute orbital congestion comprise 5 of the total of 7 points of the modified CAS system, the scoring does not reflect ocular muscle involvement [5]. GO can be classified into two main subtypes depending on the pathogenic mechanism. The first subtype, which consists mainly of inflammatory changes within orbital connective and adipose tissues, is a congestive ophthalmopathy with minimal eye muscle abnormalities. The second subtype has few inflammatory changes within orbital connective and adipose tissues. This subtype is an ocular myopathy that frequently includes marked EOM swelling and dysfunction, and diplopia [13].

The other characteristic present in the patients with progressive diplopia was that the TRAb level (TBII titers, TSI concentrations) and the rate of positivity for these antibody tests were high in both groups, regardless of modified CAS. TBII titers and TSI concentrations are related to the development and deterioration of GO. Examination of the relationship between GO myopathy and the TSH receptor revealed that as the TRAb level increases, EOM enlargement and limitation also increases [19-22]. Resensburg et al. reported that high TBII titers are associated with an increase in muscle volume and Jang et al. reported that TSI concentration is associated with EOM limitation [16, 23]. Similar to these previous studies, patients with progressive diplopia, even if modified CAS was low, had TRAb levels and positive rates comparable to those with high modified CAS.

The limitation of this study was that the clinical characteristics were only evaluated in patient groups with progressive diplopia, without a control group. It

**Discussion**

We investigated the characteristics of GO patients with progressive diplopia. We found that 44.4% (28/63) of the patients had a low modified CAS (<3 points) and no typical symptoms of inflammation. That is, EOM dysfunction increased in nearly 45% of patients, without an increase in modified CAS. Modified CAS is currently the most used index to determine the active phase of inflammation. Dagi et al. reported that in the active phase, the muscle area of GO patients is larger than that of GO patients in the inactive phase, and that there are corresponding differences in levels of motility restriction [9]. Le Moli et al. found that as GO patients’ modified CAS decrease, the ratio of EOM coronal area to total orbit coronal area decreases [8]. Kvetny et al. similarly reported that rectus muscle thickness and CAS values are related [12]. In the patients with progressive diplopia, however, both groups had EOM enlargement regardless of modified CAS; the EOM index also increased >50%. There were also no differences between the two groups in maximum muscle diameters.

These results were affected by limitations in the modified CAS scoring system and differences in GO subtype. Because the symptoms (e.g., hyperemia and edema) that result from acute orbital congestion comprise 5 of the total of 7 points of the modified CAS system, the scoring does not reflect ocular muscle involvement [5]. GO can be classified into two main subtypes depending on the pathogenic mechanism. The first subtype, which consists mainly of inflammatory changes within orbital connective and adipose tissues, is a congestive ophthalmopathy with minimal eye muscle abnormalities. The second subtype has few inflammatory changes within orbital connective and adipose tissues. This subtype is an ocular myopathy that frequently includes marked EOM swelling and dysfunction, and diplopia [13]. The reasons for the differences in the clinical manifestations of these subtypes have not been definitively clarified. They likely occur because orbital fibroblasts react heterogeneously to proproliferative and proadipogenic stimulators, depending on the differences in Thy-1 (CD90) expression in GO orbital tissues [14, 15]. There was no difference in EOM enlargement between the two groups. However, exophthalmos was more prominent in group 2, which also had higher modified CAS. Because proptosis was related to EOM enlarge-ment and fat volume increase, it is likely that marked EOM enlargement with a slight fat volume increase occurred in group 1, and marked fat volume increase and EOM enlargement occurred in group 2 patients. These two changes in group 2 patients caused congestion and resulted in higher modified CAS [16]. Thus, EOM enlargement and EOM dysfunction may not appear even in cases of high modified CAS, and EOM enlargement and EOM dysfunction may be severe even in cases of low modified CAS. This relationship was also indicated by the results of a study using an MRI that examined the relationships between EOM enlargement, diplopia, and T2 relaxation time (T2 relaxation time indicates ocular congestion and edema) [17]. Nagy et al. reported that EOM enlargement does not imply the presence of edematous swelling, and diplopia severity is not related to the degree of ocular congestion and edema [17].

Multiple EOM involvement was as high as 84.1% (53/63) in these patients with progressive diplopia. The results of studies performed in Japan revealed that 45% of 187 GO patients with EOM enlargement had multiple EOM involvement (i.e., two or more muscles) [13]. Nagy et al. reported that 72% of 43 GO patients with diplopia had multiple EOM involvement [17]. As previously reported in several studies similar to the present study, the most frequently involved muscle is the inferior rectus muscle, followed by the medial rectus muscle [13, 18].
is an established fact that more patients with higher clinical activity score (CAS ≥3) may show progressive and severe manifestations including restrictive myopathy [24]. However, although very specific, CAS is not very sensitive, as previously reported [25]. The study results show that modified CAS may be low, even in cases with progressive diplopia, suggesting that careful monitoring is required not only by using CAS but also in combination with other clinical parameters in high risk patients. This would help in early detection and management of the ocular motility impairment. However, further studies comparing patients with and without progressive diplopia are needed to support the findings of this study.

**Conclusion**

Diplopia progression occurred even in patients with low modified CAS. These patients comprised a large proportion (44.4%, 28/63) of the myopathy patients in this study. For early detection of the progression of myopathy, GO patients should have regular check-ups for changes in subjective diplopia symptoms and examination of ocular movement limitations, regardless of CAS results.

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None.

**Conflict of Interest**

The authors declare no conflict of interest.

**Disclosure**

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**Supplementary Fig. 1**

Coronal CT scan showing orbits with apical crowding due to enlarged extraocular muscles

The right orbit shows effacement of the perineural fat ≥ 50% of the circumference (grade 3 Nugent score); the left orbit shows effacement of the perineural fat up to 25% of the circumference (grade 1 Nugent score).

**References**

1. Kozaki A, Inoue R, Komoto N, Maeda T, Inoue Y, et al. (2010) Proptosis in dysthyroid ophthalmopathy: a case series of 10,931 Japanese cases. *Optom Vis Sci* 87: 200-204.
2. Hiromatsu Y, Eguchi H, Tani J, Kasaoka M, Teshima Y (2014) Graves’ ophthalmopathy: epidemiology and natural history. *Intern Med* 53: 353-360.
3. Son BJ, Lee SY, Yoon JS (2014) Evaluation of thyroid eye disease: quality-of-life questionnaire (TED-QOL) in Korean patients. *Can J Ophthalmol* 49: 167-173.
4. Bahn RS, Heufelder AE (1993) Pathogenesis of Graves’ ophthalmopathy. *N Engl J Med* 329: 1468-1475.
5. Bartalena L, Baldeschi L, Dickinson AJ, Eckstein A, Kendall-Taylor P, et al. (2008) Consensus statement of the European group on Graves’ orbitopathy (EUGOGO) on management of Graves’ orbitopathy. *Thyroid* 18: 333-346.
6. Eckstein AK, Plicht M, Lax H, Neuhauser M, Mann K, et al. (2006) Thyrotropin receptor autoantibodies are independent risk factors for Graves’ ophthalmopathy and help to predict severity and outcome of the disease. *J Clin Endocrinol Metab* 91: 3464-3470.
7. Bahn RS, Gorman CA (1987) Choice of therapy and criteria for assessing treatment outcome in thyroid-associated ophthalmopathy. *Endocrinol Metab Clin North Am* 16: 391-407.
8. Le Moli R, Pluchino A, Muscia V, Regalbuto C, Luciani B, et al. (2012) Graves’ orbitopathy: extraocular muscle/total orbit area ratio is positively related to the Clinical Activity Score. *Eur J Ophthalmol* 22: 301-308.
9. Dagi LR, Zoumalan CI, Konrad H, Trokel SL, Kazim M (2011) Correlation between extraocular muscle size and motility restriction in thyroid eye disease. *Ophthal Plast Reconstr Surg* 27: 102-110.
10. Barrett L, Glatt HJ, Burde RM, Gado MH (1988) Optic nerve dysfunction in thyroid eye disease: CT. *Radiology* 167: 503-507.
11. Nugent RA, Belkin RI, Neigel JM, Rootman J, Robertson WD, et al. (1990) Graves orbitopathy: correlation of CT and clinical findings. *Radiology* 177: 675-682.
12. Kvetny J, Puhakka KB, Rohl L (2006) Magnetic resonance imaging determination of extraocular eye muscle volume in patients with thyroid-associated ophthalmopathy and proptosis. *Acta Ophthalmol Scand* 84: 419-423.
13. Murakami Y, Kanamoto T, Tuboi T, Maeda T, Inoue Y (2001) Evaluation of extraocular muscle enlargement in dysthyroid ophthalmopathy. *Jpn J Ophthalmol* 45: 622-627.
14. Kuryyan AE, Woeller CF, O’Loughlin CW, Phipps RP, Feldon SE (2013) Orbital fibroblasts from thyroid eye disease patients differ in proliferative and adipogenic responses depending on disease subtype. *Invest Ophthalmol Vis Sci* 54: 7370-7377.
15. Koumas L, Smith TJ, Phipps RP (2002) Fibroblast subsets in the human orbit: Thy-1+ and Thy-1- subpopulations exhibit distinct phenotypes. *Eur J Immunol* 32: 477-485.
16. Regensburg NI, Wiersinga WM, Berendschot TT, Potgieter P, Mourits MP (2011) Do subtypes of Graves’ orbitopathy exist? *Ophthalmology* 118: 191-196.
17. Nagy EV, Toth J, Kaldi I, Damjanovich J, Mezosi E, et al. (2000) Graves’ ophthalmopathy: eye muscle involvement in patients with diplopia. *Eur J Endocrinol* 142: 591-597.
18. A KJ, Sadeghi-Tari A, Minae-Noshahr N, Ameri A, Anvari F, et al. (2010) Ocular movement disorders and extraocular muscle involvement in Iranian Graves’ ophthalmopathy patients. *Binocul Vis Strabismus Q* 25: 217-230.
19. Noh JY, Hamada N, Inoue Y, Abe Y, Ito K, et al. (2000) Thyroid-stimulating antibody is related to Graves’ ophthalmopathy, but thyrotropin-binding inhibitor immunoglobulin is related to hyperthyroidism in patients with Graves’ disease. *Thyroid* 10: 809-813.
20. Lytton SD, Ponto KA, Kanitz M, Matheis N, Kohn LD, et al. (2010) A novel thyroid stimulating immunoglobulin bioassay is a functional indicator of activity and severity of Graves’ orbitopathy. *J Clin Endocrinol Metab* 95: 2123-2131.
21. Ponto KA, Kanitz M, Olivo PD, Pitzi S, Pfeiffer N, et al. (2011) Clinical relevance of thyroid-stimulating immunoglobulins in graves’ ophthalmopathy. *Ophthalmology* 118: 2279-2285.
22. Dragan LR, Seiff SR, Lee DC (2006) Longitudinal correlation of thyroid-stimulating immunoglobulin with clinical activity of disease in thyroid-associated orbitopathy. *Ophthal Plast Reconstr Surg* 22: 13-19.
23. Jang SY, Shin DY, Lee EJ, Choi YJ, Lee SY, et al. (2013) Correlation between TSH receptor antibody assays and clinical manifestations of Graves’ orbitopathy. *Yonsei Med J* 54: 1033-1039.
24. Lee HJ, Lee SY, Yoon JS (2010) Risk Factors Associated with the Severity of Thyroid-Associated Orbitopathy in Korean Patients. *Korean J Ophthalmol* 24: 267-273.
25. Mourits MP, Prummel MF, Wiersinga WM, Koornneef L (1997) Clinical activity score as a guide in the management of patients with Graves’ ophthalmopathy. *Clin Endocrinol (Oxf)* 47: 9-14.