Effect of Selenium Supplementation on Mild Graves' Ophthalmopathy at a Tertiary Hospital – a Six-Month, Open-Labelled, Assessor-Masked, Randomized Controlled Trial*

Joy Mangubat Flores, MD,[1] *Niña Angelica G. Sioson, MD,*[2] *Armida L. Suller-Pansacola, MD,*[2] *Jean D. Uy-Ho, MD*[1]

ABSTRACT

Objective: This study aimed to determine if selenium supplementation for a period of six months can decrease signs and prevent worsening of mild Graves' ophthalmopathy among Filipino patients.

Methods: We conducted an open-label, assessor-masked, randomized controlled trial involving adult patients diagnosed with mild Graves' ophthalmopathy. Participants were divided into two groups: one group received standard care (eye drops) alone (control group), while the other group received an additional 200 mcg/day oral selenium supplementation alongside standard care. Inclusion criteria encompassed adult patients with Graves' hyperthyroidism presenting at least one sign of mild ophthalmopathy and a disease duration of less than 18 months. Statistical analyses were performed using independent sample t-test, Mann-Whitney U test and Fisher's Exact/Chi-square test to compare means, ranks and frequencies between the two intervention groups. Paired sample t-test, Wilcoxon signed rank test and McNemar test were employed to assess changes from baseline to the third and sixth month observations.

Results: A significant difference in clinical activity score (CAS) was observed between the selenium supplementation group and the control group. Initially, 14 eyes (33.33%) in the selenium group exhibited a CAS score of 0, which increased to 27 eyes (64.29%) at the third month of treatment and slightly decreased to 26 eyes (61.9%) at the sixth month. Conversely, the control group had 11 eyes with a CAS score of 0 at baseline, which increased to 16 eyes (38.1%) at three months and decreased to 14 eyes (33.33%) at the sixth month. The improvement in CAS was significantly associated with reductions in caruncle and plica swelling ($p = 0.040$). Further analysis revealed a statistically significant difference in CAS between the treatment and control groups ($p = 0.017$) at the sixth month mark.

✉ Joy Mangubat Flores
joymfloresmd@gmail.com

[1] Section of Endocrinology, Diabetes and Metabolism, University of Santo Tomas Hospital, Manila, Philippines

[2] Department of Ophthalmology, University of Santo Tomas Hospital, Manila, Philippines

Academic editor: Leilani B. Mercado-Asis

Submitted date: January 11, 2025

Accepted date: February 22, 2025

**This paper has been presented in the following conventions: ENDO 2024 Annual Convention of Endocrine Society (San Francisco, USA) – Abstract poster presentation – June 3, 2024; ASEAN Ophthalmology Society Congress – Philippine Academy of Ophthalmology Congress 2023 (Manila, Philippines) – October 19, 2023; EVOLVED 2023 Annual Convention of the Philippine College of Endocrinology, Diabetes and Metabolism Convention (Manila, Philippines) – March 16, 2023*

Conclusion: Selenium supplementation provided significant benefit in reducing the signs and preventing deterioration of mild Graves' ophthalmopathy, as indicated by improved CAS scores. Future research exploring baseline and end of treatment selenium concentrations in the Philippines is recommended to further substantiate these findings.

INTRODUCTION

Graves' ophthalmopathy (GO) is an autoimmune inflammation of the orbital tissues closely associated with autoimmune thyroid diseases.[1,2] Also referred to as Graves' orbitopathy, Graves' eye disease, thyroid eye disease and thyroid-associated ophthalmopathy, GO is the most prevalent orbital disorder and most common cause of unilateral and bilateral proptosis in adults.[1-4] It is the most common extrathyroidal manifestation of Graves' disease affecting 25%-50% of patients.[1,2,5] It typically develops concurrently with hyperthyroidism but may also precede or follow its onset.[2] Although uncommon, it can occur in patients with euthyroid or hypothyroid chronic autoimmune thyroiditis.[6]

The disease is more prevalent in female patients than in their male counterparts, with an annual incidence of 16 per 100,000 in women and 3 per 100,000 in men.[2] Among Asians, the prevalence of GO associated with hyperthyroidism ranges from 35% to 60%.[3] In the Philippines, a study by Palisoc, et al., (2010) reported a prevalence of 48%, with the condition occurring more frequently in patients aged between 30 and 49 years. The most common symptom identified was eye pain; while the predominant signs included eyelid retraction, proptosis and lid lag.[7] The natural history of GO features an initial active phase characterized by alternating acute inflammatory episodes and remissions, followed by stabilization (plateau phase) and ends with an inactive or burn-out phase, which typically involves regression over a period of 12 to 18 months.[6,8]

Diagnosed clinically based on symptoms and ocular signs, mild GO is frequently misdiagnosed as conjunctivitis or allergic reactions, resulting in delays in both diagnosis and treatment, which can exacerbate the condition.[2,9] Therefore, a thorough clinical examination is essential for accurate diagnosis; in cases of uncertainty, the opinion of an ophthalmologist is important.[8] Spontaneous remission is often observed in minimal-to-mild GO; however, complete resolution is rare when the condition is more than mild.[6] Early diagnosis, management of modifiable risk factors and prompt treatment of mild forms of GO can effectively limit the risk of progression to more severe forms. At this time, more severe forms of GO present a therapeutic challenge, often necessitating prolonged and multiple medical and surgical interventions, which can significantly impact the quality of life of affected individuals.[6] Previously, a wait-and-see approach was adopted for patients with mild GO, as spontaneous improvement was anticipated, requiring only local measures such as artificial tears and ointments to manage symptoms.

Graves' orbitopathy is associated with increased oxidative stress. Selenium, known for its antioxidant and immunoregulatory properties, has been proposed as an adjuvant therapy for patients with mild GO.[6] In a randomized, double-blind, placebo-controlled trial conducted in Europe in 2011, Marcocci, et al., identified that selenium administration significantly improved quality of life, reduced ocular involvement and slowed disease progression patients with mild GO.[10] Consequently, six-month selenium supplementation for patients diagnosed with mild GO was included as a recommendation in the 2016 European Thyroid Association/European Group on Graves' Orbitopathy Guidelines for the Management of Graves' Orbitopathy.[4] However, this recommendation is not endorsed by the American Thyroid Association, as patients in the United States are usually not selenium deficient and thus not in need of supplementation.[10]

To our knowledge and from our review of literature, there is a paucity of prior local studies investigating the effects of selenium supplementation on mild GO in Filipino patients. This study aimed to compare the efficacy of standard care (eye drops) with that of standard care combined with selenium supplementation. The objective was to determine whether selenium supplementation over a six-month period could reduce clinical signs and prevent progression of mild GO. Specific objectives included comparing baseline and six-month assessments of visual acuity, color vision and soft tissue signs between the selenium and control groups, as well as evaluating the percentage

change in these parameters and the CAS over the study period.

METHODOLOGY

Research Design

An open-labelled, assessor-masked, randomized controlled trial was conducted on adult patients diagnosed with mild GO. Patients were given 200 mcg of selenium daily in addition to standard care or standard of care alone, over a six-month period. The study commenced following approval from the University of Santo Tomas Hospital Research Ethics Committee (USTH REC). It adhered to both national and international ethical guidelines such as the International Council for Harmonisation Good Clinical Practice (ICH-GCP), National Ethical Guidelines for Health and Health-Related Research (NEGHHRR) 2017 and the Data Privacy Act of 2012, along with its Implementing Rules and Regulations of 2016.

Study Population

This study included patients aged 18 to 60 years with a history of Graves' hyperthyroidism who presented at least one sign of mild GO. The qualifying signs included minor lid retraction of less than 2 mm, mild soft tissue involvement, exophthalmos measuring less than 3 mm above normal and corneal exposure responsive to lubricants. Additionally, participants had to have disease duration of less than 18 months.

The exclusion criteria enlist a range of conditions that could confound the study results. Specifically, patients with soft tissue swelling classified as NO SPECS class 2c (eg, severe chemosis or severe eyelid swelling) were excluded, as were those with proptosis exceeding 19.5 mm. Other exclusions are the presence of diplopia in the primary or reading position, ocular torticollis and any restriction in mono-ocular duction of less than 20 degrees in any direction. Patients exhibiting signs or symptoms of optic nerve involvement, those with a history of ophthalmopathy treatment beyond local measures (eg, eye drops) and individuals with a history of drug and/or alcohol abuse were also excluded. In addition, patients with severe concomitant illnesses and pregnant individuals were not eligible for participation; any patient who became pregnant during the course of the study was similarly excluded.

Sample Size

Sample size computation for analysis of covariance (ANCOVA) was conducted using GPower version 3.1.9.7. The researchers used parameters estimated by Marcocci, et al. (2011), taking into account the change at six-month appearance GO-QOL score among patients with selenium (10.6 +/- 10.9) versus patients treated with standard care (-2.6 +/- 11.7). [10] With a power of 95% at a significance level of 5% (two-tailed), a minimum sample size of 42 respondents was necessary. Considering the study design, the total sample size was divided into two groups, thus each group had 21 respondents.

Outcome Measurements

The primary outcome was the objective assessment of ocular changes conducted by masked ophthalmologists. The secondary outcome was measured using the clinical activity score (CAS), in accordance with the European Group on Graves' Orbitopathy (EUGOGO) recommendations for assessing response to interventions in clinical trials. Data were collected at baseline, third month of treatment and sixth month.

A beneficial response was defined as improvement in at least one eye without any deterioration in both eyes, based on the following criteria: an increase in lid aperture of ≥2 mm; improvement by at least one grade in eyelid swelling, eyelid erythema, conjunctival redness or conjunctival edema; improvement in best-corrected visual acuity (BCVA) by ≥2 lines on the Bailey-Lovie chart, or substantial improvement in color vision.

Deterioration was defined as an increase in lid aperture of ≥2 mm; worsening by at least one grade in eyelid swelling, eyelid erythema, conjunctival redness or conjunctival edema; an increase in exophthalmos of ≥2 mm; the appearance of diplopia or limitation of eye movement; or decline in BCVA by ≥2 lines, substantial changes in color vision, visual fields, optic disc appearance or development of a relative afferent pupillary defect.

Study Procedure and Data Collection

Recruitment Process and Informed Consent

Study recruitment was initiated with the investigators obtaining patient referral from consultants and

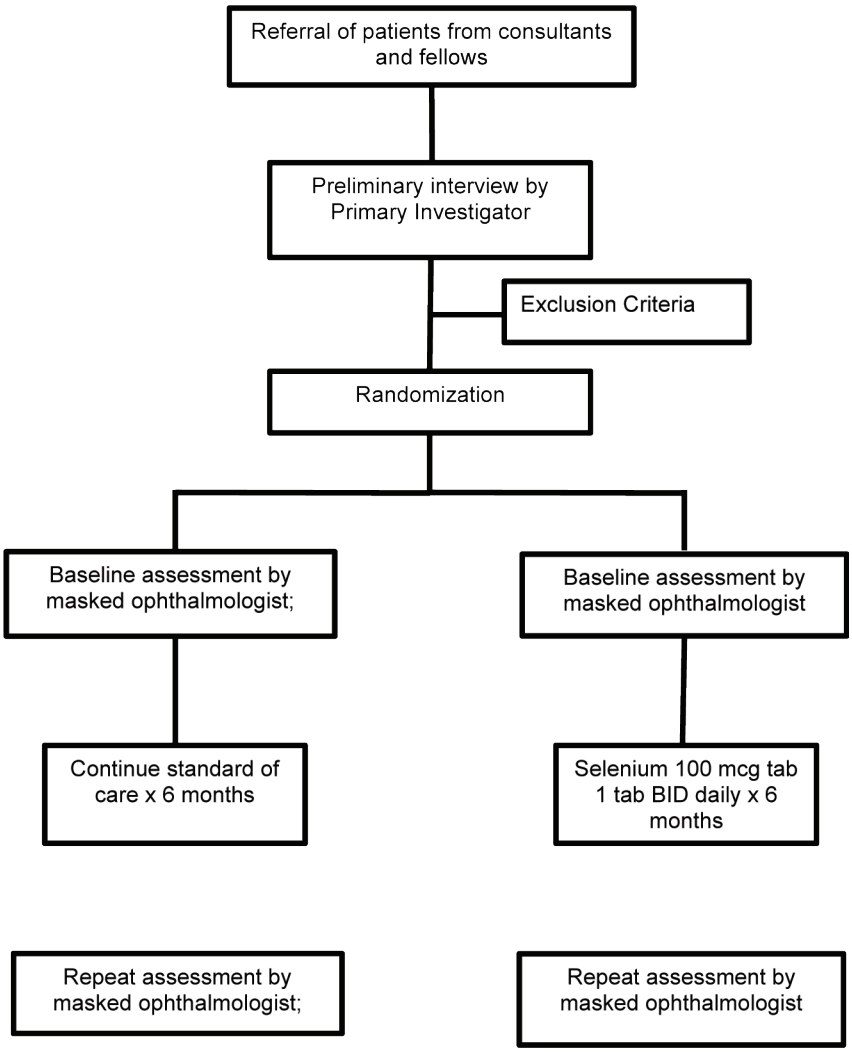

Figure 1. Flowchart for methodology

fellows of the Section of Endocrinology, Diabetes and Metabolism of the UST hospital. Referrals were sourced from private clinics or the hospital's Ambulatory Care Services Department. During the pandemic, patient recruitment also took place through the teleconsultation platform of the UST Hospital Endocrinology Ambulatory Care Services. Patients underwent a preliminary screening interview following the inclusion exclusion criteria, conducted by the primary investigator to ensure eligibility.

To participate, patients received a detailed explanation of the purpose of study as well as the study procedure, schedule of follow-up, duration of treatment, benefits and any possibility of adverse event/s or withdrawal from the study. They were then asked to sign the written informed consent following previously mentioned ethical guidelines. Researchers who are members of the healthcare team of recruited patients were not involved in obtaining informed consent for those specific patients.

Randomization and Monitoring

Once patients were confirmed eligible and have consented to the study, they were randomized to one of two groups: the treatment arm (selenium 100 mcg/capsule, one capsule taken orally twice daily for six months) or the standard of care arm (no selenium, only standard of care). Randomization was performed using sealed envelopes, whereby, after providing consent, a patient was assigned a treatment regimen based on the contents of the envelope. Patients were aware of their treatment allocation (open-label), but the ophthalmologists performing assessments were masked to the treatment group.

Ophthalmologic assessments were conducted at three time points: baseline, three months after treatment initiation and six months after observation concluded. The three-month assessments aimed at evaluating any improvements or worsening of GO based on the assigned treatment arm.

The ophthalmologic assessments included several processes: visual acuity testing, external eye examination, extraocular movements' assessment, intraocular pressure measurement, margin-to-reflex distance measurement, optic nerve visualization, tear up break time evaluation, fluorescein dye testing and exophthalmometry. These examinations were performed at no cost to participants at the Ophthalmology Clinic of the UST Hospital Ambulatory Care Services.

To objectively assess ophthalmologic changes, the EUGOGO Case Record Form was used covering the following parameters: lid aperture, soft tissue involvement, proptosis, eye muscle involvement and visual acuity using Baily-Lovie chart. The CAS, which consists of seven items (spontaneous retrobulbar pain, pain during attempted up- or down-gaze, conjunctival redness, eyelid redness, chemosis, swelling of the caruncle and eyelid swelling) was recorded during the three time points as well. The score is the sum of aforementioned items.

Safety and Tolerability Assessment

Selenium is known to be readily absorbed and has not been associated with significant side effects. Throughout the study, any subjective complaints from patients were recorded similarly during the three time points. This was done to ensure safety and tolerability. All complaints or adverse events were documented as part of routine safety assessment during the course of the trial, ensuring that any potential adverse events were appropriately managed.

Withdrawal Criteria

The analysis was conducted using the "intention-to-treat" approach. For instance, patients who withdrew from the study due to non-compliance or worsening of their eye condition, which required specific eye treatment, were included in the primary analysis. The results from the last recorded visit were carried forward and evaluated as the final visit. Only patients who were lost to follow-up before the second visit at the three-month mark were excluded from the analysis.

Confounders

Potential confounders to this study include intake of multivitamins, as well as other antioxidants like glutathione by patients. This was noted upon enrolment of patients to the study.

Statistical Analysis

Descriptive statistics was used to summarize the demographic and clinical characteristics of patients. Frequency and proportion were used for categorical variables, median and interquartile range for non-normally distributed continuous variables, and mean and standard deviation for normally distributed continuous variables. Independent sample t-test, Mann-Whitney U test and Fisher's Exact/Chi-square test was used to determine the difference of mean, rank and frequency, respectively, between patients with selenium versus patients treated with standard of care. Paired sample t-test, Wilcoxon signed-rank test and McNemar test was used to determine the difference of mean, rank and frequency, respectively, on patients from initial to third month or sixth month observation. All statistical tests were two-tailed tests. Shapiro-Wilk test was used to test the normality of continuous variables. Missing values were neither replaced nor estimated. Null hypotheses were rejected at 0.05α-level of significance. STATA 13.1 was used for data analysis.

ETHICAL CONSIDERATIONS

Privacy and Confidentiality

The study ensured privacy and confidentiality of patient records by storing collected data in a password-protected electronic database, which may contain personal identifiers. A de-identified version of database was provided to the statistician and other authorized personnel. All paper-based data were securely stored in a locked cabinet. Access to collected data and research-related documents was restricted to members of the research team. However, if necessary, access may be granted to the USTH REC for verification purposes only. All collected data will be retained for a maximum of three years and destroyed thereafter by shredding, while electronic data will be disposed of by reformatting the electronic hard drive.

Benefits

Patients did not receive any reimbursement, compensation or incentives from this study. However,

Table 1. Baseline characteristics of the study population

Characteristic	Selenium (n=21)	Standard of Care (n=21)
Age – yrs	31 ± 10	32 ± 7
Female sex – number of patients (%)	19 (90.4)	17 (80.9)
Duration of ophthalmologic symptoms - months	5	4

information from the study will help the population affected with mild GO as this can further strengthen/weaken the 2016 EUGOGO recommendation of six-month selenium supplementation and its implementation among Filipino patients.

Risks and Inconvenience

Selenium when taken below the daily intake limit of 400 mcg is generally not associated with side effects. However, one study, titled "Selenium Supplementation and Secondary Prevention of Nonmelanoma Skin Cancer" by Duffield-Lillico, et al., (JNCI: Journal of the National Cancer Institute, Volume 95, Issue 19, 1 October 2003, Pages 1477–1481) reported that "individuals at high risk of non-melanoma skin cancer continue to demonstrate that selenium supplementation increases the risk of squamous cell carcinoma and total non-melanoma skin cancer."[11] To date, this is the only published risk of selenium supplementation.

Any expenses related to side effects or adverse reactions/events occurring during this clinical trial were shouldered by the investigators.

RESULTS

A total of 42 participants were included in the study, half of which was randomized to the selenium group and half assigned to the standard of care group. Both arms were composed of predominantly female sex with median duration of ophthalmologic symptoms of five months for the selenium group and four months for the standard of care group. There were no reports of side effects or adverse events noted.

Table 2 presents the findings of eye examinations conducted over three time points, which included the key parameters of best VA (BVA), relative afferent pupillary defect (RAPD) and color vision. At the initial assessment, there were no significant differences between the two groups as to BVA and color vision. There were no instances of RAPD in either group. At the three-month assessment, follow-up indicated a significantly higher BVA for the selenium group (median of 0.1, IQR 0 to 0.2 vs 0, IQR 0 to 0.1; p = 0.030) compared to the standard of care group. Additionally, the color vision demonstrated significant difference between groups, with the selenium group having a mean score of 14.9 (SD 0.37) compared to standard of care group (14.62, SD 0.73, p = 0.027). By the six-month follow-up, there was no significant difference in BVA and color vision between the two groups. Comparative analysis between initial and subsequent assessments also revealed no significant changes for either treatment group at both follow-ups.

Eyelid position findings, which included palebral aperture, upper lid retraction, lower lid retraction, lagophthalmos and lateral flare are noted in Table 3. At the initial and three-month assessment, there were no significant differences between the two groups across the measured parameters. By the six-month follow-up, significant differences emerged in lower lid retraction, where a median of 1 m (IQR: 0 to 1, p = 0.009) was recorded for both groups. Comparing the initial and six-month assessments, a significant change was noted for lower lid retraction for the selenium group (p = 0.002). For the other time points, there was insufficient evidence to state a statistically significant difference.

The CAS results are presented in Table 4 and at initial evaluation, spontaneous pain was reported by 15.48% of the total participants, with a significantly higher occurrence in the standard of care group (26.19% vs 4.76%, p = 0.007). Eyelid erythema was present in 4.76% of the total population, with all cases occurring in the standard of care group (9.52% vs 0, p = 0.040). Conjunctival redness on one hand was observed only in the selenium group (9.52% vs 0, p = 0.040). Lastly, caruncle/plical swelling was predominantly observed in the selenium group (33.33% vs 14.29%, p = 0.040). At three-month follow-up, a marked decrease in spontaneous pain was observed in the selenium group, with no participants reporting this symptom, while 26.19%

Table 2. Eye examination findings at three time points

	Treatment group			P-value
	Total (n=84)	Selenium (n=42)	Standard of Care (n=42)	
	Frequency (%); Mean ± SD; Median (IQR)			
Initial				
BVA	0 (0 to 0.2)	0.1 (0 to 0.2)	0 (0 to 0.2)	0.389
RAPD	0	0	0	-
Color Vision	14.75 ± 0.60	14.74 ± 0.54	14.76 ± 0.66	0.857
3rd month				
BVA	0 (0 to 0.2)	0.1 (0 to 0.2)	0 (0 to 0.1)	**0.030**
RAPD	0	0	0	-
Color Vision	14.76 ± 0.59	14.90 ± 0.37	14.62 ± 0.73	**0.027**
6th month				
BVA	0 (0 to 0.2)	0.1 (0 to 0.2)	0 (0 to 0.2)	0.126
RAPD	0	0	0	-
Color Vision	14.69 ± 0.64	14.76 ± 0.53	14.62 ± 0.73	0.309
Initial vs 3rd month				
BVA	0.420	0.951	0.197	
RAPD	-	-	-	
Color Vision	0.897	0.104	0.349	
Initial vs 6th month				
BVA	0.269	0.652	0.242	
RAPD	-	-	-	
Color Vision	0.534	0.840	0.349	

of those in the standard of care group continued to experience it (p<0.001). The CAS scores reflected a significant shift overall, with more eyes having a score of 0 compared to a score of 1 or 2 (p = 0.049). Notably eyelid swelling remained prevalent, but no significant differences were found between the two groups. At the six-month assessment, spontaneous pain continued to be significantly lower in the selenium group (4.76% vs 19.05%, p = 0.043). Eyelid erythema remained significant, as it was noted in 4.76% of the eyes of the total population, all of whom were in the standard of care group (p = 0.040). The CAS scores showed improvement with 47.64% of all participants having a score of zero (p = 0.017), which was highest in frequency in the selenium group at 61.9%. Comparing the initial assessment to three-month evaluation, frequency of caruncle/plical swelling was less overall (23.18% to 8.33%, p = 0.006) and in the selenium group (33.33% to 4.76%, p = 0.005). The CAS scores at this interval also indicated significant improvement in both groups with a score of zero more frequent overall (29.76% to 51.19%, p = 0.016) and in the selenium group (33.33% to 64.29%, p = 0.018). When comparing initial to six-month values, the trend remains consistent, with notable decrease in caruncle/plical swelling and increase in frequency of CAS score of zero overall and in the selenium group.

The significant difference in caruncle/plical swelling was enough to cause significant difference in CAS between the two groups (selenium and non-selenium) in the third month up to the sixth month with a p-value of 0.016 and 0.036, respectively.

It showed that on initial examination for the selenium group, 14 eyes (33.33%) had a CAS score of 0, which increased to 27 eyes (64.29%) in the third month and ended to a total of 26 eyes (61.9%) at the sixth month of treatment. While for the non-selenium group, 11 eyes had a CAS score of zero initially, increased to 16 eyes (and 38.1%), then finally arrived to a total count of 14 eyes (33.33%).

Table 3. Eyelid position findings

	Treatment group			P-value
	Total (n=84)	**Selenium (n=42)**	**Standard of Care (n=42)**	
	Frequency (%); Median (IQR)			
Initial				
1st Fixation	0	0	0	-
Palpebral Aperture, mm	9 (8 to 11)	9 (8 to 11)	9 (8 to 11)	0.480
Upper Lid Retract, mm	0 (0 to 1)	0 (0 to 0)	0 (0 to 1)	0.648
Lower Lid Retract, mm	1 (0 to 1)	1 (0 to 1)	1 (0 to 1)	0.543
Lagophthalmos	0 (0 to 1)	0 (0 to 1)	0 (0 to 1)	0.409
Lateral Flare	0	0	0	-
3rd month				
1st Fixation	0	0	0	-
Palpebral Aperture, mm	9 (8 to 10)	9 (8 to 10)	9 (8 to 10)	0.756
Upper Lid Retract, mm	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0.273
Lower Lid Retract, mm	1 (0 to 1)	1 (0 to 1)	1 (0 to 1)	0.808
Lagophthalmos	0 (0 to 1)	0 (0 to 1)	0 (0 to 1)	0.885
Lateral Flare	3 (3.57)	3 (7.14)	0	0.241
6th month				
1st Fixation	0	0	0	-
Palpebral Aperture, mm	9 (8 to 10)	9 (8 to 9)	9 (8 to 10)	0.815
Upper Lid Retract, mm	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	0.100
Lower Lid Retract, mm	1 (0 to 1)	1 (0 to 1)	1 (0 to 1)	**0.009**
Lagophthalmos	0 (0 to 0)	0 (0 to 0)	0 (0 to 1)	0.058
Lateral Flare	0	0	0	-
Initial vs 3rd month				
1st Fixation	-	-	-	
Palpebral Aperture	0.196	0.316	0.413	
Upper Lid Retract	0.089	0.148	0.337	
Lower Lid Retract	0.167	0.663	0.110	
Lagophthalmos	0.081	0.080	-	
Lateral Flare	-	-	-	
Initial vs 6th month				
1st Fixation	-	-	-	
Palpebral Aperture	0.061	0.213	0.269	
Upper Lid Retract	0.090	0.085	0.467	
Lower Lid Retract	**0.002**	**0.008**	0.114	
Lagophthalmos	-	-	-	
Lateral Flare	-	-	-	

Analyzing the proportion of patients who achieved CAS score 1 among the two groups, it has also been shown how 21 (50) eyes in the selenium group showed statistically significant improvement in terms of decrease in number to 11 and 12 eyes, respectively (26%-28%) for the third and sixth month of treatment.

Lastly, the same pattern was observed for CAS 2, wherein a statistically significant decrease in the number of eyes obtaining CAS score 2 was shown in the selenium group, from 7 eyes (16.67) to 4 eyes

Table 4. CAS score

	Treatment group			P-value
	Total (n=84)	**Selenium (n=42)**	**No selenium (control) (n=42)**	
	Frequency (%)			
Initial				
Spontaneous pain	13 (15.48)	2 (4.76)	11 (26.19)	**0.007**
Gaze pain	2 (2.38)	0	2 (4.76)	0.152
Eyelid swelling	30 (35.71)	13 (30.95)	17 (40.48)	0.62
Eyelid erythema	4 (4.76)	0	4 (9.52)	**0.040**
Conjunctival redness	4 (4.76)	4 (9.52)	0	**0.040**
Chemosis	2 (2.38)	2 (4.76)	0	0.152
Caruncle/Plical swelling	20 (23.81)	14 (33.33)	6 (14.29)	**0.040**
CAS score				0.729
0	25 (29.76)	14 (33.33)	11 (26.19)	
1	43 (51.19)	21 (50)	22 (52.38)	
2	16 (19.05)	7 (16.67)	9 (21.43)	
3rd month				
Spontaneous pain	11 (13.1)	0	11 (26.19)	**<0.001**
Gaze pain	0	0	0	-
Eyelid swelling	27 (32.14)	11 (26.19)	16 (38.1)	0.243
Eyelid erythema	2 (2.38)	0	2 (4.76)	0.152
Conjunctival redness	4 (4.76)	2 (4.76)	2 (4.76)	1.000
Chemosis	0	0	0	-
Caruncle/Plical swelling	7 (8.33)	3 (7.14)	4 (9.52)	0.693
Decreased VA	3 (3.57)	3 (7.14)	0	0.078
Increased proptosis	0	0	0	-
Decreased EOMs	0	0	0	-
CAS score				**0.049**
0	43 (51.19)	27 (64.29)	16 (38.1)	
1	28 (33.33)	11 (26.19)	17 (40.48)	
2	13 (15.48)	4 (9.52)	9 (21.43)	
6th month				
Spontaneous pain	10 (11.9)	2 (4.76)	8 (19.05)	**0.043**
Gaze pain	2 (2.38)	0	2 (4.76)	0.152
Eyelid swelling	32 (38.1)	12 (28.57)	20 (47.62)	0.072
Eyelid erythema	4 (4.76)	0	4 (9.52)	**0.040**
Conjunctival redness	2 (2.38)	0	2 (4.76)	0.152
Chemosis	0	0	0	-
Caruncle/Plical swelling	8 (9.52)	6 (14.29)	2 (4.76)	0.137
Decreased VA	2 (2.38)	0	2 (4.76)	0.152
Increased proptosis	0	0	0	-
Decreased EOMs	0	0	0	-
CAS score				**0.017**
0	40 (47.62)	26 (61.9)	14 (33.33)	
1	28 (33.33)	12 (28.57)	16 (38.1)	
2	16 (19.05)	4 (9.52)	12 (28.57)	

Table 4. CAS score (continued)

	Treatment group			P-value
	Total (n=84)	Selenium (n=42)	No selenium (control) (n=42)	
	Frequency (%)			
Initial vs 3rd month (p-value)				
Spontaneous pain	0.659	0.494	1.000	
Gaze pain	0.497	-	0.494	
Eyelid swelling	0.625	0.629	0.823	
Eyelid erythema	0.406	-	0.397	
Conjunctival redness	1.000	0.397	0.152	
Chemosis	0.497	0.494	-	
Caruncle/Plical swelling	**0.006**	**0.005**	0.738	
CAS score	**0.016**	**0.018**	0.457	
Initial vs 6th month (p-value)				
Spontaneous pain	0.501	1.000	0.434	
Gaze pain	1.000	-	1.000	
Eyelid swelling	0.749	0.811	0.182	
Eyelid erythema	1.000	-	1.000	
Conjunctival redness	0.682	0.116	0.494	
Chemosis	0.155	0.494	-	
Caruncle/Plical swelling	**0.013**	**0.040**	0.265	
CAS score	**0.036**	**0.033**	0.420	

Table 5. Number of patients with CAS 0

	Initial	3 months	6 months
Selenium	14 (33.33)	27 (64.29)	26 (61.9)
Non-selenium	11 (26.19)	16 (38.1)	14 (33.33)

Table 6. Number of patients with CAS 1

	Initial	3 months	6 months
Selenium	21 (50)	11 (26.19)	12 (28.57)
Non-selenium	22 (52.38)	17 (40.48)	16 (38.1)

Table 7. Number of patients with CAS 2

CAS score	Initial	3 months	6 months
Selenium	7 (16.67)	4 (9.42)	4(9.52)
Non-selenium	9 (21.43)	9 (21.43)	12(28.57)

(9.52). This pattern was not seen in the non-selenium group.

DISCUSSION

This study showed that by the three-month follow-up, the selenium group demonstrated significantly higher BVA and color vision values, but this change was not sustained by the six-month assessment. Significant findings also emerged in eyelid position, particularly lower lid retraction, with the selenium group showing notable improvement compared to the initial assessment. In terms of spontaneous pain, at the onset, this was significantly lower in the selenium group and was further decreased by the three-month period and sustained up to the six-month period. The CAS score indicated overall improvement, with a higher frequency of participants scoring zero in the selenium group at six months. The caruncle/plical swelling decreased significantly in both groups over time, with the selenium group showing a substantial reduction.

These findings align with the study of Marcocci, et al., which demonstrated significantly better overall ophthalmic outcome in patients receiving selenium supplementation compared to the standard care group at the six-month evaluation.[10] In both studies, patients receiving selenium supplementation exhibited a lower CAS and visual acuity remained stable across groups throughout the study periods. Marcocci, et al., also observed significantly lower CAS in the selenium group, corroborating improvements in soft tissue signs and lid retraction

in our study.[10] However, the study findings from Kahaly, et al., conducted in Germany, concluded that selenium supplementation did not significantly affect the clinical course or serological parameters in selenium-sufficient hyperthyroid patients with Graves' disease.[12]

In a more recent study of a cohort of 74 patients, they explored the efficacy of selenium supplementation in patients with mild-to-moderate GO over a five-year period. Those receiving selenium showed significant improvement in symptoms such as tearing, grittiness and conjunctival congestion, as well as better clinical activity and quality of life scores at the six-month follow-up compared to placebo. Selenium also led to a higher rate of improvement and lower rate of worsening in early disease progression. However, while both selenium and placebo groups showed long-term improvement in proptosis and quality of life at the five-year mark, the effects of selenium did not significantly influence long-term outcomes. Thus, as with our study findings, selenium appears beneficial in modifying early GO progression, but does not offer sustained long-term benefits.[13]

One limitation of the current study is the absence of baseline selenium level measurements, which could have provided insight into whether participants were selenium-deficient. This factor might have influenced the efficacy of selenium supplementation in this study. Nevertheless, a study conducted by Wang, et al., in China, involving participants without selenium deficiency, found that selenium supplementation led to decreased thyroglobulin and thyroid-stimulating hormone (TSH) levels, improved quality of life and delayed progression of GO.[14] Additionally, a review by Lanzolla, et al., which included studies with both selenium-sufficient and selenium-deficient participants, concluded that selenium supplementation may positively influence the course of GO.[15]

Last, it is important to note that the study sample size was limited, partly due to challenges posed by the COVID-19 pandemic. Future studies should aim to include large sample sizes to further validate these findings and refine the recommendations for selenium supplementation in the management of mild GO.

CONCLUSION

Selenium supplementation appears to provide significant short-term benefits, particularly in having better BVA, color vision and reducing spontaneous pain in patients compared to standard of care. The selenium group also showed notable improvements in eyelid position, with a reduction in lower lid retraction and caruncle/plical swelling over time. While the differences in visual improvements were not sustained beyond three months, the continued reduction in pain and inflammatory signs, such as pain and eyelid erythema at six months suggests that selenium may offer longer-term anti-inflammatory benefits. Overall, selenium supplementation shows promise as supportive therapy for improving clinical outcomes, particularly in reducing inflammation and enhancing ocular function in the short-term, though more research is needed to assess its long-term efficacy.

Statement of Authorship

All authors claim fulfillment of International Committee of Medical Journal Editors (ICMJE) authorship criteria.

Credit Author Statement

JMF: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization, Project administration, Funding acquisition;

NADS: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization, Project administration;

JDUH: Conceptualization, Methodology, Validation, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision, Project administration, Funding acquisition;

ASP: Conceptualization, Methodology, Validation, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision,

Author Disclosure

The authors declared no conflict of interest.

Funding Source

2023 Philippine College of Endocrinology Research Grant

REFERENCES

1. Gontarz-Nowak K, Szychlińska M, Matuszewski W, Stefanowicz-Rutkowska M, Bandurska-Stankiewicz E. Current knowledge on Graves' orbitopathy. *J Clin Med* [Internet]. 2020;10(1):16. Available from: http://dx.doi.org/10.3390/jcm10010016
2. Hiromatsu Y, Eguchi H, Tani J, Kasaoka M, Teshima Y. Graves' ophthalmopathy: epidemiology and natural history. *Intern Med* [Internet]. 2014;53(5):353–60. Available from: http://dx.doi.org/10.2169/internalmedicine.53.1518
3. Lat AM, Jauculan MC, Sanchez CA, Jimeno C, Sison-Peña CM, Pe-Yan MR, et al. Risk factors associated with the activity and severity of Graves' ophthalmopathy among patients at the university of the Philippines manila-Philippine General Hospital. *J ASEAN Fed Endocr Soc* [Internet]. 2017;32(2):151–7. Available from: http://dx.doi.org/10.15605/jafes.032.02.09
4. Bartalena L, Baldeschi L, Boboridis K, Eckstein A, Kahaly GJ, Marcocci C, et al. The 2016 European thyroid association/European group on Graves' orbitopathy guidelines for the management of Graves' orbitopathy. *Eur Thyroid J* [Internet]. 2016;5(1):9–26. Available from: http://dx.doi.org/10.1159/000443828
5. Chaudhry IA. Thyroid associated orbitopathy: Understanding pathophysiology. *Saudi J Ophthalmol* [Internet]. 2011;25(1):1–2. Available from: http://dx.doi.org/10.1016/j.sjopt.2010.11.001
6. Bartalena L, Piantanida E, Gallo D, Lai A, Tanda ML. Epidemiology, natural history, risk factors, and prevention of Graves' orbitopathy. *Front Endocrinol (Lausanne)* [Internet]. 2020;11:615993. Available from: http://dx.doi.org/10.3389/fendo.2020.615993
7. Palisoc E, Morabe E, Pagkatipunan PM. Prevalence of Graves' ophthalmopathy among patients with thyroid disease. *Philipp J Ophthalmol.* 2010;35(1):32–5.
8. Drui D, Du Pasquier Fediaevski L, Vignal Clermont C, Daumerie C. Graves' orbitopathy: Diagnosis and treatment. *Ann Endocrinol (Paris)* [Internet]. 2018;79(6):656–64. Available from: http://dx.doi.org/10.1016/j.ando.2018.08.005
9. Bednarczuk T, Schomburg L. Challenges and perspectives of selenium supplementation in Graves' disease and orbitopathy. *Hormones (Athens)* [Internet]. 2020;19(1):31–9. Available from: http://dx.doi.org/10.1007/s42000-019-00133-5
10. Marcocci C, Kahaly GJ, Krassas GE, Bartalena L, Prummel M, Stahl M, et al. Selenium and the course of mild Graves' orbitopathy. *N Engl J Med* [Internet]. 2011;364(20):1920–31. Available from: http://dx.doi.org/10.1056/NEJMoa1012985
11. Duffield-Lillico AJ, Slate EH, Reid ME, Turnbull BW, Wilkins PA, Combs GF Jr, et al. Selenium supplementation and secondary prevention of nonmelanoma skin cancer in a randomized trial. *J Natl Cancer Inst* [Internet]. 2003;95(19):1477–81. Available from: http://dx.doi.org/10.1093/jnci/djg061
12. Kahaly GJ, Riedl M, König J, Diana T, Schomburg L. Double-blind, placebo-controlled, randomized trial of selenium in Graves' hyperthyroidism. *J Clin Endocrinol Metab.* 2017;102(11):4333–41.
13. Wang C, Qiao J, Liu S, Piao S, Zhou Y, Hu Y, et al. Selenium in the treatment of mild-to-moderate Graves' orbitopathy: a 5-year prospective controlled cohort study. *Endocrine* [Internet]. 2024;84(3):1072–80. Available from: http://dx.doi.org/10.1007/s12020-023-03672-5
14. Wang Y, Patel A, Douglas RS. Thyroid eye disease: How a novel therapy may change the treatment paradigm. *Ther Clin Risk Manag* [Internet]. 2019;15:1305–18. Available from: http://dx.doi.org/10.2147/TCRM.S193018
15. Lanzolla G, Marinò M, Marcocci C. Selenium in the treatment of Graves' hyperthyroidism and eye disease. *Front Endocrinol (Lausanne)* [Internet]. 2020;11:608428. Available from: http://dx.doi.org/10.3389/fendo.2020.608428

APPENDIX 1: EUGOGO GO QUALITY OF LIFE QUESTIONNAIRE

GO-Quality Of Life Questionnaire ☐ initial ☐ follow-up Date

The following questions deal specifically with your thyroid eye disease. Please focus on the past week while answering these questions.

During the past week, to what extent were you limited in carrying out the following activities, because of your thyroid eye disease?

Tick the box that matches your answer. The boxes correspond with the answers above them.
Please tick only one box for each question.

		Yes seriously limited	Yes a little limited	No not at all limited
1)	Bicycling (never learned to ride a bike☐)	☐	☐	☐
2)	Driving (no driver's licence ☐)	☐	☐	☐
3)	Moving around the house	☐	☐	☐
4)	Walking outdoors	☐	☐	☐
5)	Reading	☐	☐	☐
6)	Watching TV	☐	☐	☐
7)	Hobby or pastime, i.e.	☐	☐	☐

		Yes severely hindered	Yes a little hindered	No not at all hindered	
8)	During the past week, did you feel hindered from something that you wanted to do because of your thyroid eye disease?	☐	☐	☐	Score

The following questions deal with your thyroid eye disease in general

		Yes, very much so	Yes a little	No not at all	
9)	Do you feel that you appearance has changed because of your thyroid eye disease?	☐	☐	☐	
10)	Do you feel that you are stared at in the streets because of thyroid eye disease	☐	☐	☐	
11)	Do you feel that people react unpleasantly because of your thyroid eye disease?	☐	☐	☐	
12)	Do you feel that your thyroid eye disease has an influence on your self-confidence?	☐	☐	☐	
13)	Do you feel socially isolated because of your thyroid eye disease	☐	☐	☐	
14)	Do you feel that your thyroid eye disease has an influence on making friends?	☐	☐	☐	
15)	Do you feel that you appear less often on photos than before you had thyroid eye disease?	☐	☐	☐	
16)	Do you try mask changes in appearance caused by your thyroid eye disease?	☐	☐	☐	Score

GO-Quality Of Life Questionnaire ☐ initial ☐ follow-up Date

The following questions deal specifically with your thyroid eye disease. Please focus on the past week while answering these questions.

During the past week, to what extent were you limited in carrying out the following activities, because of your thyroid eye disease?

Tick the box that matches your answer. The boxes correspond with the answers above them.
Please tick only one box for each question.

		Yes seriously limited	Yes a little limited	No not at all limited
1)	Bicycling (never learned to ride a bike☐)	☐	☐	☐
2)	Driving (no driver's licence ☐)	☐	☐	☐
3)	Moving around the house	☐	☐	☐
4)	Walking outdoors	☐	☐	☐
5)	Reading	☐	☐	☐
6)	Watching TV	☐	☐	☐
7)	Hobby or pastime, i.e.	☐	☐	☐

		Yes severely hindered	Yes a little hindered	No not at all hindered	
8)	During the past week, did you feel hindered from something that you wanted to do because of your thyroid eye disease?	☐	☐	☐	Score

The following questions deal with your thyroid eye disease in general

		Yes, very much so	Yes a little	No not at all	
9)	Do you feel that you appearance has changed because of your thyroid eye disease?	☐	☐	☐	
10)	Do you feel that you are stared at in the streets because of thyroid eye disease	☐	☐	☐	
11)	Do you feel that people react unpleasantly because of your thyroid eye disease?	☐	☐	☐	
12)	Do you feel that your thyroid eye disease has an influence on your self-confidence?	☐	☐	☐	
13)	Do you feel socially isolated because of your thyroid eye disease	☐	☐	☐	
14)	Do you feel that your thyroid eye disease has an influence on making friends?	☐	☐	☐	
15)	Do you feel that you appear less often on photos than before you had thyroid eye disease?	☐	☐	☐	
16)	Do you try mask changes in appearance caused by your thyroid eye disease?	☐	☐	☐	Score

APPENDIX 2: EUGOGO INITIAL ASSESSMENT FORM

EUGOGO CENTRE CODE Study CODE (letter) EUGOGO patient number

EUGOGO initial assessment proforma

Please complete **non-italicised boxes** except where indicated, plus relevant ***italicised*** ones.
For queries on entering dates click here. *For hard copies, ensure header complete for each page*

1. Date of inclusion

dd *mm* *yyyy*

Year of birth

Sex | **Body Weigth (kg)** | **Height (cm)**

Race | Other (specify)

2. Thyroid history

Onset of thyroid symptoms (mm (or season) / yyyy)

Date of diagnosis

Has the patient relapsed after treatment?

2.1 Previous thyroid treatments:

a) ATD *commenced* *No.courses*

Current ? *stopped*

b) Radio-iodine

Dates of treatment *1.* *2.* *3.*

Total dose given (mBq)

c) Thyroidedectomy *Date of last operation*

3. Current thyroid status

3.1 Visible goiter?

3.2 Thyroid dermopathy?

3.2.1 Clinical status

3.3 Current thyroid medication:

carbimazole mg **OR** methimazole mg

PTU mg

T4 µg

T3 µg

3.4 Thyroid tests:

fT4 , pmo/L / , ng/dl

fT3 , pmo/L / , ng/dl / **OR T3** , nmol/L

TSH , mU/L

TRAb *specify units* *and assay*

TPO Ab *kU/L* *specify assay*

4. Patient co-morbidity (non-ocular)

diabetes ☐
Addison's ☐
pernicious anaemia ☐
vitiligo ☐
rheumatoid arthritis ☐
other autoimmune ☐

5. Smoking history ☐

If current or ex-smoker of cigarettes:

total consumption ☐ *packyears (yers x packs per day)*

current daily intake ☐

If ex-smoker, when stopped: ☐ ☐ *(mm / yyyy)*

6. Family history

FH autoimmune thyroid disease ☐
FH autoimmune diabetes ☐
FH other autoimmune disease ☐

7. GO history

7.1 Date of eye symptom onset ☐ ☐ *(mm / yyyy)*

7.2 Previous and current treatments (please tick "c" if treatment continuing

7.2.1 Topical eye preparations ☐ *commenced* ☐ ☐

7.2.2 Systemic steroids ☐ *from* ☐ ☐ *until* c☐ *OR* ☐ ☐

If second course *from* ☐ ☐ *until* c☐ *OR* ☐ ☐

If third course *from* ☐ ☐ *until* c☐ *OR* ☐ ☐

7.2.3 Orbital irradiation ☐ *from* ☐ ☐ *until* ☐ ☐

7.2.4 Surgery for GO ☐

If Surgery for GO:

orbital decompression ☐ *date* ☐ ☐ *specify* ☐

eye muscule surgery ☐ *date* ☐ ☐ *specify* ☐

eyelid surgery ☐ *date* ☐ ☐ *specify* ☐

Other (specify) ☐

7.2.5 Other previous or current treatment for GO

☐ *date* ☐ ☐ *specify* ☐

Is this treatment continuing ☐

8. Current medications *(please list all medications)*

Drug	Dose	Times per day

9. Graves' orbitopathy: current status

SYMPTOMS-during last four weeks

1. Painful oppressive feeling in or behind the globe ☐
2. Gaze evoked pain ☐
3. Excessive watering ☐
4. Photophobia ☐
5. Grittiness ☐
6. Double vision ☐
7. Gorman score (NB: if wearing prism then score as "constant" ☐
6. Blurred vision ☐

10. Examination of eyes

	Right / OD	Left / OS
Best visual acuity (decimalised)	☐,☐	☐,☐
RAPD	☐	☐
Color vision	☐	☐

SOFT TISSUE SIGNS

'Active' eyelid swelling	☐	☐
Eyelid erythema	☐	☐
Conjunctival redness	☐	☐
Chemosis	☐	☐
Caruncle swelling	☐	☐
Pilcal swelling	☐	☐
Redness Lat.Rect. insertion	☐	☐
Sup. limbic keratoconjunctiv.	☐	☐

Eyelid Positions: (examine with **distance** fixation)

	Right / OD	Left / OS
1° fixation impossible if no AHP	☐	☐
Palprebral aperture	☐ mm	☐ mm

(+ / -) Upper lid retraction ☐☐ mm ☐☐ mm (relative to limbus)

(+ / -) Lower lid retraction ☐☐ mm ☐☐ mm (relative to limbus)

Lagophthalmos ☐ ☐

Lateral flare ☐ ☐

Proptosis (mm) ☐ ☐

Intercanthal distance ☐

Exophalmometer ☐

MOTILITY:

Abnormal head posture present ☐

Eye position with preferred *distance* fixation when AHP corrected

esotropia ☐

exotropia ☐

hypotropia ☐

hypertropia ☐

Binocular single vision possible *without* prism ☐

Monocular duction	Right / OD	Left / OS
adduction	☐°	☐°
abduction	☐°	☐°
90° elevation	☐°	☐°
270° depression	☐°	☐°

	Right / OD	Left / OS
CORNEA	☐	☐

Bell's phenomenon ☐

Intraocular pressure (1° position)

Right / OD	Left / OS
☐	☐

OPTIC NEUTROPATHY ASSESSMENT: (in addition to VA, colour + pupil assessments)

Disc	☐	☐
Choroidal folds	☐	☐
Is there evidence of optic neuropathy ?	☐	☐

please specify any additional evidence for e.g. visual fields, VEP, contrast sensitivity

☐

11. Ocular co-morbidity with influence on GO assessment

glaucoma	
cataract	
other	
if yes, please specify what effect on GO signs	

12. Summary of GO

Evidence of orbitopathy	
Clinically active GO	

13. CAS score

Sum of symptoms 9.1, 9.2 plus all 5 soft tissue signs if score in either eye 2mm proptosis increase; >8° ocular excursion decrease; acuity loss of 1 Snellen lin	
Total CAS (insert possible total in 2nd box	

14. NOSPECS

N	☐	O	☐	2		3		4		5		6	

(please encircle "N" or "O", or otherwise complete all numbered boxes with O,a,b or c)

15. Initial management plan

Immunosuppression		
Irradiation		
Surgery		
Close observation		
Discharge		
Other		*specify*

a) IF immunosuppression is planned:

Steroids		
If yes		
Initial dose		*mg (prednisolone eqivalent)*
Planned Duration		*months*
Lanreoide		
Octreotide		
IV Ig		
Other (specify		

b) IF irradiation is planned:

dose		Gy	Fractions
Durations		weeks	

c) If surgical procedures are planned:

Decompression

if yes (a)

(b)

Approach Right

If other, or combination of above, please specify

Approach Left

If other, or combination of above, please specify

Removal of bony walls	Right / OD	Left / OS
inferior		
medial		
lateral		
superior		
posterior		
Removal of fat		

Strabismus surgery

If yes, which muscles and what:	Right / OD	Left / OS
rectus medialis		
rectus lateralis		
rectus superior		
rectus inferior		
superior olique		
inferior oblique		

Eyelid surgery

If yes, which lid and what:	Right / OD	Left / OS
eyelid lengthening		
skin removal		
fat removal		
shortening		
tarsorrhaphy		

Other treatment for GO

Antioxidants		*specify*	
Tropical lubricants			
Diuretics			
Other (please specify)			

End of proforma for initial assessment: any other remarks

APPENDIX 3: EUGOGO FOLLOW-UP ASSESSMENT FORM

EUGOGO CENTRE CODE Study CODE (letter) EUGOGO patient number

EUGOGO follow-up assessment proforma

Please complete **non-italicised boxes** except where indicated, plus relevant ***italicised*** ones. For queries on entering dates click here. *For hard copies, ensure header complete for each page*

Date of follow up ☐☐ ☐☐ ☐☐☐☐ *(dd mm yyyy)*

Year of birth ☐☐☐☐ (dd mm yyyy) **Body Weigth (kg)** ☐☐☐

F2. Recent thyroid Status

2.0 Dysthyroidism since last data sent ☐

If yes, please specify changes only *(please encircle "C" if treatment is continuing)*

2.2 Thyroid treatment since data last sent

ATD ☐

Commenced ☐☐ ☐☐☐☐ *until* C☐ *OR* ☐☐ ☐☐☐☐

Radio-iodine ☐

Date of treatment ☐☐ ☐☐ ☐☐☐☐
dd mm yyyy

Total Dose given (mBQ) ☐☐☐☐

Thyroidectomy ☐

Date of operation ☐☐ ☐☐ ☐☐☐☐
dd mm yyyy

F3. Current thyroid status

3.3. Current thyroid medication Time since starting (months)

carbimazole	☐☐	*mg/d*	☐☐☐☐
methimazole	☐☐	*mg/d*	☐☐☐☐
PTU	☐☐☐☐	*mg/d*	☐☐☐☐
T4	☐☐☐☐	*µg/d*	☐☐☐☐
T3	☐☐☐☐	*µg/d*	☐☐☐☐

No medication ☐

3.4 Thyroid tests

fT4 ☐☐,☐ pmo/L / ☐☐,☐ ng/dl

fT3 ☐☐,☐ pmo/L / ☐☐,☐ ng/dl / **OR T3** ☐☐,☐ nmol/L

TSH ☐☐,☐ mU/L

TRAb ☐☐☐☐ *specify units* ☐☐☐☐ *and assay* ☐☐☐☐☐☐☐☐

TPO Ab ☐☐☐☐ *kU/L* *specify assay* ☐☐☐☐☐☐☐☐

F4. Patient co-morbidity

Any significant change ☐☐☐☐ *specify* ☐☐☐☐☐☐☐☐

F5. Smoking

Never smoked	☐	***if you have ticked this box go straight to section F9***
Ex-smoker	☐	*when stopped* *(dd mm yyyy)*
Current smoker	☐	*current dailyintake*
Passive smoker	☐	

F9. Graves orbitopathy: current status

SYMPTOMS - during last four weeks

1. painful oppressive feeling in or behind the globe ☐
2. Gaze evoked pain ☐
3. Exessive watering ☐
4. Photophobia ☐
5. Grittiness ☐
6. Double vision ☐
7. Gorman score (NB: if wearing prism then score as "constant") ☐
8. Blurred vision ☐

F10. Examination of eyes

	Right / OD	Left / OS
Best visual acuity	☐, ☐	☐, ☐
RAPD	☐	☐
Color vision	☐	☐

SOFT TISSUE SIGNS

'Active'eyelid swelling	☐	☐
Eyelid erythema	☐	☐
Conjunctival redness	☐	☐
Chemosis	☐	☐
Caruncle swelling	☐	☐
Plical swelling	☐	☐
Redness Lat.Rect. insertion	☐	☐
Sup. limbic keratoconjunctiv.	☐	☐

Eyelid Positions: (examine with distance fixation)

	Right / OD	Left / OS
1° fixation impossible if no AHP	☐	☐
Palprebral aperture	☐ mm	☐ mm
(+ / -) Upper lid retraction	☐ ☐ mm	☐ ☐ mm (relative to limbus)
(+ / -) Lower lid retraction	☐ ☐ mm	☐ ☐ mm (relative to limbus)
Lagophthalmos	☐	☐

Lateral flare

Proptosis (mm)

Intercanthal distance

Exophalmometer

Motility:

a) Abnormal head posture present

b) Orthotropic

Eye position with preferred *distance* fixation when AHP corrected

esotropia

exotropia

hypotropia

hypertropia

Binocular single vision possible *without* prism

Monocular ductions	Right / OD	Left / OS
adduction	°	°
abduction	°	°
90° elevation	°	°
270° depression	°	°

	Right / OD	Left / OS
CORNEA		

Intraocular pressure (1° position)

Right / OD	Left / OS

OPTIC NEUROPATHY ASSESSMENT: (in addition to VA, colour + pupil assessments)

Disc

Choroidal folds

Is there evidence of optic neuropathy ?

please specify any additional evidence for e.g. visual fields, VEP, contrast sensitivity

F11. Ocular co-morbidity with influence on GO assessment

glaucoma

cataract

other

if yes, please specify what effect on GO signs

F12. Summary of GO

12.1Evidence of orbitopathy

12.2Clinically active GO

F13. CAS score

Sum of symptoms 9.1, 9.2 plus all 5 soft tissue signs if score in either eye
2mm proptosis increase; >8° ocular excursion decrease; acuity loss of 1 Snellen lin

Total CAS (insert possible total in 2nd box

F14. NOSPECS

N		O		2		3		4		5		6	

(please encircle "N" or "O", or otherwise complete all numbered boxes with O,a,b or c)

F16. Changes in orbitopathy since last data sent

16.1 subjective symptoms: Overall trend

Overall change in signs of severity

Overall change in signs of activity

Active GO treatment since last data

16.2 GO treatment since last data

16.2.1 Topical lubricants

16.2.2 Immunosuppression *If yes, agent used?*

initial dose *duration (weeks)* Or current

change from initial plan data?

16.2.3 Orbital irradiation *Gy* *fractions* *Duration weeks*

change from initial plan data?

16.2.4 Surgery for GO *(what, and which side*

change from initial plan data?

F17. Further management plans

a) Immunosuppression

b) Irradiation

c) Surgery *specify*

d) Other ☐ specify ☐

e) Discharge ☐

a) IF immunosuppression is planned:

Steroids ☐

If yes ☐

Initial dose *mg (prednisolone eqivalent)*

Planned Duration *months*

Lanreotide ☐

Octreotide ☐

IV Ig ☐

Other (specify) ☐

b) IF irradiation is planned:

dose ☐ *Gy* *Fractions* ☐

Durations ☐ *weeks*

c) If surgical procedures are planned:

1. Decompression ☐ *if yes (a)* ☐

(b) ☐

Approach Right ☐

If other, or combination of above, please specify ☐

Approach Left ☐

If other, or combination of above, please specify ☐

Removal of bony walls	**Right / OD**	**Left / OS**
inferior	☐	☐
medial	☐	☐
lateral	☐	☐
superior	☐	☐
posterior	☐	☐
Removal of fat	☐	☐

2. Strabismus surgery ☐

If yes, which muscles and what:	**Right / OD**	**Left / OS**
rectus medialis	☐	☐
rectus lateralis	☐	☐
rectus superior	☐	☐

rectus inferior		
superior olique		
inferior oblique		

3. Eyelid surgery

If yes, which lid and what:	*Right / OD*	*Left / OS*
eyelid lengthening		
skin removal		
fat removal		
shortening		
tarsorrhaphy		

Other treatment for GO

Antioxidants		*specify*
Tropical lubricants		
Diuretics		
Other (please specify)		

End of proforma for follow-up assessment: any other remarks

APPENDIX 4: EUGOGO RECOMMENDATIONS FOR ASSESSING RESPONSE TO INTERVENTION IN CLINICAL TRIALS 18

Primary outcomes	
Objective parameters	Change required
CAS	≥2 Points
Lid aperture	≥2 mm
Soft tissue involvement	≥One grade in any of the following: Eyelid swelling, eyelid erythema, conjunctival redness or conjunctival oedema
Exophthalmos	≥2 mm
Subjective diplopia	≥One grade
Ductions	≥8° In at least one direction of gaze
Visual function	Change of best corrected visual acuity by ≥2 lines on Snellen chart, or Substantial colour vision change, or Significant change of visual fields, or Significant change in optic disc appearance, or (Dis-)appearance of relative afferent pupillary defect
Subjective parameters	
Disease-specific quality-of-life questionnaire (GO-QOL) (10, 11)	
Visual functioning (score 0–100)	≥6 Points
Appearance (score 0–100)	≥6 Points
Secondary outcome	
Orbital volume changes by serial imaging may be included as a secondary outcome, although the clinical importance of volume changes remain to be defined	

The left hand column lists the parameters assessed; the right hand column defines the minimum change required in each parameter for an individual patient before and after an intervention, for the purposes of classifying the overall response.

APPENDIX 5: EUGOGO SEVERITY CLASSIFICATION 19

European Group on Graves'orbitopathy (EUGOGO) recommends the following classification of patients with GO

Sight-threatening GO	Patients with dysthyroid optic neuropathy (DON) and/or corneal breakdown. This category warrants immediate intervention.
Moderate-to-severe GO	These patients usually have any one or more of the following: lid retraction >2 mm, moderate or severe soft tissue involvement, exophthalmos >3 mm above normal for race and gender, inconstant, or constant diplopia.
Mild GO	These patients usually have only one or more of the following: minor lid retraction (<2 mm), mild soft tissue involvement, exophthalmos <3 mm above normal for race and gender, transient or no diplopia, and corneal exposure responsive to lubricants.

APPENDIX 6: NO SPECS CLASSIFICATION 19

NO SPECS Classification

Class	Grade	
0		No signs or Symptoms
1		Only Signs
2		**Soft tissue Involvement, with symptoms and sign**
	0	Absent
	A	Minimal
	B	Moderate
	C	Marked
3		**Proptosis**
	0	<23mm
	A	23-24mm
	B	25-27mm
	C	≥28mm
4		**Extraocular muscle Involvement**
	0	Absent
	A	Limitation of motion in extremes of gaze
	B	Evident restriction of movement
	C	Fixed eyeball
5		**Corneal Involvement**
	0	Absent
	A	Stippling of cornea
	B	Ulceration
	C	Clouding
6		**Sight loss**
	0	Absent
	A	20/20 – 20/60
	B	20/70 – 20/200
	C	<20/200

APPENDIX 7: CLINICAL ACTIVITY SCORE 20

CAS	For initial assessment, only score items 1–7
1	Spontaneous orbital pain
2	Gaze evoked orbital pain
3	Eyelid swelling; considered due to active TED
4	Eyelid erythema
5	Conjunctival redness; considered due to active TED
6	Chemosis
7	Inflammation of caruncle or plica
	Follow-up assessment at 1–3 months can be scored out of 10
8	Increase of >2mm in proptosis
9	Decrease in uniocular excursion in any one direction of >8 degrees
10	Decreased acuity equivalent to 1 Snellen line

Note: One point is given for the presence of each parameter. Clinical activity is defined as the sum of all the points. Active ophthalmopathy is considered if the initial assessment is ≥3/7, or follow-up assessments are ≥4/10. [a]Amended by EUGOGO. Modified from. Modified from Barrio-Barrio J, Sabater AL, Bonet-Farriol E, Velazquez-Villoria A, Galofre JC. Graves' ophthalmopathy: VISA versus EUGOGO classification, assessment, and management. *J Ophthalmol.* 2015;2015:249125. Creative Commons License and Disclaimer available from: http://creativecommons.org/licenses/by/4.0/legalcode.[52]

Abbreviations: CAS, clinical activity score; EUGOGO, European Group of Graves' Orbitopathy; TED, thyroid eye disease.