Predictive Factors for Changes in Quality of Life after Steroid Treatment for Active Moderate-to-Severe Graves' Orbitopathy: A Prospective Trial

Elena Hoppe^{a, b} Alan Chun Hong Lee^a David Hoppe^c George J. Kahaly^a

^aDepartment of Medicine I, Johannes Gutenberg University Medical Center, Mainz, Germany; ^bDepartment of Paediatrics, Johannes Gutenberg University Medical Center, Mainz, Germany; ^cDepartment of Psychology, Technical University of Darmstadt, Darmstadt, Germany

Keywords

Predictive factors · Quality of life · Prospective · Multivariate analysis · Graves' orbitopathy

Abstract

Objectives: To investigate the predictive factors for changes in the quality of life (GO-QoL) of patients with Graves' orbitopathy (GO) prior to and after specific treatment. **Methods:** A prospective follow-up study was conducted at an academic tertiary referral orbital center with a joint thyroid-eye clinic on 100 consecutive patients with GO. Before and after the standard 12-week course of weekly intravenous methylprednisolone (cumulative dose 4.5 g), the GO-QoL questionnaire provided by the European Group on Graves' Orbitopathy (EUGOGO) was completed. Endocrine and ophthalmic assessments were performed at each visit. **Results:** All patients were biochemically euthyroid and untreated for GO at baseline and presented with active and moderate-to-severe disease. Both GO-QoL subscales (visual functioning [VF] and appearance [AP]) significantly increased after immunosuppressive therapy and showed a sustained improvement for 6 months. At baseline, demographic variables (sex, age, and smoking) influenced QoL in the stepwise linear regression

($p < 0.01$, adjusted $R^2 = 0.24$ for VF and $p < 0.01$, adjusted $R^2 = 0.21$ for AP). In contrast, 6 months after treatment, the improved QoL was now exclusively associated with ophthalmic parameters ($p < 0.01$, adjusted $R^2 = 0.47$ for VF; $p < 0.01$, adjusted $R^2 = 0.23$ for AP). **Conclusions:** Predictive factors for GO-QoL differed not only between the 2 subscales but also before and after the first treatment of GO.

© 2020 European Thyroid Association
Published by S. Karger AG, Basel

Introduction

Graves' orbitopathy (GO) is the major extrathyroidal manifestation of Graves' disease (GD) [1–3]. The clinical phenotype is associated with serum concentrations of thyrotropin receptor autoantibodies [4–8]. Apart from its well-characterized clinical manifestations [1], the significant impact of GO on quality of life (QoL) [9], psychological well-being [10] and socioeconomic burden [11, 12] are being increasingly recognized. Across the whole

E.H. and A.C.H.L. contributed equally as co-first authors.

disease spectrum [9], impaired QoL among GO patients is evident worldwide [13]. Psychotherapy, as an important factor for coping but also for reducing public health resources can be required as often as 60 times the national average [9]. Patients are also more likely to display mental signs or symptoms which may suggest underlying neuropsychiatric disorders [10]. Even death from suicide was associated with a hazard ratio of 3.30 in a cohort study [14]. From a public health viewpoint, the loss of productivity and the prolonged therapy required for GO incur tremendous indirect and direct costs [12].

The European Group on Graves' Orbitopathy (EUGOGO) recommends the evaluation of QoL and psychological well-being by means of the GO-QoL questionnaire as an integral part of patient-focused management [1]. Originally developed in Dutch [15], the GO-QoL questionnaire has already become available in 18 languages over the past 20 years [16]. A recent systematic review suggested that GO-QoL is the best disease-specific QoL assessment tool with its high validity, reliability, and cultural applicability [13]. Previous studies showed that certain demographic (e.g., age, sex, and smoking) and clinical characteristics (e.g., disease activity and severity) could predict both subscales, i.e., visual functioning (VF) and appearance (AP) [9, 17–26], but results were not consistent. Not all studies recruited patients explicitly in a consecutive manner [18, 22, 23, 25, 26] and selection bias was likely. Only a few reports specified that they recruited patients who were euthyroid [19, 24] or treatment-naïve [21, 25]. The QoL assessment may thus have been confounded as hyperthyroidism was associated with worse QoL [26] and previous GO treatment could have led to varying degrees of QoL improvement [16].

Most previous QoL studies were conducted in GO patients with an unselected disease spectrum at a single time point [9, 17–23, 25, 26]. Information regarding individual patient subgroups and the trend of QoL is lacking. We performed a prospective, follow-up trial, recruiting consecutive patients with active moderate-to-severe GO who were euthyroid and treatment-naïve prior to study inclusion. Our aim was to determine predictive factors for QoL at baseline and 6 months after therapy.

Material and Methods

Study Design and Participants

In total, 100 consecutive unselected GO patients, treated at the multidisciplinary joint thyroid-eye clinic of the Johannes Gutenberg University, were prospectively included in the study. Patients aged 18–75 years were eligible for recruitment if they had (1) active

(a clinical activity score [CAS] of ≥ 3) moderate-to-severe GO, i.e., at least 1 of the following symptoms was present: moderate-to-severe soft tissue involvement according to the EUGOGO Color Atlas evaluation, proptosis ≥ 22 mm, eye muscle involvement with mono-ocular ductions in any direction of gaze of $<30^\circ$, or evident dysmotility, or diplopia; (2) presented euthyroidism for at least 2 months; and (3) not undergone previous immunosuppressive treatment for GO. Patients with optic neuropathy, viral hepatitis, any relevant malignancy, or chronic renal failure, and pregnant or breastfeeding women were excluded.

Relevant history and demographic data were gathered from all patients and they underwent a comprehensive ophthalmic and endocrine assessment at baseline (week 0) and at weeks 12, 24, and 36. Disease activity and severity were evaluated according to the CAS and the clinical severity score (CSS) based on the NOSPECS classification [1, 27] (online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000508071). Routine blood tests, thyroid function tests, and thyrotropin receptor auto-antibody (TSH-R-Ab) measurements were checked at weeks 0, 12, 24, and 36. All patients received the standard 12-week course of weekly intravenous methylprednisolone with a cumulative dose of 4.5 g as recommended by the EUGOGO [1].

All patients were asked to complete the GO-QoL questionnaire at weeks 0, 12, 24, and 36. It consists of 2 subscales, each with 8 questions, which measure 2 different aspects of health-related QoL: (1) VF as a consequence of double vision and decreased visual acuity, and (2) psychosocial functioning as a consequence of a changed appearance (AP). The questions are scored as seriously limited (1 point), a little limited (2 points), or not limited at all (3 points). The 2 raw scores from each subscale (8–24 points) can be transformed to total scores (0–100 points) using the formula: total score = $100 \times (\text{raw score} - y) / 2y$, where y represents the number of valid answers in each subscale. For both VF and AP, higher scores indicated better QoL.

Statistical Analysis

Statistical analysis was computed using SPSS v18 (SPSS Inc., Chicago, IL, USA). The descriptive statistic was performed by calculation of the mean with SD. Given the considerable number of patients with asymmetric findings, only the worst value was considered. Depending on the purpose of the analysis, some interval or ratio type variables were transformed into groups following an ordinal scale. The Mann-Whitney U test was performed to detect statistical significance in differences of the mean between 2 groups with respect to ordinal or interval type variables. For independent variables with >2 levels, differences of the mean were examined using the Kruskal-Wallis Test, another nonparametric test. For the analysis of the linear relationship between 2 interval and ratio type variables, Spearman's rho (or Spearman's rank correlation coefficient) was calculated and a scatter plot was generated.

To determine the mean difference between 2 visits, we used the paired-samples t test. As the same patient was measured twice, the resulting pair of observations could be compared. Stepwise linear regression is a method of determining a suitable subset of potential predictors. In backward elimination, a single variable is omitted from the model and the influence on the fit of the model is quantified. Only variables that improve the model fit criterion are kept. Repeated application of this procedure yields the best subset of potential explanatory variables. A statistically significant difference for all statistical tests was assumed for cases when the two-sided p value was ≤ 0.05 .

Results

Demographics and GO-QoL

The baseline demographic and clinical characteristics are shown in Table 1. The male-to-female ratio was 1:3. Almost 60% were current smokers. The majority were TSH-R-Ab-positive, with a high titer of at least 10 IU/L detected in around 50% of cases. Asymmetric proptosis was detected in more than one-third of our cohort. All 100 patients completed GO-QoL questionnaires at baseline; by week 36, the number of valid questionnaires was gradually reduced to 80 due to various reasons (the trial was terminated for 7 patients who developed dysthyroid optic neuropathy, and the rest either defaulted follow-up or withdrew their consent). We did not identify any significant ceiling or floor effects for the 2 GO-QoL subscales.

Mean GO-QoL scores rose steadily, and sustained improvement from baseline was observed throughout the study period (Fig. 1a). There was a delay in the improvement of VF which occurred after completion of treatment (Fig. 1b). On the contrary, AP improved earlier at week 12, reached an apparent plateau after this, and maintained significantly better at weeks 24 and 36 than at baseline (Fig. 1c). The mean improvement in mean GO-QoL score and its subscales at week 36 (vs. week 0) was around 6 points, considered a clinically important difference [28] (even though even greater changes were reported previously [29]). Improvement was associated with the response to treatment ($p = 0.10$ for VF; $p = 0.01$ for AP) but not with GO duration (Spearman's $r = 0.14$ and $p = 0.13$ for AP; Spearman's $r = 0.01$ and $p = 0.90$ for VF). The number of responses to individual questions at weeks 0 and 36 are shown in online supplementary Table 2.

Univariate and Multivariate Analysis

Univariate analysis yielded a list of predictors of VF and AP at baseline and week 36 (Table 2). In addition, we performed multivariate analysis using stepwise linear regression (Table 3). Age, CSS, and Gorman score best predicted VF at baseline ($p < 0.01$, adjusted $R^2 = 0.24$) while CAS, chemosis, and proptosis were removed from the model in the statistical process. The predictive factors of VF were different at week 36 (i.e., 6 months posttreatment), when the model comprising 7-item CAS, upper-lid retraction, and Gorman score yielded the best prediction ($p < 0.01$, adjusted $R^2 = 0.47$), with the following parameters being excluded: 10-item CAS, orbital pain, CSS, and abnormal head posture (Table 3). AP at baseline was best predicted by a model comprising younger age, female gender, current smoking, and CSS ($p < 0.01$, adjusted $R^2 = 0.21$), while excluding CAS

Table 1. Baseline demographic and clinical characteristics

<i>Demographics</i>	
Age, years	50.6±10.7
Male/female, <i>n</i>	28/72
Premenopausal women, <i>n</i>	22
Smoking status	
Current smoker	57 (57)
Ex-smoker	26 (26)
Never-smoker	17 (17)
<i>Clinical characteristics of thyroid disease</i>	
Duration of thyroid disease, months	16 (8–59)
Underlying thyroid disease	
GD	94 (94)
Hashimoto's thyroiditis	3 (3)
No history, i.e., euthyroid GO	3 (3)
Current thyroid medications	
Antithyroid drugs	35 (35)
T ₄ or T ₄ + T ₃ replacement	51 (51)
No medication	14 (14)
Relapse of Graves' hyperthyroidism	
All GD patients, <i>n</i>	17
After antithyroid drugs	9
After radioiodine	2
After partial thyroidectomy	6
TSH-R-Ab	
Positive, i.e., ≥1.8 IU/L	84 (84)
Titer, IU/L	8.9 (3.6–16)
Titer ≥10 IU/L	45 (45)
<i>Clinical characteristics of orbital disease</i>	
Duration of GO, months	9.5 (5–20)
Symptoms	
Excessive watering	87 (87)
Grittiness	69 (69)
Photophobia	81 (81)
Blurred vision	72 (72)
7-Item CAS ^a	4 (3–6)
Any orbital pain in ≥1 eye	81 (81)
Spontaneous pain in ≥1 eye	73
Gaze evoked pain in ≥1 eye	48
CSS ^a	6.3 (4.5–8)
0–3	11
>3 to ≤5	28
>5	61
Upper-lid retraction	59 (59)
Proptosis ^a , mm	
≤20 mm, i.e., no proptosis	21.8±3.2
21–23 mm	36 (36)
≥24 mm	32 (32)
Proptosis asymmetry ^b	32 (32)
Palpebral aperture ^a , mm	38 (38)
Gorman score	11.7±2.0
No diplopia (0 points)	32 (32)
Intermittent diplopia (1 point)	24 (24)
Inconstant diplopia (2 points)	28 (28)
Constant diplopia (3 points)	16 (16)
Abnormal head posture	13 (13)

Data are presented as *n*, mean ± SD, *n* (%), or median (range). GD, Graves' disease; GO, Graves' orbitopathy; CAS, clinical activity score; CSS, clinical severity score.

^a If the findings were asymmetric, the readings from the worse eye were selected. ^b A difference between both eyes ≥2 mm.

Table 2. Univariate analysis for predictors of VF at weeks 0 and 36

Covariate	Week 0	Spearman's <i>r</i>	<i>p</i> value*	Week 36	Spearman's <i>r</i>	<i>p</i> value*
Age, years		−0.202	0.043		−0.131	0.152
7-Item CAS			0.008			0.004
10-Point CAS			n.a.		−0.471	0.000
Pain in primary gaze			0.075			0.029
Yes	46.96			32.61		
No	58.02			44.52		
Pain in upgaze		0.803				0.006
Yes	50.97			29.07		
No	49.40			44.85		
Chemosis			0.006			n.a.
Yes	43.19					
No	63.49					
CSS		−0.321	0.001		−0.469	0.000
Upper-lid retraction, mm		−0.029	0.772		−0.354	0.001
Proptosis, mm			0.012		−0.107	0.349
Diplopia			0.003			0.000
Yes	50.45			43.85		
No	50.61			81.76		
Gorman score			0.000			0.000
No diplopia	62.98			82.39		
Intermittent	60.25			43.14		
Inconstant	35.36			56.55		
Constant	37.41			26.25		
Abnormal head posture			0.049		0.000	0.001
Yes	35.08			34.18		
No	51.71			63.76		

* Statistically significant results appear in grey boxes. Values for week 0 and week 36 represent the mean ranks of the respective groups. VF, visual functioning; CAS, clinical activity score; CSS, clinical severity score, n.a., not available.

Fig. 1. Serial GO-QoL score and its subscales. **a** Mean GO-QoL scores. **b** Visual functioning subscale. **c** Appearance subscale. The *p* values shown referred to the comparisons with week 0. The error bars represented the mean ± SD of mean QoL scores or subscales.

The detailed scores and the statistical comparisons between different time points are shown in online supplementary Table 3. * Statistically significant difference when comparing with week 0. ^ Statistically significant difference between weeks 12 and 36.

Table 3.**A** Multivariate analysis of predictors of VF at weeks 0 and 36 (multiple linear regressions with stepwise variable selection)

	<i>t</i>	95% CI	<i>p</i> value	β	<i>F</i>	df	<i>p</i> value	Adjusted <i>R</i> ²
<i>Week 0^a</i>								
Overall model					11.56	3.99	<0.01	0.24
Age, years	-2.87	-0.91 to -0.17	0.005	-0.25				
CSS	-2.70	-4.48 to -0.68	0.008	-0.26				
Gorman score	-3.22	-10.30 to -2.44	0.002	-0.30				
<i>Week 36^b</i>								
Overall model					23.97	3.75	<0.01	0.47
7-Item CAS	-4.43	-9.71 to -3.25	0.000	-0.38				
Upper-lid retraction	-2.06	-11.68 to -1.55	0.043	-0.18				
Gorman score	-5.59	-14.75 to -6.94	0.000	-0.49				

VF, visual functioning; CAS, clinical activity score; CSS, clinical severity score.

^a Variables excluded at week 0: CAS, chemosis, proptosis.^b Variables excluded at week 36: 10-item CAS, orbital pain (spontaneous/gaze evoked), CSS, abnormal head posture.**B** Multivariate analysis of predictors of AP at weeks 0 and 36 (multiple linear regressions with stepwise variable selection)

	<i>t</i>	95% CI	<i>p</i> value	β	<i>F</i>	df	<i>p</i> value	Adjusted <i>R</i> ²
<i>Week 0^c</i>								
Overall model					6.92	4.95	<0.01	0.21
Age, years	2.02	-0.00 to 0.75	0.047	0.19				
Sex	-3.27	-21.9 to -4.47	0.002	-0.30				
Smoking history	-2.20	-6.51 to -0.52	0.031	-0.21				
CSS	-2.36	-3.67 to -0.21	0.020	-0.22				
<i>Week 36^d</i>								
Overall model					10.47	2.78	<0.01	0.23
CSS	-3.57	-12.78 to 0.04	0.001	-0.39				
Upper-lid retraction	-2.01	-6.06 to -1.31	0.049	-0.29				

AP, appearance subscale; CSS, clinical severity score.

^c Variables excluded at week 0: CAS, proptosis.^d Variables excluded at week 36: 7-item/10-item CAS, proptosis, abnormal head posture, TSH-R-Ab.

and proptosis. Predictors of AP also changed at week 36, when CSS and upper-lid retraction showed the best results ($p < 0.01$, adjusted $R^2 = 0.23$) while 7-item or 10-item CAS, proptosis, abnormal head posture, and TSH-R-Ab were excluded. Figure 2 depicts the correlations between age and VF as well as age and AP at baseline, respectively.

Discussion

To our knowledge, this is the first report which prospectively evaluates predictive factors of QoL in GO patients both at baseline and after treatment. By including a

cohort of consecutive, euthyroid, and treatment-naïve patients with active moderate-to-severe GO, we minimized, if not eliminated, selection bias and the effects of dysthyroidism and previous immunosuppressive treatment on QoL. We demonstrated that both demographic and ophthalmic parameters predicted QoL at baseline. However, only ophthalmic parameters were significant predictors of QoL post-treatment. This finding is clinically relevant, as treatment strategies which better correct ophthalmic abnormalities can potentially enhance QoL to a greater extent in the long run.

Our study showed, for the first time, that age was an independent predictor of both QoL subscales at baseline

Fig. 2. **a** Negative correlation between age and visual functioning subscale. **b** Positive correlation between age and appearance subscale.

in the same cohort, where older patients reported lower VF and younger patients scored lower for AP. This contrasts with previous studies which were able to demonstrate a correlation with VF only [18, 19, 25] or with AP only [24]. As our analysis was dedicated to a more severe disease spectrum, rather than an unselected [18, 19, 25] or milder spectrum [24], this may have enabled us to illustrate this divergent relationship simultaneously. Age-related visual decline and more prevalent systemic or non-GO ophthalmic diseases may contribute to poorer VF. Younger patients show greater stress concerning their own physical perception and impaired participation in social activities, while the more well-established social

support network and stable relationships of older patients may limit the impact of GO on AP.

Female gender was independently associated with poorer AP at baseline in our study, a finding shared by a recent Chinese series [25]. It was shown previously that the perception of body dissatisfaction is more common and stronger in women [30], and that females tend to associate body dissatisfaction with the concept of self-esteem [31].

The detrimental effects of smoking on GO are numerous [32–34]: smoking increases both the risk of developing GO and the disease severity as well as promoting resistance to treatment. Our multivariate analysis revealed that current smokers had significantly lower AP scores at baseline than nonsmokers. This finding has not been reported before; probably because the prevalence of smoking in previous QoL studies was much lower (18–40%) [9, 18, 21, 22, 24–26] than in our study (approx. 60%). The severe course of disease in our cohort might be one explanation for the high proportion due to the negative impact of smoking as mentioned above. Attending physicians should therefore emphasize smoking cessation to all smoking patients with GO [1] in view of the reported dual physical and psychosocial harm.

The above demographic parameters, however, lost their impact on QoL 6 months after the standard treatment of active moderate-to-severe GO. In contrast, ophthalmic parameters were significant predictors of QoL both at baseline and after treatment.

As opposed to previous studies [18, 19, 21, 25], we did not observe any correlation between QoL and CAS. The homogeneity of CAS in our cohort (80% of cases had CAS 3–4) may have limited our predictions, but we did show that 7-item CAS predicted post-treatment VF. Persistent inflammation promotes orbital-tissue remodeling, leading to various mechanical consequences and, ultimately, impaired VF [3]. We showed that CSS and/or diplopia were significant predictors of both the QoL subscales at baseline as well as after treatment. We also, for the first time, identified upper-lid retraction as a predictor of both VF and AP. A common manifestation in GO, lid retraction results in impaired tear-film formation and the subsequent irritation of the ocular surface and keratopathy in severe cases. It also gives rise to a “negative” facial expression, which may impact psychosocial well-being.

In contrast to previous reports [9, 24], proptosis was not associated with worse AP in our multivariate analysis. In a randomized controlled trial, teprotumumab was shown to markedly reduce proptosis but, interestingly, only a nonsignificant trend towards an improvement in

AP was observed [35]. Even though proptosis is one of the most prominent features of GO, other reasons can contribute to the loss of significance. Patients might be dissatisfied with treatment success as a whole and shift their focus from specific findings. In summary, parameters of disease severity including CSS, diplopia, and upper-lid retraction impact QoL throughout the whole course of the disease. Treatment strategies which specifically target these factors should be considered for optimizing the QoL of GO patients.

The obvious strength of our study was the prospective follow-up design which allowed for evaluation of predictive factors of QoL longitudinally. The requirement of euthyroidism and untreated GO also eliminated a confounding effect on QoL assessment. Our study was the first to provide ample information on QoL, specifically in patients with active moderate-to-severe GO. There were several limitations. The patients completed GO-QoL questionnaires either before or after endocrine/ophthalmic assessments, but not in any predefined order. The interaction between patients and health care professionals can influence the comprehension of disease impact, with bias or inconsistency in the QoL assessment being introduced as a result. Furthermore, self-assessment by patients can distort raw data. For example, patients with a shorter treatment duration were able to recall more specific details. Some patients were also reluctant to state the current daily number of cigarettes that they smoked. Regarding the severe course of their disease that led them to seek help at a specialized center, they may show a socially more desirable response. Certain heterogeneity in the assessment of disease severity has been noted across studies on QoL (classical NOSPECS score, modified NOSPECS score, and EUGOGO categorical classification). This can hinder comparison between studies and lead to inconsistent findings. We advocate the standardization of disease assessment.

In conclusion, regular assessment of QoL in GO patients is mandatory in routine clinical practice. Recent drug trials have already incorporated GO-QoL assessment as a secondary end point. Arguably, the inclusion of QoL improvement as a primary end point can better describe the benefits of GO interventions. Treatment strategies which effectively reduce disease severity can significantly enhance QoL.

Acknowledgements

The authors are grateful to Ms. Lara Frommer (JGU Thyroid Lab) for her editorial assistance. This manuscript contains part of the doctoral thesis of E.H.

Statement of Ethics

The patients gave their written informed consent and the study protocol was approved by the institute's committee on human research.

Disclosure Statement

The authors have no conflicts of interest to declare.

Funding Sources

There was no funding.

Author Contributions

Work and concept were initiated by G.J.K. and E.H.; literature search and data interpretation were performed by E.H., A.C.H.L., D.H., and G.J.K.; the manuscript was written and critically reviewed by A.C.H.L., E.H., and G.J.K.

References

- 1 Bartalena L, Baldeschi L, Boboridis K, Eckstein A, Kahaly GJ, Marcocci C, et al.; European Group on Graves' Orbitopathy (EUGOGO). The 2016 European Thyroid Association/European Group on Graves' Orbitopathy Guidelines for the Management of Graves' Orbitopathy. *Eur Thyroid J*. 2016 Mar;5(1):9–26.
- 2 Kahaly GJ, Bartalena L, Hegedüs L, Leenhardt L, Poppe K, Pearce SH. 2018 European Thyroid Association Guideline for the Management of Graves' Hyperthyroidism. *Eur Thyroid J*. 2018 Aug;7(4):167–86.
- 3 Hai YP, Lee AC, Frommer L, Diana T, Kahaly GJ. Immunohistochemical analysis of human orbital tissue in Graves' orbitopathy. *J Endocrinol Invest*. 2020 Feb;43(2):123–37.
- 4 Kahaly GJ. Bioassays for TSH Receptor Antibodies: quo Vadis? *Eur Thyroid J*. 2015 Mar;4(1):3–5.
- 5 Diana T, Wüster C, Olivo PD, Unterrainer A, König J, Kanitz M, et al. Performance and Specificity of 6 Immunoassays for TSH Receptor Antibodies: A Multicenter Study. *Eur Thyroid J*. 2017 Sep;6(5):243–9.
- 6 Kahaly GJ, Wüster C, Olivo PD, Diana T. High Titers of Thyrotropin Receptor Antibodies Are Associated with Orbitopathy in Patients with Graves Disease. *J Clin Endocrinol Metab*. 2019 Jul;104(7):2561–8.
- 7 Kahaly GJ, Diana T, Glang J, Kanitz M, Pitz S, König J. Thyroid Stimulating Antibodies Are Highly Prevalent in Hashimoto's Thyroiditis and Associated Orbitopathy. *J Clin Endocrinol Metab*. 2016 May;101(5):1998–2004.

- 8 Kampmann E, Diana T, Kanitz M, Hoppe D, Kahaly GJ. Thyroid Stimulating but Not Blocking Autoantibodies Are Highly Prevalent in Severe and Active Thyroid-Associated Orbitopathy: A Prospective Study. *Int J Endocrinol*. 2015;2015:678194.
- 9 Ponto KA, Hommel G, Pitz S, Elflein H, Pfeiffer N, Kahaly GJ. Quality of life in a German graves orbitopathy population. *Am J Ophthalmol*. 2011 Sep;152(3):483–90.e1.
- 10 Bruscolini A, Sacchetti M, La Cava M, Nebbio M, Iannitelli A, Quartini A, et al. Quality of life and neuropsychiatric disorders in patients with Graves' Orbitopathy: current concepts. *Autoimmun Rev*. 2018 Jul;17(7):639–43.
- 11 Ponto KA, Pitz S, Pfeiffer N, Hommel G, Weber MM, Kahaly GJ. Quality of life and occupational disability in endocrine orbitopathy. *Dtsch Arztebl Int*. 2009 Apr;106(17):283–9.
- 12 Ponto KA, Merkesdal S, Hommel G, Pitz S, Pfeiffer N, Kahaly GJ. Public health relevance of Graves' orbitopathy. *J Clin Endocrinol Metab*. 2013 Jan;98(1):145–52.
- 13 Lee TH, Sundar G. Quality of Life in Thyroid Eye Disease: A Systematic Review. *Ophthalm Plast Reconstr Surg*. 2020 Mar/Apr;36(2):118–26.
- 14 Ferlov-Schwensen C, Brix TH, Hegedüs L. Death by Suicide in Graves' Disease and Graves' Orbitopathy: A Nationwide Danish Register Study. *Thyroid*. 2017 Dec;27(12):1475–80.
- 15 Terwee CB, Gerding MN, Dekker FW, Prummel MF, Wiersinga WM. Development of a disease specific quality of life questionnaire for patients with Graves' ophthalmopathy: the GO-QOL. *Br J Ophthalmol*. 1998 Jul;82(7):773–9.
- 16 Wiersinga WM, Kahaly G, editors. Graves' Orbitopathy: A Multidisciplinary Approach: Questions and Answers. 3rd edition (revised and expanded). Basel: Karger; 2017. pp. 260–74.
- 17 Park JJ, Sullivan TJ, Mortimer RH, Wagenaar M, Perry-Keene DA. Assessing quality of life in Australian patients with Graves' ophthalmopathy. *Br J Ophthalmol*. 2004 Jan;88(1):75–8.
- 18 Choi YJ, Lim HT, Lee SJ, Lee SY, Yoon JS. Assessing Graves' ophthalmopathy-specific quality of life in Korean patients. *Eye (Lond)*. 2012 Apr;26(4):544–51.
- 19 Lin IC, Lee CC, Liao SL. Assessing quality of life in Taiwanese patients with Graves' ophthalmopathy. *J Formos Med Assoc*. 2015 Nov;114(11):1047–54.
- 20 Kashkoul MB, Karimi N, Aghamirsalam M, Abtahi MB, Nojomi M, Shahrad-Bejestani H, et al. Measurement Properties of the Persian Translated Version of Graves Orbitopathy Quality of Life Questionnaire: A Validation Study. *Ophthalmic Epidemiol*. 2017 Feb;24(1):3–10.
- 21 Shen L, Zhu H, Li XX, Liu DD, Chen XY, Liu H. The influence factors of quality-of-life in patients with thyroid-associated ophthalmopathy. *Zhonghua Yan Ke Za Zhi*. 2017 Aug;53(8):575–82. Chinese.
- 22 Delfino LC, Zunino A, Sapia V, Croome MD, Ilera V, Gauna AT. Related quality of life questionnaire specific to dysthyroid ophthalmopathy evaluated in a population of patients with Graves' disease. *Arch Endocrinol Metab*. 2017 Jul-Aug;61(4):374–81.
- 23 Zeng P, Fan SX, Li ZJ, Peng YY, Hu YX, Xu MT, et al. Evaluation of the Graves' Orbitopathy-Specific Quality of Life Questionnaire in the Mainland Chinese Population. *J Ophthalmol*. 2019 Mar;2019:7602419.
- 24 Villagelin D, Romaldini J, Andrade J, Santos R, Milkos A, Teixeira PF, et al. Evaluation of Quality of Life in the Brazilian Graves' Disease Population: Focus on Mild and Moderate Graves' Orbitopathy Patients. *Front Endocrinol (Lausanne)*. 2019 Apr;10:192.
- 25 Weng CY, Li ZF, Hu SD, Luo YS, Feng XT, Zhong Q, et al. Evaluation of quality of life in patients with Graves orbitopathy and its influencing factors. *Zhonghua Nei Ke Za Zhi*. 2019 Aug;58(8):577–83. Chinese.
- 26 Rigueto CM, Neto AM, Tambascia MA, Zantut-Wittmann DE. The relationship between quality of life, cognition, and thyroid status in Graves' disease. *Endocrine*. 2019 Jan;63(1):87–93.
- 27 Werner SC. Modification of the classification of the eye changes of Graves' disease: recommendations of the Ad Hoc Committee of the American Thyroid Association. *J Clin Endocrinol Metab*. 1977 Jan;44(1):203–4.
- 28 Terwee CB, Dekker FW, Mourits MP, Gerding MN, Baldeschi L, Kalmann R, et al. Interpretation and validity of changes in scores on the Graves' ophthalmopathy quality of life questionnaire (GO-QOL) after different treatments. *Clin Endocrinol (Oxf)*. 2001 Mar;54(3):391–8.
- 29 Bartalena L, Krassas GE, Wiersinga W, Marcocci C, Salvi M, Daumerie C, et al.; European Group on Graves' Orbitopathy. Efficacy and safety of three different cumulative doses of intravenous methylprednisolone for moderate to severe and active Graves' orbitopathy. *J Clin Endocrinol Metab*. 2012 Dec;97(12):4454–63.
- 30 Brennan MA, Bain JL. Body image perceptions: do gender differences exist? *Psi Chi J Undergrad Res*. 2010;15(3):130.
- 31 Furnham A, Badmin N, Sneade I. Body image dissatisfaction: gender differences in eating attitudes, self-esteem, and reasons for exercise. *J Psychol*. 2002 Nov;136(6):581–96.
- 32 Bartalena L, Pinchera A, Marcocci C. Management of Graves' ophthalmopathy: reality and perspectives. *Endocr Rev*. 2000 Apr;21(2):168–99.
- 33 Vestergaard P. Smoking and thyroid disorders—a meta-analysis. *Eur J Endocrinol*. 2002 Feb;146(2):153–61.
- 34 Wiersinga WM. Smoking and thyroid. *Clin Endocrinol (Oxf)*. 2013 Aug;79(2):145–51.
- 35 Smith TJ, Kahaly GJ, Ezra DG, Fleming JC, Dailey RA, Tang RA, et al. Teprotumumab for Thyroid-Associated Ophthalmopathy. *N Engl J Med*. 2017 May;376(18):1748–61.