

# Chapter 22

## Quality of Life in Graves' Ophthalmopathy

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### Clinical Impact of Graves' Ophthalmopathy

Clinicians involved in the diagnosis and treatment of thyroid eye disease have the responsibility of addressing both the physical and psychological sequelae of this disease. Graves' disease is rarely life threatening and Graves' ophthalmopathy (GO) is rarely sight threatening, so the primary focus of care is on minimizing the negative effects of the disease on ocular health. The success with which patients' signs and symptoms are ameliorated and visual and social functioning are improved by treatment has a direct and significant impact on the quality of their lives. Thus, it behooves care providers to assess each patient's health-related quality of life (HRQL) at each stage along the course of the disease, allowing for changes in HRQL to help guide the next phase of treatment.

GO is the most common cause of proptosis and eyelid retraction in adults and is a frequent cause of adult-onset strabismus. In addition, patients with GO report a variety of symptoms including altered appearance, ocular pain, diplopia, and vision loss. These changes lead to significant alteration in psychosocial functioning, mood, and ability to work, with both personal and economic ramifications. Some symptoms tend to be transient, so conservative measures are able to provide relief while the disease follows its natural course to spontaneous resolution, while other symptoms are potentially permanent, requiring a patient to invoke a variety of coping mechanisms and life adaptations to find a "new normal." The degree to which a patient's life is altered by the disease course is deeply personal and, by definition, subjective. HRQL is a multifactorial concept incorporating physical, psychological, and social issues and is influenced by an individual's perceptions, interactions, and adaptability [1]. Thus, the only way to assess the effect of GO on HRQL is to ask the patient.

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Throughout the course of the disease, both medical and surgical therapies are available to aid in the management of GO, but unfortunately, some of the side effects or risks of these therapies have the potential to negatively affect HRQL while others are simply incompletely effective at improving HRQL. Steroids are able to limit the inflammatory congestive symptoms of GO, but the side effects of steroids, including weight gain, osteoporosis, blood sugar elevation, hypertension, mood alteration, glaucoma, and cataracts, often counter their beneficial effects. Additionally, steroids are ineffective against the fibrotic changes of GO such as extraocular motility restriction and eyelid retraction [2]. Surgical treatment of GO includes decompression of the orbit, strabismus surgery, and eyelid retraction repair. The most common potential sequela of orbital decompression is the development of diplopia, occurring in up to 64 % of patients who do not have preoperative diplopia [3]. Although most of these patients ultimately achieve single vision through spontaneous improvement, strabismus surgery or prism glasses, the high rate of postoperative diplopia tempers enthusiasm for the procedure. Additionally, while decompression decreases the degree of proptosis, and eyelid lengthening surgery diminishes the palpebral aperture in an attempt to lessen ocular exposure and altered appearance, surgery cannot necessarily restore patients to their original appearance. Bartley et al. surveyed 120 patients up to 17 years after the diagnosis of thyroid-associated eye disease and found that 60 % of respondents felt their appearance was dissimilar to before thyroid disease, 52 % felt that appearance was abnormal, and 38 % were unhappy about their eyes' appearance. Furthermore, almost a third of those surveyed reported eye discomfort, most often related to dry eyes [4]. Clearly, GO is a chronic disease with the potential to affect HRQL for the rest of a patient's life.

Because GO manifests as a complex constellation of symptoms and signs and is treated with therapies that carry significant potential side effects, no single measure can be used to assess disease severity and treatment outcome. Although objective measures exist for some GO manifestations, these measures fail to provide a comprehensive assessment of the impact of the disease and its treatment on HRQL. Moreover, assessments of quality of life have been found to be predictive of treatment costs and outcomes, independent of clinical indices and laboratory results [5]. Therefore, the ability to measure change in HRQL provides an important endpoint for evaluating medical and surgical treatment of GO. This allows the clinician and patient to have common treatment goals and expectations in order to achieve an acceptable outcome.

## Indices of Disease Severity

Historically, clinicians have favored instruments of disease assessment which offer an objection measurement. Given the complexity of presentations of thyroid eye disease, the use of composite measures has been integrated into clinical practice. Numerous quantitative scales of severity have been used to assess GO, including the Clinical Assessment Score (CAS) [6], "NOSPECS" [7], and Gorman diplopia scale [8]. Although NOSPECS is a useful mnemonic for the clinical characteristics of GO,

it is a composite index that includes both subjective and objective measures of disease severity and is subject to imprecision from interobserver variation. Additionally, a patient who worsens in an important aspect of the disease such as optic neuropathy but improves in a less important feature, such as eyelid swelling, could be reported as being unchanged. Similarly, CAS allows for the presence or absence of a clinical feature without grading of its severity, and with equal weight contributed by each of the included symptoms. The limitations of these scales prompted the committees of the World Thyroid Associations to recommend that these classifications be abandoned in favor of separate objective measures of the various manifestations of GO [9].

A significant obstacle to adequate clinical appraisal of GO is the fact that several of the most bothersome characteristics are difficult to assess objectively, including external appearance, diplopia, and pain symptoms. Additionally, objective measures do not necessarily correlate well with HRQL [10]. For example, evidence of improved extraocular muscle alignment may not correlate with a lessening of diplopia symptoms. In patients with GO, diplopia is a bimodal symptom which is either present or absent in a particular gaze. A small degree of ocular deviation may produce symptoms that are just as bothersome as those produced by a large degree of ocular deviation. Similarly, eyelid retraction in GO leads to widened palpebral fissures and lagophthalmos, which in turn cause symptoms of dry eye, foreign body sensation, tearing, and decreased vision. Eyelid position can be improved with lid lengthening surgery, but any residual lagophthalmos or ocular exposure may continue to cause symptoms that the patient perceives as equally severe. Thus, demonstrating that an intervention lessens, but does not completely eliminate, symptoms may not be a clinically relevant finding. Finally, because vision loss from optic neuropathy is relatively rare in GO, assessments of optic nerve function such as visual acuity, color vision, and visual field tests have a narrow window of applicability in studies of GO. Recognizing the need to include patient-reported outcomes in monitoring thyroid eye disease and response to treatments, the World Thyroid Association consensus statement suggested that “investigators, in addition to the objective measurements... should include self-assessment of the eye condition by the patient. Such assessments...should include commentary on appearance, visual acuity, eye discomfort, and diplopia” [9].

## Overview of HRQL Instruments

As the importance of evaluating the impact of diseases and their treatments on health-related quality of life has been recognized, instruments that measure HRQL have been developed. Recently designed and implemented measures of HRQL include generic, disease-specific, and vision-specific instruments. General health instruments include the Medical Outcomes Short Form (SF-36) [11] and the Sickness Impact Profile (SIP) [12]. Although generic measures allow the comparison of HRQL across different diseases, they have been shown in several randomized trials to be less powerful than disease-specific instruments in detecting treatment effects [13, 14].

Disease-specific instruments are therefore more appropriate for clinical trials evaluating therapeutic interventions [15]. The National Eye Institute has recognized that “a patient’s quality of life is an important facet to consider in assessing visual health” [16] and has supported the development of the National Eye Institute-Visual Function Questionnaire (NEI-VFQ). The NEI-VFQ was developed to measure the symptomatic effect of common ophthalmic conditions, including cataract, age-related macular degeneration, primary open angle glaucoma, diabetic retinopathy, CMV retinitis, and low vision [17]. The VFQ has been used by several groups to assess HRQL in GO. Ultimately all available instruments have strengths and weaknesses, and their use in clinical practice needs to be tailored to the needs of the patients and goals of the care providers.

## General Health

The Medical Outcomes Study Short Form Health Status Survey (MOS-36 or SF-36) is a commonly used instrument to assess HRQL in thyroid disease and its ophthalmic manifestations. The survey probes eight subtopics: physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue, and general health perceptions [11]. The general questionnaire can be scored to create a Mental Component Summary and a Physical Component Summary. To improve the convenience of the survey for clinical use, it has also been used in shorter formats as the SF-24 or SF-12.

To determine if the type of treatment used to make a patient with Graves’ disease euthyroid affects the long-term HRQL, 172 Swedish patients were surveyed with the SF-36. Patients in all treatment groups (thyroidectomy, antithyroid medications, or radioactive iodine (RAI)) had a decreased quality of life compared to the control population without thyroid disease. There was no difference in quality of life associated with the type of treatment for thyroid disease. Younger patients were more likely than older patients to report eye symptoms with only 13–15 % of young patients bothered compared to 20–38 % of older patients [18]. The authors were unable to determine if the patients with chronic eye symptoms had a lower quality of life; therefore they later undertook a study to determine if treatment modality for Graves’ disease led to a change in incidence of GO and altered HRQL. A total of 308 patients were recruited into treatment with RAI or antithyroid medications, and then followed for 4 years. The RAI group contained 53 de novo cases of GO while the antithyroid medication group had 23 new cases of GO, a statistically significant difference. While there was no difference in the SF-36 QOL score between treatment groups, when divided into GO versus non-GO patients, those with GO have a significantly worse QOL. Finally, GO patients’ physical recovery preceded their mental recovery [19]. The patients’ objective clinic eye exam did not correlate with the SF-36 scores, again reinforcing the idea that HRQL assessments need to be performed separately and in addition to objective clinical measures.

In Amsterdam, Gerding published a study of 70 euthyroid patients with GO of various degrees of severity and compared the SF-24 with 3 subscales of the Sickness Impact Profile (SIP) which assesses 136 items in 12 categories [12, 20]. GO patients had lower SF-24 scores on 6 subscales, including a physical functioning score that was 28 points less than the control population. SIP scores were also lower in GO patients than in the control group. In comparison to patients with other diseases, those with GO scored lower than diabetes mellitus, emphysema, and heart failure. The QOL scores did not correlate with the clinical severity or duration of GO symptoms.

A similar study was completed in Germany using the SF-36, assessing 102 patients with varying severity of thyroid-associated ophthalmopathy. Patients scored much lower than the control group, particularly on energy/fatigue, social functioning, mental health, general health perceptions, and bodily pain. The presence of a high degree of anxiety or depression as quantified by The Hospital Anxiety and Depression Scale correlated with lower SF-36 results. Again, the SF-36 scores did not correlate with duration or clinical severity of ophthalmopathy [21]. To examine the role of steroids in medical treatment of GO, the same group employed the SF-36 to follow 70 euthyroid patients with untreated, active, and severe disease. Scores improved to a much greater degree in the patients receiving IV steroids compared to those taking oral steroids. Whereas before treatment 9 % and 11 % of patients in the IV and oral steroid groups, respectively, reported good or excellent QOL, after treatment positive responses increased to 80 % and 54 % [22].

Conversely, a Polish study of 29 euthyroid patients sought to determine if a combination of IV steroids and orbital radiation therapy could improve QOL in GO. Patients underwent 6 cycles of 1 g of methylprednisolone and between cycle 2 and 4 they received orbital radiation. Similar to previous studies, pretreatment scores were lower than a control population in all 8 subscales. While treatment led to improvement in the clinical features of the disease by objective measures, QOL scores increased for only 3 subscales of the SF-36: physical role functioning, bodily pain, and vitality (energy/fatigue) [23].

Several authors have specifically looked at the emotional component of dealing with GO by incorporating a mood assessment into their studies. Lee et al. used the Beck Depression Inventory in addition to the SF-36 to analyze 49 Korean patients with various severities of GO, including 4 with sight-threatening disease. Those patients with lower depression scores had lower SF-36 scores and this correlated with higher clinical activity scores. Additionally, patients with higher Gorman diplopia scores or with sight-threatening GO had lower Physical Component Summary scores on the SF-36 [24]. Farid et al. recruited 48 euthyroid GO patients who were using no mood altering medications and submitted them to the Profile of Mood States survey, a 65-item survey with a 5-point Likert scale. Patients were divided into high or low clinical severity and categorized as predominantly proptotic or restrictive. Those with higher disease severity were found to have higher levels of emotional distress, and the disfiguring signs of disease correlated more strongly than functional deficits with emotional distress, in other words proptosis was more distressing than diplopia [25].

## Vision-Specific Instruments

Given that GO is a disease affecting the visual system, it is possible that a HRQL instrument designed to assess visual health would be more sensitive and highly correlated with clinical features of GO than a general health instrument. A wide variety of diseases which alter visual functioning have been analyzed for their influence on HRQL with the NEI-VFQ. The diseases differ from GO in that they are not disfiguring and typically are not associated with ocular discomfort and binocular diplopia. Conversely, vision loss, which is a major feature of all of the diseases for which the NEI-VFQ was developed, is rare in GO. The original VFQ was a 51-item questionnaire with 12 vision-related subscales scored 0–100 [17]. It has since been shorted to a 25-question version with confirmation of validity and reliability in numerous ocular diseases. Bradley et al. tested whether the VFQ-25 could adequately assess the HRQL of GO patients, with the knowledge that several important issues relating to binocular function and body image are not assessed by the NEI-VFQ. Thirty consecutive patients with GO were administered the VFQ-25 after which they were invited to offer feedback in an interview. Respondents demonstrated moderately impaired HRQL, most impaired for the subscales of Mental Health (50) and Role Difficulties (50) and least impaired for Color Vision (100) and Social Function (88). The overall median composite score was 69 but was lower in patients with diplopia (61) than those without diplopia (90). Interestingly, there was no difference in Role Difficulties based on the presence or absence of diplopia, but Driving and Peripheral Vision both scored significantly lower in patients with diplopia. The high scores observed in the Social Functioning subscale suggest that this subscale fails to capture the concerns with appearance and self-consciousness in social settings that are important to many GO patients. Indeed, in the feedback interview, 10 patients reported that the instrument did not adequately address altered physical appearance. Other issues the patients recommended addressing included additional pain-related items, tearing, ocular irritation, and psychosocial issues such as frustration, fear, and self-consciousness [26]. More recently, the Chinese translation of the VFQ-25 was used to assess HRQL in dysthyroid optic neuropathy (DON). Patient with moderate to severe thyroid-associated ophthalmopathy were divided into a group of 23 with DON and 13 without DON. DON patients had significantly lower VFQ-25 scores with comparative composite scores of 54 versus 77. Similar to the previous study, Role limitations and Mental Health were the most affected subscales. While diplopia and exophthalmos were not correlated with any subscale, most subscales did show moderate correlation with activity and severity of ophthalmopathy quantified by NOSPECS or CAS [27].

## Disease-Specific Instruments

The most specific and potentially most sensitive method for determining changes in HRQL in GO is in applying a disease-specific instrument. Simple measures of patients' perceptions of ocular health have been included in several studies evaluating GO therapy. In a clinical trial of oral prednisone versus orbital radiotherapy,

investigators asked patients to rate their ocular condition on a 1–10 scale, and termed this measure the “subjective eye score.” While the primary outcome, improvement in the NOSPECS score, suggested that approximately half of patients responded to either treatment, improvements in the subjective eye score were modest [7]. A subsequent placebo-controlled trial of orbital radiotherapy indicated that orbital radiation resulted in improved ocular motility, but no difference was detected in the subjective eye score [28].

Several studies from the Mayo Clinic have attempted to quantify subjective patient concerns relating to GO and its treatment by using simple three- or five-point scales. In a case series of 428 patients who underwent orbital decompression surgery for functional indications, a follow-up questionnaire revealed significant cosmetic concerns: only 21 % of patients were very satisfied with their appearance, 32.5 % were satisfied, 35.6 % considered their appearance to be acceptable, and 10.9 % were dissatisfied or very dissatisfied with their appearance [3]. In a later study of 34 patients who underwent orbital decompression primarily for physical disfigurement, 37.9 % of the 29 patients who completed the follow-up questionnaire were very satisfied with their appearance, 31.0 % were satisfied, and 31.0 % reported that their appearance was acceptable [29]. While this type of evaluation may enlighten the clinician about a patient’s emotional concerns, it addresses a single clinical issue and only indirectly addresses quality of life, leaving the field still wanting for a comprehensive HRQL instrument.

In an attempt to create a questionnaire that could assess patients during the longitudinal course of Graves’ disease, a Swedish group surveyed 149 patients with hyperthyroidism using a three-part instrument. The first section comprised 8 questions about life from disease onset to initiation of treatment for hyperthyroidism. Another set of 25 questions pertained to their experience once treatment was started. The final section included 5 questions about ophthalmopathy. Patients were treated with thyroidectomy, RAI, or antithyroid medications and followed for 4 years. Of the 93 % of patients employed at the onset of their disease, 63 % reported that treatment affected their ability to work very little or not at all, but 19 % were not able to work for at least 1 month. There was no significant difference in economic impact or HRQL between the three treatment groups [30].

Watt et al. gathered 13 physicians and two nurses who treat patients with thyroid disease and 80 patients with thyroid disease, including 17 with ophthalmopathy, to rate survey questions for their relevance to quality of life. Of the 15 domains deemed most relevant to thyroid-related QOL, less than half overlapped between the patient and clinician groups. Care providers rated questions about disease-associated symptoms like eye complaints in patients with ophthalmopathy as most relevant, whereas patients rated psychological issues like nervousness and emotional concerns as most important [31]. This highlights the need for patient input into HRQL instrument development and confirms the finding that objective measures may not necessarily be correlated with QOL scores.

Previous research on the importance of input by both the patient and clinician was highlighted by the Food and Drug Administration. In the early 2000s, a task force consisting of members from the International Society for Quality of Life Research, the International Society for Pharmacoeconomics and Outcomes Research, the

Pharmaceutical Manufacturer's Association Health Outcomes Committee, and the European Regulatory Issues on Quality of Life Assessment was assembled to unify and standardize criteria for patient-reported outcome measures, a subset of which are HRQL measures. In their formal report, they state, "There are several potential sources of data..., i.e., patients, clinicians, and caregivers. Each source... may provide a unique and valuable perspective on the disease and the efficacy of a therapy. For example, patients may focus on the changes in their own health; families may react not only to the impact on the patients, but also to the impact on family life; and clinicians and researchers view disease and its treatment from a clinical perspective." [32] To that end, more formal HRQL instruments have been created with an attempt to broadly assess both clinical and psychosocial patient issues.

The Graves' Ophthalmopathy Quality of Life (GO-QOL) instrument is a Dutch language instrument consisting of a total of 16 questions, with 8 questions assessing each of 2 subscales: Visual Functioning and Appearance [33]. It was developed from a combination of previously employed HRQL instruments and free-form responses from a group of 24 GO patients to address the need for a disease-specific HRQL measure. The scores range from 0 to 100 and in their pilot study of 70 euthyroid GO patients, the mean score for Visual Functioning was 54.7 and for Appearance was 60.1. It has been shown to be a reliable instrument in a Dutch population based on both test-retest reliability and internal consistency studies [34]. The Visual Functioning subscale correlated with SF-24 and SIP, and lower scores were associated with increased age and more severe motility dysfunction. The Appearance subscale correlated well with mental health and was found to be more troublesome to women. Surprisingly, proptosis did not correlate with the Appearance score. Several years later, the same group looked at long-term follow-up of a median of 11.7 years for 163 euthyroid patients who had been treated with steroids or orbital radiation. More than half of patients had diplopia and proptosis greater than 20 mm, and those with diplopia had lower scores. Radiotherapy-treated patients scored an average of 3–15 points lower than prednisone-treated patients. Overall scores for the entire group were worse than healthy controls, but better than newly diagnosed patients by 23.5 points for Visual Functioning and 17.1 points for Appearance [35].

The GO-QOL has been translated into six languages and used around the world in countries such as Germany, Australia, Taiwan, and Korea [36–39] (English language version available free to the public at [http://www.eugogo.eu/\\_downloads/clinical\\_evaluation/GO\\_QOL\\_EN.pdf](http://www.eugogo.eu/_downloads/clinical_evaluation/GO_QOL_EN.pdf)). Several issues should be acknowledged when considering the use of this HRQL instrument internationally. The GO-QOL instrument asks about cycling and outdoor walking, which might be less applicable to GO patients in societies where those activities are less prevalent. The Australian version of the GO-QOL, for example, replaced the questions about cycling with inquiries about effects on work and performing domestic activities. Next, the instrument has only been validated in its native language; third, it does not include a subscale that assesses ocular pain; and finally, the visual functioning and appearance subscales do not correlate strongly with disease severity [33]. Taking these caveats into consideration, there have been numerous studies using the GO-QOL which have evaluated the HRQL of GO patients and the success of treatments for GO. When the GO-QOL



was administered in Korea, the composite scores were 67.8 for total QOL with Visual Functioning subscore of 73.7 and Appearance subscore of 61.9. Unlike in the original study, the Korean study found that GO-QOL scores correlated with the clinical assessment scores of NOSPECS and CAS. Additionally, lower Visual Functioning scores were correlated with higher extraocular muscle involvement, and lower Appearance scores were correlated with higher severity of proptosis and soft tissue involvement [39]. In Germany, 310 patients with thyroid eye disease were assessed and stratified by clinical severity. GO-QOL scores were lower in moderate-severe cases compared to mild cases, in active versus inactive cases, and in patients with sight-threatening orbitopathy or diplopia [36]. Appearance scores were lower in patients undergoing psychotherapy. A significant limitation to this tool is the ceiling effect, which the authors set at >15 % of respondents choosing the highest score, being reached in 27 % of patients on Visual Functioning and 19 % of patients on Appearance with respective composite scores of 72.5 and 71.3. These scores are higher than in other countries and may limit the sensitivity of GO-QOL in German patients with more mild disease or mild changes in HRQL. The Australian GO-QOL, utilized after several adjustments, resulted in a Visual Functioning score of 59.0 and Appearance score of 54.5. Additionally, when asked about the usefulness of counseling and education, only a quarter of patients felt it was beneficial or adequate, highlighting an area in need of improved quality of care [37]. In Taiwan, the GO-QOL was administered to 271 GO patients and, similar to the results in Australia, the composite scores were 58 for Visual Functioning and 54 for Appearance. Both scales correlated with clinical disease severity, with lower Visual Functioning scores in active disease and lower Appearance scores in patients with diplopia [38]. This is in contrast to the Korean study where Appearance was correlated with proptosis rather than diplopia [39].

With the ability to monitor a patient's HRQL comes the ability to measure the impact of treatment on the disease process. Implementation of a standardized survey and interpretation of the results requires clinicians to understand what change in the score represents clinically significant improvements in HRQL. Terwee et al. enrolled 164 patients at various stages of treatment for GO from radiotherapy to eyelid surgery. Patients who experienced a moderate to large subjective improvement in QOL had an average increase in GO-QOL of 5 points in Visual Functioning and 8 points in Appearance. Correlation between the objective score and subjective report of change in HRQL was only moderate [40].

Bartalena et al. used the GO-QOL in a randomized, double-blind clinical trial to determine how several doses of intravenous methylprednisolone affected clinical signs and patient experiences. Three different doses were given as 12 weekly infusions to 159 patients with active, moderate to severe GO. CAS scores were improved in the high and medium dose groups, and extraocular muscle motility improved in the high dose group, but the benefit was transient. When GO-QOL scores were gathered 24 weeks after the initiation of treatment, there was no difference between dosage groups [41]. The role of selenium replacement for treatment of mild GO has also been assessed with GO-QOL. GO patients were given oral selenium, pentoxifylline, or placebo twice daily for 6 months. Of the 53 patients treated with selenium,

62 % had an increased Visual Functioning score and 75 % had an increased Appearance score, while there was no significant difference in QOL in the placebo or pentoxifylline groups [42].

Surgical outcomes have also been investigated for influence on HRQL, especially given that surgical treatments tend to be more expensive, warranting evidence that patients experience improved quality of life in exchange for the increased costs. In 2008, the European Group on Graves' Orbitopathy published a multicenter report on outcomes of decompression. Eleven countries included 139 euthyroid patients with stable GO who underwent decompression for disfiguring proptosis. A total of 18 different surgical approaches were used, including 132 two-wall decompression and 112 three-wall decompression, with an average reduction in proptosis of 5 mm. The range of preoperative Appearance scores was 17.7–55.1 and decompression led to an average increase of 20.5 points. There was no difference in the Appearance scores between groups, except that trans-lid and endoscopic approaches led to only an average of 1.8 point change. Visual Functioning scores decreased after decompression, particularly in the patients who underwent coronal approach which led to the largest incidence of new onset diplopia [43]. In contrast, Fichter et al. analyzed the outcomes of the single surgical technique of en bloc resection of the lateral orbital wall with fat excision and found an increased GO-QOL score for both subscales. Thirty orbits of 18 patients were included and the GO-QOL composite scores improved from 34.1 to 26.1 for Visual Functioning and Appearance, respectively, to 69.0 and 50.1 at 6 months postoperatively. The improvement in Visual Functioning score correlated with decreased proptosis and vertical palpebral fissures. Finally, two patients with dysthyroid optic neuropathy had their Visual Functioning scores increase from 14.3 and 18.8 to 64.3 and 93.8 [44].

Given the lack of validation of the GO-QOL in the United States and the previously mentioned limitations of this instrument, the field of quality of life in thyroid eye disease was still lacking. To fill this void, Dr. Yeatts undertook a comprehensive plan to formulate an American English questionnaire designed to examine the multitude of factors that contribute to QOL in GO [45]. He created a survey of 105 questions adapted from other pertinent and validated instruments: SF-12 for general and mental health, Dermatology-Specific QOL Questionnaire for self-perception and social function, VFQ-51 for general visual function, and Graves' ophthalmopathy assessments for disease-specific visual function. After administering the questionnaire to 203 GO patients, he reported good validity, with the scores from GO patients being lower than those for the control group for physical and mental health, self-image, sleep, social and work function. The individual items engineered to evaluate symptoms, such as diplopia, dry eye, and blurred vision, were correlated with clinical disease severity. Additionally, several of the vision function questions which correlated well with visual quality of life asked about visual discrimination, as in finding an item on a crowded shelf or recognizing a face from across the room. This is in contrast to GO-QOL questions that ask about reading or driving, activities which did not strongly correlate with overall visual QOL. Clearly a 105-item instrument may be difficult to integrate into regular clinical practice, so Yeatts also created a 9-item questionnaire with face validity and good clinical correlation for use

in a more practical setting, titled Graves Ophthalmopathy Quality-of-Life-Scale (GO-QLS).

In the interest of clinical efficiency, a group in British Columbia created a three-question instrument, TED-QOL. The three questions inquired about overall quality of life, appearance, and visual functioning, asking the patient to assign a 0–10 score for each. The survey showed good correlation with the GO-QOL and GO-QLS and good test-retest reliability. Patients reported good clarity and ease of survey completion. The main benefits of this instrument are the low burden on the patient, leading to high completion rate, and time efficient administration requiring only 1.6 min to complete. Again, there was only moderate correlation between the TED-QOL results and the clinically apparent disease severity [46].

## Qualitative Studies

The final means of determining the personal impact of GO on patients is to step away from the desire to quantify individual components of life. The qualitative approach is reasonably intuitive to physicians since it is the method by which most patient symptoms are identified during daily patient encounters. While it may be harder to standardize and schedule into a finite window of time, qualitative assessments can offer powerful data about the issues GO patients are facing.

Estcourt et al. conducted interviews of 25 British patients with thyroid eye disease and distilled commonly mentioned topics into three major themes. The first is an altered identity which developed due to change in appearance, adjustments in role functioning, and limited abilities from the consequences of eye disease. The second was the development of new coping mechanisms, including emotional stoicism, social avoidance, and denial. Third, patients highlighted anger, frustration, and disenchantment with the medical establishment due to uncertainty with their diagnosis, treatment, or disease course, which in turn led to more difficult interactions with healthcare providers [47]. This evidence bolsters the idea that the medical system needs to improve the quality of communication and be aware of the issues at the forefront of the patient's mind, since it may not be the same issue that is at the forefront of the practitioner's mind.

A separate study of 250 German patients looked at levels of work disability and participation in psychotherapy to further elucidate the emotional and economic stressors that were contributing to decreased HRQL. Nearly half of patients complained of significant restrictions on daily activities because of their symptoms, 36 % were on sick leave from work, 28 % were on disability, and 5 % had chosen to take early retirement. The severity of disease and ocular dysmotility were correlated with longer time on sick leave and likelihood of being on disability. In addition, 21 % of patients were undergoing psychotherapy and they were more likely to be on sick leave or disability. Interestingly, proptosis was not correlated with limited ability to work, though both patients with severe proptosis and patients with ocular dysmotility were more likely to be receiving psychotherapy [48]. The same authors

followed up the first study with another report looking specifically at the economic burden of GO. Of the 215 GO patients they analyzed, 22 % were temporarily disabled and 5.6 % were permanently disabled. The average amount of sick leave taken was twice the national average: 22.3 days per year compared to 11.6 days per year for the general population, with the disease severity correlating with length of sick leave. A multivariate analysis found diplopia to be the primary predictor for work disability [49].

## Conclusions

Graves' ophthalmopathy is a complicated disease with a multitude of effects on patients suffering its sequelae. While the medical world works to gain further insight into disease mechanisms and improved treatment modalities, patients are left struggling to cope with seemingly innumerable physical and psychosocial issues. As healthcare providers, it is our responsibility to identify those issues and offer assistance by whatever means are available. The HRQL questionnaires reviewed here all have a potential place in clinical practice. While there is no clearly ideal instrument for measuring the effect of GO on HRQL, the only way we will be able to improve patients' lives is by asking how we can help, and asking about quality of life is as important as asking about eye pain or diplopia. Implementing an assessment of HRQL into standard practice will go a long way towards giving patients the voice they need to best participate in their own care.

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