Edelweiss Applied Science and Technology
ISSN: 2576-8484
Vol. 8, No. 6, 9500-9510
2024
Publisher: Learning Gate
DOI: 10.55214/25768484.v8i6.4029

The relationship between quality of life assessed by go-qol and clinical activities score in patients with thyroid eye disease in the integrated oncology eye clinic of Dr. Soetomo General hospital, Indonesia: A literature review

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Abstract: Managing thyroid eye disease (TED) is challenging because of its complexity and diverse clinical manifestations. TED treatment strategies are tailored to disease severity, ranging from conservative options, such as artificial tears and prism glasses for mild cases, to more aggressive treatments, including intravenous methylprednisolone and orbital decompression, for moderate to severe cases with potential vision loss. TED can significantly impact patients' quality of life and psychological well-being, particularly through changes in visual acuity and facial aesthetics. Various sequelae of TED, such as eye discomfort, diplopia, keratitis, and visual impairment, can negatively impact quality of life, emphasizing the necessity for comprehensive management strategies. Assessments of quality of life using tools such as the Graves' Ophthalmopathy Quality of Life (GO-QoL) questionnaire underscore the substantial effects of TED on patients' physical and mental well-being. Further research is essential to understand the link between clinical activity scores and quality of life in TED patients. This review seeks to address the literature gap and enhance comprehensive care for these patients.

Keywords: *Good Health, Grave's Ophthalmopathy Quality of Life Questionnaire, Quality of Life, Thyroid Eye Disease.*

1. Introduction

Thyroid Eye Disease (TED), also known as Graves' ophthalmopathy or orbitopathy (GO), is a prevalent and significant extra-thyroidal complication associated with Graves' disease. This condition is characterized by a complex inflammatory process that affects various ocular structures, including orbital fibroblasts, adipose tissue, extraocular muscles, the optic nerve, and the surrounding vasculature. The systemic thyroid status of an individual can significantly influence the development and progression of TED [1]. Approximately 25-50% of individuals with hyperthyroidism are at risk of vision impairment due to TED **Error! Reference source not found.**. TED can also occur sporadically in patients who are euthyroid or hypothyroid, often as a consequence of chronic thyroiditis [3].

The primary goal of managing GO/TED is to improve visual function and enhance patients' overall well-being. The management of TED primarily focuses on immunosuppressive therapies; however, achieving optimal treatment outcomes remains challenging. Inadequate management can significantly impair a patient's quality of life. Therefore, there is an urgent need for developing safer and more effective treatment options for TED. Currently, available therapeutic strategies are limited, highlighting the importance of deepening our understanding of TED's pathophysiology to facilitate the development of more targeted therapies [4]. For patients with inactive moderate to severe TED, surgical interventions such as orbital decompression, strabismus surgery, or eyelid surgery may be necessary. Effective management of TED requires distinguishing between its active and inactive phases, which can

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be done using scoring systems like the Clinical Activity Score (CAS), the European Group on Graves' Orbitopathy (EUGOGO) guidelines, or the VISA (vision, inflammation, strabismus, and appearance) guidelines [5].

TED can significantly impact patients' quality of life and psychological well-being, particularly through changes in visual acuity and facial aesthetics. Various sequelae of TED, such as eye discomfort, diplopia, keratitis, and visual impairment, can negatively impact quality of life. Additionally, changes in eye appearance, such as exophthalmos, eyelid retraction, and proptosis, can alter facial aesthetics and psychological distress [6] It is essential to assess patients' perceptions of these outcomes as part of clinical trials [2].

The Graves' Ophthalmopathy Quality of Life (GO-QoL) questionnaire is a specific tool used to assess patients' quality of life with TED. This instrument effectively measures the significant reduction in GO patients' quality of life [7]. Research exploring the relationship between quality of life and the severity of TED remains limited, particularly in Surabaya, at RSUD Dr. Soetomo. Considering the potential sociodemographic variations among different populations, this study aims to explore the relationship between quality of life, as evaluated by the GO-QoL, and the severity of TED in patients attending the oncology eye clinic at Dr. Soetomo Surabaya Hospital.

2. Thyroid Eye Disease

2.1. Definition

TED is an autoimmune disorder characterized by inflammation and tissue remodeling within the orbital region. This process includes the accumulation of extracellular macromolecules and fat deposits. As the most prevalent extra-thyroidal manifestation of Graves' disease, TED represents an autoimmune-mediated orbitopathy that can lead to a range of ocular complications. The condition is marked by inflammatory infiltrations in the orbital tissues, particularly affecting the extraocular muscles. These complications may result in visual impairment throughout the disease due to lagophthalmos, exposure keratitis, corneal ulceration, or optic neuropathy. TED is the primary cause of both unilateral and bilateral proptosis in adults and can lead to permanent facial disfigurement [1]. While the majority of TED cases occur in individuals with hyperthyroidism, TED can also manifest in individuals who are hypothyroid, usually linked to Hashimoto's thyroiditis or euthyroid [6][8].

2.2. Epidemiology

In Caucasians with Graves' disease (GD), the prevalence of TED is estimated to be around 50%. In the United States, the annual incidence of TED is approximately 16 per 100,000 women and 3 per 100,000 men, correlating with the higher incidence of hyperthyroidism in women. Active and inactive TED prevalence in Europe is about 10 per 10,000 people.(1) Around 40% of patients with GD will develop TED during their lifetime, typically between the ages of 30 and 50, with severity often increasing after age 50. TED frequently presents within 18 months of a GD diagnosis [4].

Among patients with GD, nearly 70% may experience subclinical enlargement of the extraocular muscles. While most cases of TED are mild and self-limiting, 20% to 30% are moderate to severe, and 3% to 5% may progress to vision-threatening stages, such as compressive optic neuropathy (CON). In newly diagnosed Graves' patients, the prevalence of mild, moderate to severe, and vision-threatening TED is approximately 20%, 5.8%, and 0.3%, respectively [4].

2.3. Etiology

The etiology of TED involves a complex interaction of autoimmune, genetic, and environmental factors. TED is often associated with Graves' disease, wherein autoantibodies target the thyroid-stimulating hormone receptor, leading to thyroid dysfunction and ocular manifestations. The autoimmune response also extends to antigens within the orbital tissues, triggering inflammation and subsequent tissue remodeling. This process includes the activation of orbital fibroblasts, the formation of adipocytes and myofibroblasts, and increased production of hyaluronan, all of which contribute to clinical features such as exophthalmos [9].

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2.4. Pathophysiology

The pathophysiology of TED is driven by immune mechanisms that activate orbital fibroblasts, adipocytes, and lymphocytes, leading to increased levels of pro-inflammatory cytokines like IL-1 and prostaglandins. Orbital fibroblasts, which express elevated levels of TSH receptors, can differentiate into mature adipocytes. Thy-1+ fibroblasts tend to differentiate into myofibroblasts, while Thy-1- fibroblasts can transform into adipocytes under the influence of TGF-β [9]. TSH receptors are central to the autoimmune cascade seen in TED, with TRAb levels closely correlating with disease severity [11].

PPAR-γ in Thy-1- fibroblasts regulates the process of adipogenesis, while IGF-1R in Thy-1+ fibroblasts attracts inflammatory CD4+ T cells. The inflammatory cascade involves TRAb-activated Thy-1- fibroblasts secreting IL-6 to recruit B cells and plasma cells, and IGF-1R-activated Thy-1+ fibroblasts secreting IL-16 and RANTES to attract T cells, thereby establishing a positive feedback loop of inflammation. T cells produce IFN-gamma and TNF-α, which stimulate myofibroblast activity and hyaluronate production, while IL-6 promotes the production of additional TRAb autoantibodies by B cells. Prolonged inflammation leads to fibrosis in the extraocular muscles (EOM), with the phenotype of TED varying by age: younger patients often present with fat-dominant orbitopathy. In comparison, older patients typically exhibit muscle-dominant orbitopathy [12].

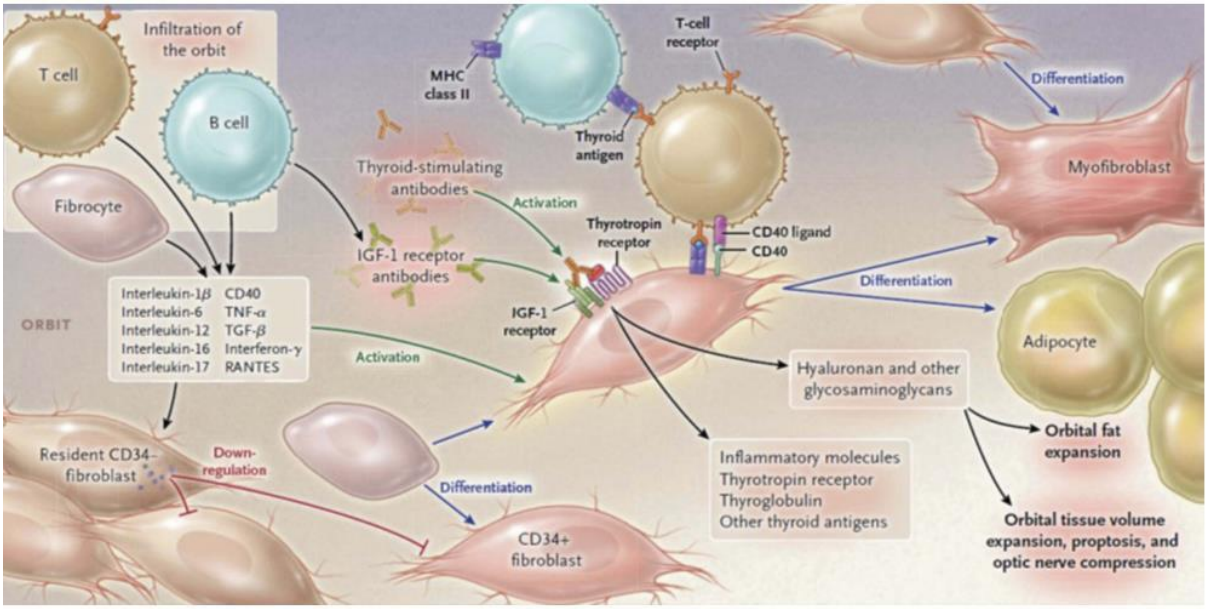

Figure 1.
Pathophysiology of thyroid eye disease (TED) [11].

2.5. Risk Factors

Key risk factors for TED include females, smoking, and middle age. Smoking increases the risk of developing TED by 7 to 8 times and can also reduce the effectiveness of treatment. The American Thyroid Association recommends that healthcare providers advise individuals diagnosed with Graves' disease to quit smoking and refer them to smoking cessation programs. Additionally, patients should be informed about the harmful effects of passive smoking and exposure to secondhand smoke, as these factors further elevate the risk of TED. [13] The thyroid function status at the time of diagnosis is crucial, with most TED cases presenting as hyperthyroid, followed by smaller percentages of euthyroid, Hashimoto's thyroiditis, or hypothyroid cases [8].

In addition, other risk factors for TED include genetic polymorphisms in Cytotoxic T-lymphocyte antigen 4 (CTLA-4), Human leukocyte antigen-DRB1 (HLA-DRB1), interleukin 23-receptor (IL23R), protein tyrosine phosphatase nonreceptor 22 (PTPN22), CD40, CD86, thyroglobulin, and thyroid-

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stimulating hormone receptor (TSHR), which are believed to increase susceptibility to TED. Psychological stress can also exacerbate TED by triggering an enhanced immune response, particularly following prolonged use of corticosteroids for immunosuppression [10][14].

3. Clinical Activity Score (CAS)

The Clinical Activity Score (CAS) was developed by Mourits et al. in 1996 to quantify TED's inflammatory activity based on specific clinical signs such as pain, redness, swelling, and visual impairment. The CAS not only aids in identifying patients who may benefit from aggressive treatment but also helps in monitoring the response to therapies, including corticosteroids [15]. CAS employs a binary scale, assigning one point for each of the seven symptoms and signs of periocular soft tissue inflammation, which are surrogate markers of disease activity. The scoring system comprises ten points, with four points dedicated to acute inflammatory signs: pain, redness, swelling, and impaired function [15]. During follow-up visits, patients may receive additional points based on the presence of elevated proptosis (≥2 mm), restricted ocular motility (≥8°), or decreased visual acuity within the preceding three months. However, the CAS has limitations; it does not correlate with risk factors for TED complications, such as diplopia or Dysthyroid Optic Neuropathy (DON). CAS score higher than 4 has demonstrated an 80% accuracy in predicting a positive response to corticosteroid therapy and a 64% accuracy in predicting a negative response [16].

Table 1.
Clinical activity score (CAS) [16].

Pain	- Retroorbital pain in the last four weeks - Gaze-evoked pain, especially during right-left gaze and downgaze
Redness	- Eyelid redness - Diffuse conjunctival redness in at least one quadrant
Swelling	- Eyelid swelling - Chemosis - Caruncle swelling - Proptosis ≥2 mm within a 1-3 month period
Decrease in function	- Eye movement limitations in all gazes > 5 degrees within a 1 to 3-month period - Visual acuity decreases by more than one Snellen chart line (using pinhole) within a 1-3 month period

4. Diagnostic Criteria

The TED diagnosis relies on three primary factors: clinical symptoms, laboratory evaluations, and imaging studies [1].

4.1. Clinical Manifestations of TED

Patients with TED often experience ocular discomfort, such as dryness, redness, photophobia, and pain. The prominent clinical features of TED include proptosis, lid retraction, chemosis, conjunctival injection, exposure keratopathy, periorbital swelling, restricted ocular motility, and optic neuropathy. Lid retraction is observed in approximately 90% of patients, proptosis in 60%, and restricted ocular motility in 40%. Optic neuropathy and exposure keratopathy are particularly concerning due to their potential to cause vision loss. Figure 2 below illustrates the clinical manifestations of a patient with TED [1].

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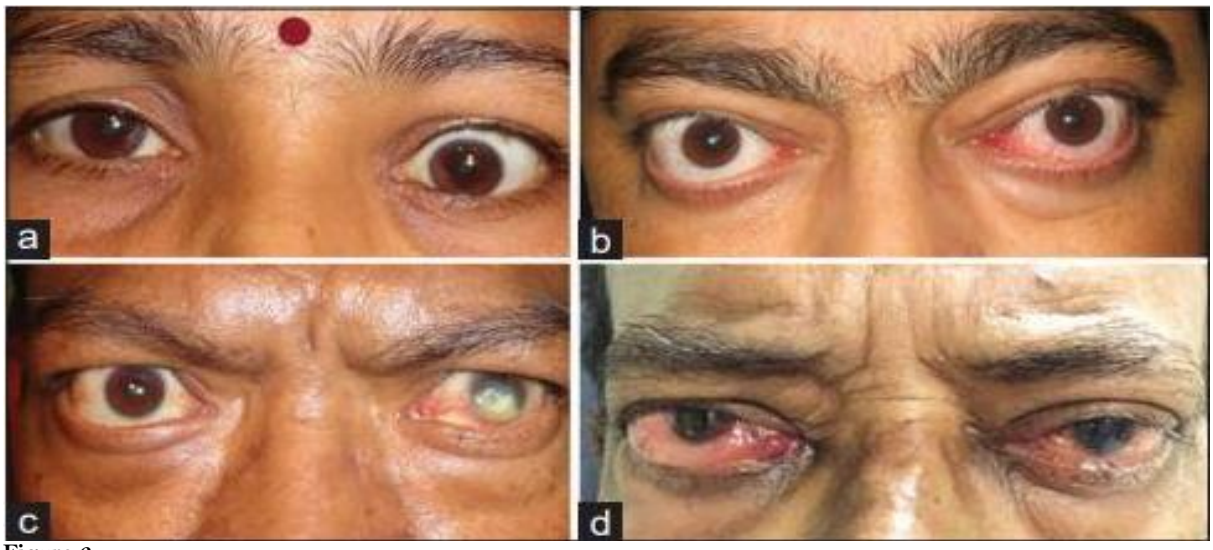

Figure 2.
The clinical manifestations of TED: (a) Upper left eyelid retraction in mild inactive TED. (b) Left eye conjunctival congestion, chemosis, caruncular edema, eyelid edema, and erythema in moderate to severe active disease. (c) Severe cases may lead to sight-threatening eye disease, resulting in corneal exposure, keratopathy, and infiltration due to severe lagophthalmos. (d) Compressive optic neuropathy of the right eye can occur in patients with active bilateral TED [3].

The progression of TED typically follows a clinical course as described by Francis Rundle (illustrated in Figure 3), with an active phase lasting from 6 to 24 months and up to 3 years in some cases, followed by an inactive, chronic phase that may involve permanent damage and infrequent clinical improvement. Although the disease generally stabilizes during the inactive phase, 5-16% of patients may experience reactivation with worsening proptosis [11].

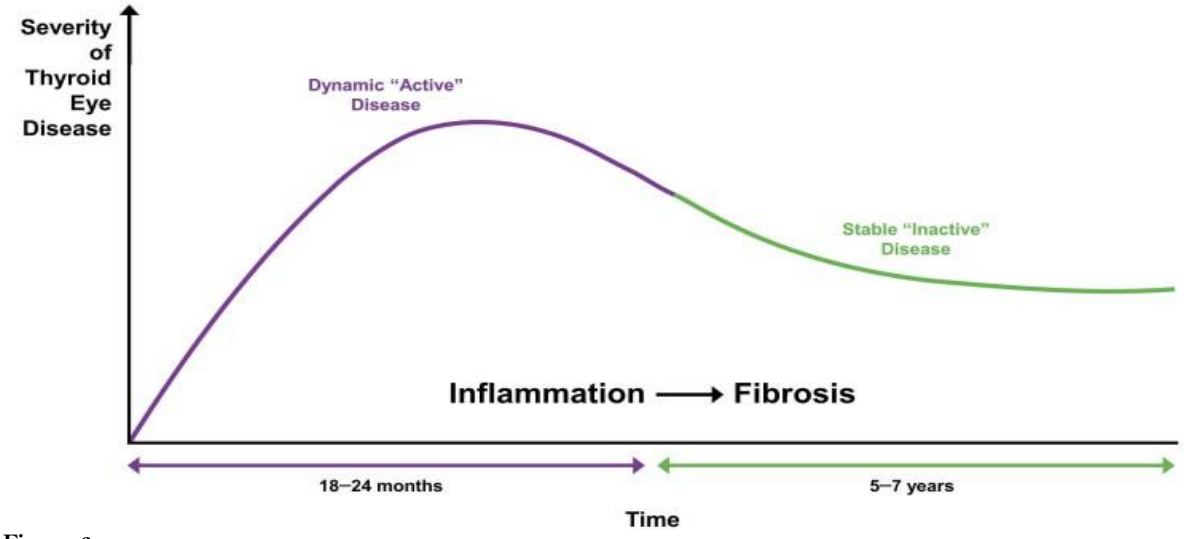

Figure 3.
Rundle chart displaying the progression of TED severity over time [11].

4.2. Radiological Examination

Radiological assessment is crucial for evaluating and managing TED. Non-contrast computed tomography (CT) is commonly used to assess the orbit's bony anatomy and is more cost-effective than magnetic resonance imaging (MRI). CT scans allow for assessing orbital fat and bone structures, contributing to the diagnosis and staging of TED, monitoring disease progression, and guiding

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treatment strategies, including evaluating responses to intravenous corticosteroids. CT is also effective in measuring the thickness of the extraocular muscles and detecting muscle hypertrophy, which assists in differentiating TED from other orbital disorders and monitoring treatment response. Additionally, CT scans are particularly valuable for surgical planning, especially in decompression surgery, as they provide detailed visualization of the orbital bones [17].

MRI is the preferred modality for identifying active TED due to its superior ability to visualize muscle inflammation and enlargement while sparing the tendons. MRI is crucial for evaluating soft tissue changes, inflammatory processes, and concurrent neoplasms, providing comprehensive information necessary to manage TED effectively. It can reveal fusiform enlargement of the extraocular muscles and other indicators of orbital inflammation. Quantitative MRI techniques, such as diffusion-weighted imaging, are particularly beneficial for detecting microstructural changes, which can assist in predicting disease activity and treatment response. MRI is especially valuable in the early stages of TED, as it aids in treatment planning and facilitates monitoring of disease progression over time [17].

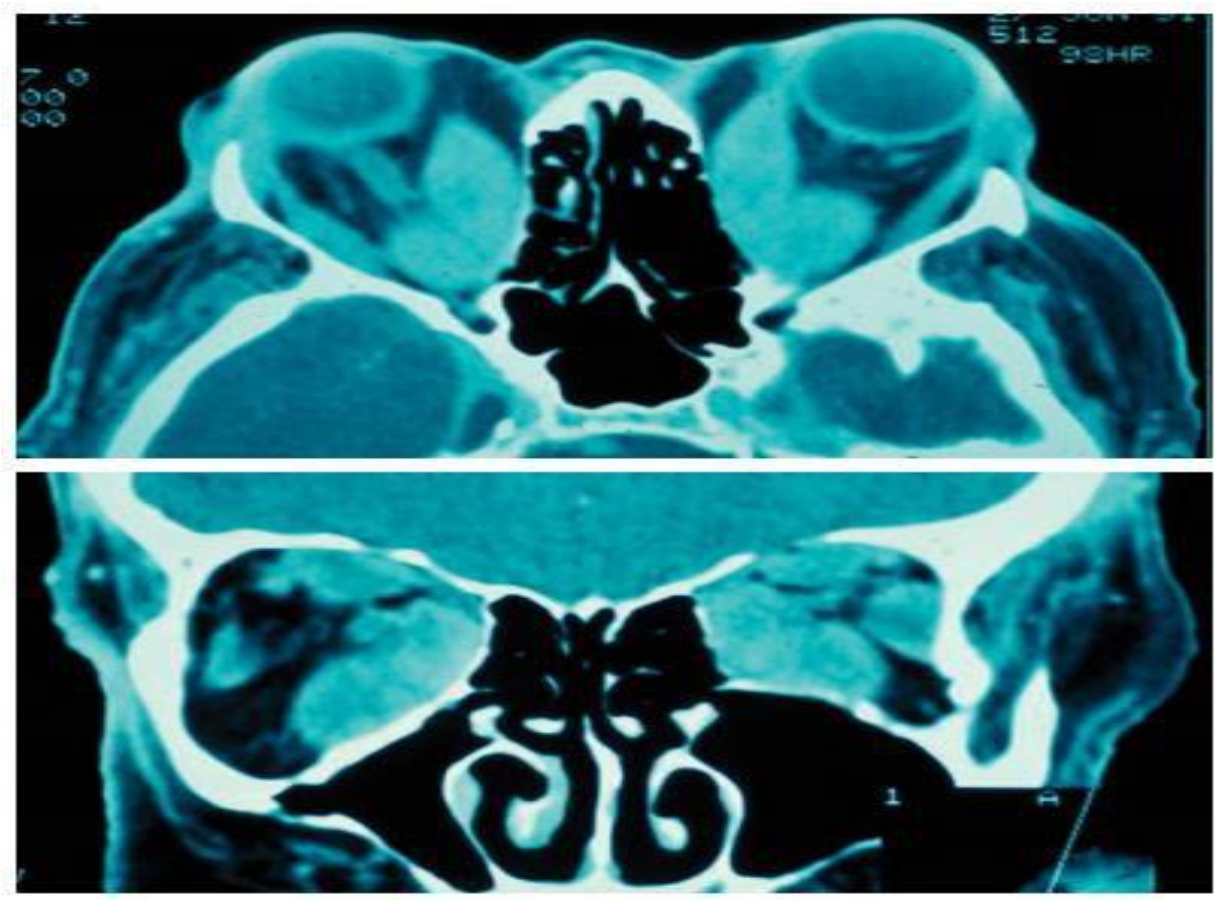

Figure 4.
Axial and coronal CT images of a 65-year-old female smoker with TED and compressive optic neuropathy. The images show the enlargement of all rectus muscles, impinging on the optic nerve in the retrobulbar orbit [17].

4.3. Laboratory Examination

The diagnosis of TED can often be made based on clinical observations, particularly the disease's restrictive nature and its association with systemic thyroid disorders. While these clinical features are suggestive, they are not conclusive. Laboratory tests measuring levels of thyroid hormones, such as thyroid-stimulating immunoglobulin (TSI), T3, T4, TSH, free T4 (fT4), and anti-thyroid antibodies, provide stronger evidence for the presence of TED. In euthyroid cases, further testing is required,

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ISSN: 2576-8484
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including thyroid peroxidase (TPO) antibody testing, to identify any underlying thyroid autoimmunity that may be contributing to TED [8][13].

5. Management

The management of TED is detailed in Table 2 below.

Table 2.
The management of TED based on EUGOGO 2021 consensus [5].

Severity/Condition	Management Approach
Mild and Active GO	- Control risk factors (e.g., smoking cessation, managing thyroid dysfunction) - Local treatments - Selenium supplementation (6 months) in selenium-deficient areas - Low-dose oral prednisone prophylaxis if radioactive iodine (RAI) treatment is selected
Moderate-to-severe and Active GO	**First-line:** - Combination of intravenous methylprednisolone (totaling 4.5 g across 12 weekly infusions) paired with mycophenolate sodium **Alternative:** - Higher cumulative doses of i.v. methylprednisolone (up to 8 g) as monotherapy in severe cases **Second-line:** (a) Second course of i.v. methylprednisolone (7.5 g) (b) Oral prednisone/prednisolone with cyclosporine or azathioprine (c) Orbital radiotherapy with oral or i.v. glucocorticoids (d) Teprotumumab (e) Rituximab (f) Tocilizumab
Sight-Threatening GO	- Immediate high single doses of i.v. methylprednisolone (0.5–1 g daily for 3 consecutive days or every other day) - Urgent orbital decompression if unresponsive within 1–2 weeks - Severe corneal exposure: Urgent medical or surgical treatment to prevent corneal breakdown
Inactive Residual GO	- Rehabilitative surgery (orbital decompression, squint surgery, and eyelid surgery)
Thyroid Treatment in GO	- Mild and inactive GO: Any hyperthyroidism treatment based on standardized criteria and patient choice - Sight-threatening GO: Treat hyperthyroidism with antithyroid drugs (ATDs) until GO treatment is completed

6. Impact of Ted on Patient's Quality of Life

Ocular manifestations of TED can significantly impact the quality of life in patients [18]. Although the signs and symptoms of TED may improve as inflammation diminishes, the long-term consequences often persist, continuing to impact quality of life substantially. Patients with TED frequently encounter challenges in maintaining their work, daily activities, and social interactions, which adversely affect their psychological well-being [18]. A study conducted in Australia demonstrated that increased clinical severity of TED is strongly associated with a reduced quality of life, primarily due to impaired vision and changes in appearance. Patients with higher clinical severity scores exhibited significantly lower quality of life, driven by compromised visual function and the psychosocial effects of appearance changes, compared to those with milder forms of the disease. Furthermore, elderly patients (aged 60-80

Edelweiss Applied Science and Technology
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Vol. 8, No. 6: 9500-9510, 2024
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years) reported a more substantial impact from changes in visual function compared to the effects of changes in appearance [19].

6.1. Quality of Life

Quality of Life (QoL) seeks to capture the overall well-being of individuals or groups, encompassing both positive and negative aspects at any given time. It includes various domains such as personal health (physical, mental, and spiritual), interpersonal relationships, education, work conditions, social status, financial security, freedom, autonomy in decision-making, and the surrounding physical environment [20].

The World Health Organization (WHO) defines quality of life as an individual's perception of their position in life within the context of their culture, goals, expectations, standards, and concerns. Understanding a patient's quality of life is crucial for effective symptom management and rehabilitation, as it provides valuable insights into the impact of diseases or treatments [21].

The WHO Quality of Life: Brief Version (WHOQoL-BREF) assesses QoL across four key domains: physical health, psychological well-being, social relationships, and environment. Age, gender, location (rural or urban), and health status can influence QoL within these domains. The WHOQoL-BREF comprises 28 questions, each scored on a 5-point Likert scale, with raw scores converted to 100 for each subscale, where higher scores indicate greater life satisfaction [2].

Health-Related Quality of Life (HRQoL) measures how an illness and its treatment affect a patient's overall functioning and well-being. The US Food and Drug Administration (FDA) defines HRQoL as "a multi-domain concept that represents patients' general perceptions of the effects of illness and its management on the physical, psychological, and social aspects of life" [22].

The Medical Outcomes Study (MOS) SF-36 questionnaire is a widely used generic tool for assessing both physical and mental health status. It evaluates QoL across eight dimensions frequently used in health studies: general health, mental health, physical functioning, limitations in work or daily activities due to physical or emotional impairment, vitality, pain, and social functioning [23].

6.2. Grave's Ophthalmopathy-Quality of Life (Go-Qol) Questionnaire

The GO-QoL questionnaire, introduced in 1998 by Terwee, Gerding, Dekker, Prummel, and Wiersinga, is designed to evaluate the quality of life in individuals with TED. The GO-QoL questionnaire comprises 16 items: 8 focus on visual function and 8 on appearance. Each subscale is scored from 0 (worst) to 100 (best). For invasive treatments, a change exceeding 10 points is considered clinically significant. However, even a 6-point shift on either subscale is viewed positively by patients and is linked with notable improvements in daily activities. The GO-QoL is thoroughly validated, extensively used, and available in eight languages, making it a recommended primary outcome measure for randomized clinical trials. Its incorporation into routine TED assessments is advisable. While not yet confirmed, it is hoped that using the GO-QoL will improve care quality by identifying patients who might benefit from psychological support to address poor psychosocial functioning and low self-esteem [7].

Key Features of GO-QoL [2]:

- The TED-specific quality of life measure was validated in the Netherlands.
- It has two subscales: 'visual functioning' and 'appearance,' each containing 8 questions.
- Responses are categorized as: 1 = no decreased value; 2 = slightly disturbed; 3 = severely disturbed.
- Raw scores are transformed to a total of 100 for each subscale using a specified formula, illustrated in Figure 5.

$$total\ score = \frac{(raw\ score - 8)}{16} \times 100$$

Figure 5 Raw score conversion formula used in GO-QoL [2].

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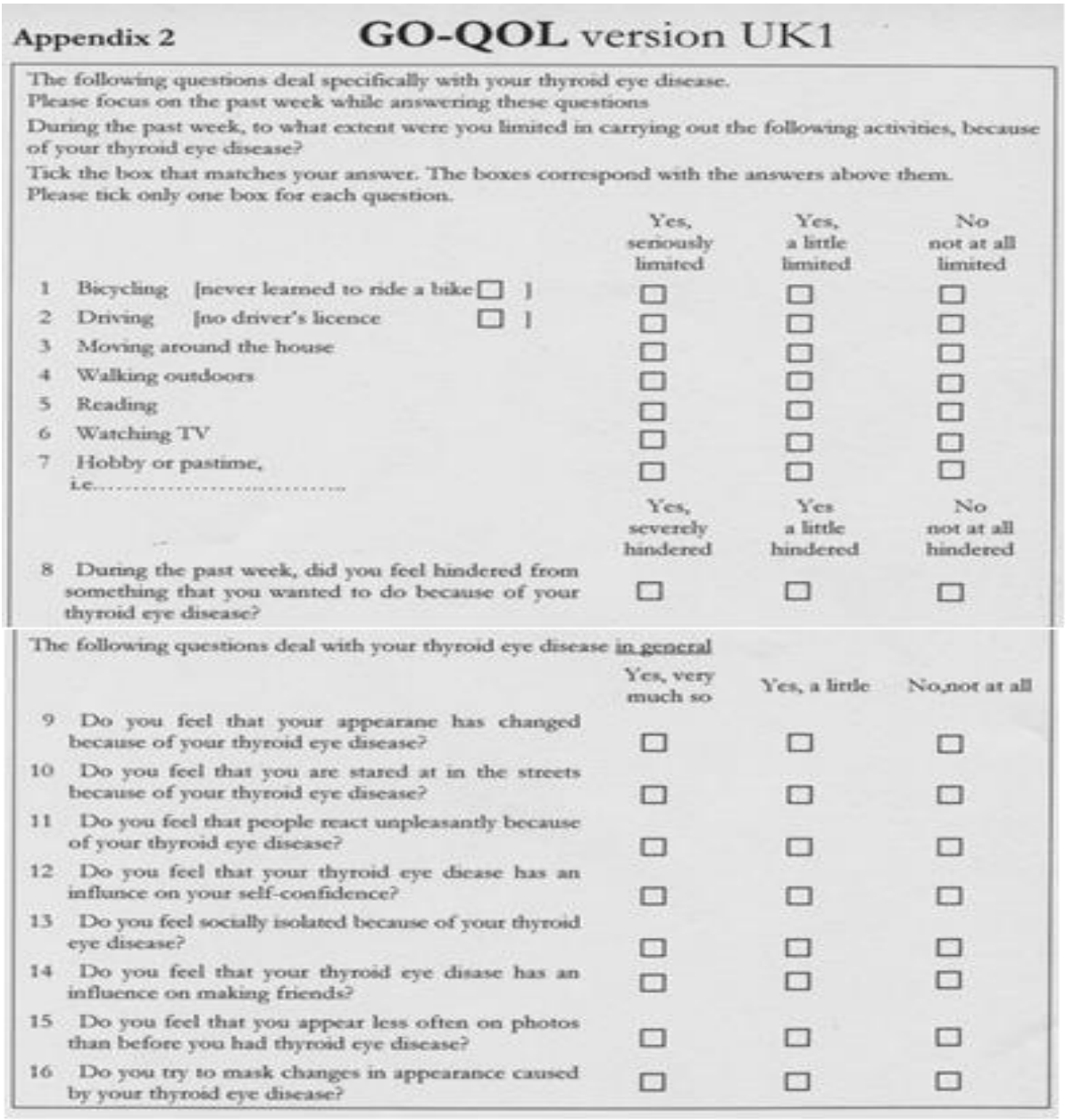

Appendix 2 **GO-QOL version UK1**

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?	☐	☐	☐

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 your appearane has changed because of your thyroid eye disease?	☐	☐	☐
10	Do you feel that you are stared at in the streets because of your 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 diease has an influnce on your self-confidence?	☐	☐	☐
13	Do you feel socially isolated because of your thyroid eye disease?	☐	☐	☐
14	Do you feel that your thyroid eye disase 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 to mask changes in appearance caused by your thyroid eye disease?	☐	☐	☐

Figure 5.
The GO-QoL questionnaire includes 16 items: 8 questions related to visual function (items 1-8) and 8 questions rela*ted* to appearance (items 9-16) [7].

Quality of Life (QoL) scores are categorized as low (<50), moderate (50-75), or high (>75) (10). Generally, GO-QoL scores related to vision and appearance average around 60 points, reflecting a significantly compromised quality of life. These findings align with clinical research on teprotumumab, which reported similar outcomes in participants with recent (≤ 9 months) moderate-to-severe active TED [15].

Cockerham identified several factors influencing well-being, notably the number of TED symptoms and manifestations. Symptoms such as retroorbital discomfort, blurred vision, photophobia, and diplopia were more prevalent among individuals with lower well-being. This supports earlier studies linking TED-related discomfort and visual disturbances to diminished well-being. Moreover, patients who

Edelweiss Applied Science and Technology
ISSN: 2576-8484
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underwent surgical interventions for TED reported notably lower well-being than those who did not. Terwee et al. also observed reduced GO-QoL scores for aesthetics and visual function in patients with persistent TED following TED-specific surgeries [18][24].

The global socio-emotional impact of TED shows that 34% of individuals experienced distress and 28% experienced depression, similar to those undergoing orbital decompression surgery (37% and 26%). Distress was more common as QoL decreased, rising from 17% in high QoL groups to 48% in low QoL groups. Depression rates, however, remained consistent across different QoL levels [18].

In Cockerham's research, individuals with chronic TED sought medical care about 20 times per year before the survey. The number of healthcare visits ranged from around 5 visits annually for patients in the high QoL group to 40 visits annually for those in the low QoL group, indicating more severe TED in the latter group. Previous studies have shown a connection between deteriorating QoL and increased TED severity, suggesting that patients with more severe TED may pursue medical attention more frequently or require more intensive oversight. Additionally, some TED patients encounter negative experiences with healthcare providers, affecting their QoL. Only 25% of patients felt sufficiently supported in managing the psychological effects of TED. There is often a disparity between physicians' and patients' views of TED's impact, with doctors generally underestimating the condition's facial changes and QoL effects. This discrepancy likely contributes to the higher healthcare utilization among chronic TED patients with low QoL [18].

6. Conclusion

Although substantial research has been conducted, there are still considerable gaps in our understanding of the full relationship between QoL and clinical activity in TED patients. The inconsistencies between patient-reported outcomes and clinical evaluations highlight the necessity for more refined methods of assessing QoL in TED. Future research should investigate the correlation between QoL, as measured by the GO-QoL questionnaire, and clinical activity scores in TED patients. This research is crucial for improving patient care and treatment approaches and enhancing the quality of life for those suffering from TED.

Ethical Consideration:

This literature review follows the guidelines for publication ethics set by the Committee on Publication Ethics (COPE) and the International Committee of Medical Journal Editors (ICMJE). It also aligns with the Declaration of Helsinki—Ethical Principles for Medical Research Involving Human Subjects.

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