A Multidisciplinary Thyroid Eye Clinic: A One-stop Shop

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ABSTRACT **Background:** Little is known about the success of multidisciplinary thyroid eye disease (TED) clinic.
Objectives: To present the characteristics, treatments, and outcomes of patients treated in a multidisciplinary TED clinic
Methods: A medical record review of all patients who attended a TED clinic was performed. Data included demographics, medical history, laboratory tests, visual function tests, ocular examinations, clinical activity score (CAS), and assessment of quality of life (QOL).
Results: Clinic visits included 132 patients seen during 385 appointments at a TED clinic (mean 12 appointments per patient). Management of TED included medical treatments for 48 patients (36.3%) and surgical treatment for 56 (42.4%). There was a positive significant correlation between the CAS and thyroid-stimulating immunoglobulin (TSI) activity at the first visit and at the last follow-up visit ($P < 0.01$ and $P < 0.02$, respectively). However, no correlation was found between the CAS and the thyroid-stimulating hormone levels or between the free triiodothyronine (fT3) and fT4 levels at the first or last visit. There was a significant negative correlation between the CAS and color vision (-0.347, $P < 0.01$, Pearson correlation) at the first visit, but not between the CAS and visual acuity and visual field at either the first or last visit. Changes in the QOL and the CAS scores were significantly negatively correlated (-0.240, $P < 0.01$).
Conclusions: Treatment and management decisions for TED should be based on multiple parameters including clinical examinations by ophthalmologists and endocrinologists, laboratory tests, and CAS and QOL scores.

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KEY WORDS: clinical activity score (CAS), European Group on Graves' Orbitopathy (EUGOGO), Graves' disease, quality of life (QOL), thyroid eye disease (TED)

Thyroid eye disease (TED), also known as Graves' disease, is an autoimmune multisystem disorder [1]. The specific pathogenesis of the disease remains unknown. However, the hypothesis is that the same antibodies that attack the thyroid gland and cause systemic problems also recognize orbital fat and extraocular muscles as antigenic, causing orbital inflammation, eye muscle expansion, and fat expansion [1]. Fifty percent of patients with Graves' disease report symptoms of TED that are generally mild [2].

Patients with TED commonly present with soft tissue features of infiltrative disease, such as eyelid retraction and swelling, conjunctival injection, exophthalmos, and restrictive myopathy. Conditions that cause blindness, such as corneal ulcer and optic neuropathy (ON), can manifest in severe cases [3]. Symptoms and signs have a severe negative impact on a patient's self-image, economic stability, and quality of life (QOL) [4]. The management of patients with TED is challenging and requires the involvement of physicians from various disciplines to personalize optimal treatment.

In 2008, the European Group on Graves' Orbitopathy (EUGOGO) presented their recommendations for improving the management of patients with TED. One of those recommendations was to establish specialized multidisciplinary TED clinics [5]. which since then have been established worldwide [6–8]. However, there are only a few reports on the results achieved by those clinics [9-11]. The first multidisciplinary TED clinic in Israel was established in a tertiary referral center in 2016. This clinic includes consultant ophthalmologists, oculoplastic surgeons, neuro-ophthalmologists, pediatric ophthalmologists, consultant endocrinologists, consultant immunologists, orthoptists, and social workers. The purpose of our study was to present the characteristics, treatments, and outcomes of patients who were treated in such a multidisciplinary TED clinic.

PATIENTS AND METHODS

MULTIDISCIPLINARY TED CLINIC

A multidisciplinary TED clinic was established at the Ophthalmology Institute at the Sheba Medical Center, Tel Hashomer, Israel, in May 2016. Patients who attended the clinic could be seen by consulting ophthalmologists, endocrinologists, and orthoptists, as well as by a social worker either on the same day or different days. Patients who had been treated by corticosteroids for active disease with some improvement and experienced re-

currence of the active disease as well as those with persistent active disease were referred to an immunologist to personalize optimal immunotherapy. Comprehensive discussions were conducted with all of the consultants to select the best disease management protocol for each patient.

STUDY PARTICIPANTS

A retrospective review of medical records of all patients who attended the TED clinic during the first 3 years was performed. Data on demographics, medical history, social history, laboratory tests, visual function tests, slit-lamp examinations, eyelid examinations, assessment of disease activity, and assessment of QOL were collected.

The study was approved by the local institutional review board at the Sheba Medical Center.

BLOOD TESTS

The serum levels of thyroid-stimulating hormone (TSH), free triiodothyronine 4 (fT4), and free triiodothyronine (fT3) were measured with chemiluminescent microparticle immunoassays that have analytic sensitivities of 0.02 mIU/L, 0.4 ng/dl, and 1 pg/ml, respectively (Architect Analytical System Third Generation kits, Abbott Diagnostics, Abbott Park, IL, USA). TSH levels were measured with an FDA-validated bioassay (Thyretain, Quidel Corp, San Diego, CA, USA).

Serum thyroid-stimulating immunoglobulin (TSI) activity was measured with a functional cell-based TSHR bioassay (Thyretain, Quidel Corp, San Diego, CA, USA) according to the manufacturer's instructions. The levels of TSI activity were measured in triplicate with the Infinite M200 microplate reader (Tecan, Crailsheim, Germany). All measured values were corrected for the plate's internal auto-luminescence by reduction of the mean value in blank wells. The results were reported as percentage of specimen-to-reference ratio (SRR%). SRR% values were calculated according to the following formula: SRR% = average TSI specimen relative light units (RLU)/average reference standard RLU × 100. The patient's serum was considered positive for the presence of TSI activity if the resultant SRR% measured ≥ 140% over the reference control.

EYE EVALUATION

Clinical ophthalmic exam included the following tests:

- Visual function tests consisting of visual acuity (VA), color vision (CV), relative afferent pupillary defect (RAPD), and visual field were conducted. Snellen VA was converted to log MAR (logarithm of the minimum angle of resolution) value. Each participant underwent a visual field test (Humphrey 24-2), and the mean deviation result was recorded. CV was examined by the Hardy-Rand-Rittler test and represented by the number of plates recognized by the patient out of the six screening plates
- Motility and orthoptic tests were used to identify and measure strabismus. Hess screen test was done in cases where a deviation was recorded
- Orbit evaluation with Hertel exophthalmometry was employed to evaluate proptosis in patients who had not undergone decompression surgery and Naugle exophthalmometry for patients who had undergone decompression surgery
- Eyelids evaluation by margin reflex distance 1 (MRD1), margin reflex distance 2 (MRD2), palpebral fissure (PF) height, eyelid edema, lagophthalmos, and 7th nerve palsy were conducted
- Evaluation of anterior and posterior eye segments and intraocular pressure (IOP) in primary and upward gaze by slit-lamp assessment were completed

ASSESSING DISEASE ACTIVITY

TED activity was evaluated during every clinic visit by the clinical activity score (CAS), a validated scoring system [12]. The CAS is based on the classical signs of inflammation, and it consists of seven criteria: spontaneous pain behind the globe, pain on attempted upward gaze, redness of the conjunctiva, redness of the eyelid, chemosis, swelling of the lacrimal caruncle, and eyelid swelling. One point is added for each item present. Scores of CAS < 3 suggest inactive Graves' orbitopathy (GO), while scores ≥ 3 suggest active GO. An expanded 10-point CAS scoring system is applicable for patients who had previous assessments, with additional points allocated for decreases in VA, worsening diplopia, and increasing proptosis, and with scores > 3 indicative of clinically active disease [12].

ASSESSING QUALITY OF LIFE

At each visit, patients completed a subjective validated questionnaire (Graves' Orbitopathy - Quality of Life, GO-QOL) [13] translated into Hebrew. In brief, the GO-QOL questionnaire contains two subscales of QOL as it relates to GO, specifically, visual functioning and appearance. Each subscale contains eight items, and each item is scored on a 3-point scale according to the extent to which GO affects the patient's QOL: 1 = severe, 2 = moderate to slight, and 3 = not at all. The scores on the two subscales are counted from 0 to 100 using the following formula: (total scores – #)/(2 × #) × 100, where # indicates the number of completed items. In all scores, 100 represents the best health state while 0 represents the worst health state. The responses are scored as missing if the participants could not complete the questions for any reason. Lower scores indicate a poorer QOL while higher scores indicate a better QOL.

STATISTICAL ANALYSIS

Quantitative variables were described as mean ± standard deviation. Categorical variables were described as absolute and relative frequencies. Chi-square analyses were used to calculate proportional differences between the groups, and a paired *t*-test

analysis was performed to evaluate differences in test results of the first visit in the TED clinic in comparison to those of the last follow-up visit. The correlation between various parameters were tested with Pearson's correlation analysis. The overall significance level was set to an alpha of 0.05. The statistical analysis was conducted with Microsoft Excel™ 2017 (Microsoft Corporation, Redmond, WA, USA) and using IBM Statistical Package for the Social Sciences statistics software, version 24 (SPSS, IBM Corp, Armonk, NY, USA).

RESULTS

THYROID CLINIC

During the 36-month study period, a total of 33 combined TED clinics were developed. These clinics examined 132 patients during 385 appointments, with a mean of 12 patients per clinic. The mean number of visits to the TED clinic was 2.29 (2.29 ± 1.62, range 1–9); 75 patients (56.81%) had more than one appointment: mean of 3.24 appointments (3.24 ± 1.68, range 2–9). Mean follow-up time from the first visit at the TED clinic to the last visit before the study closure was 21.26 months (21.26 ± 14.61, 1–36).

PATIENT CHARACTERISTICS

Of the total number of patients, 38 were men (28.8%) and 94 (71.2%) were women. Their mean age was 51.04 years (51.04 ± 16.88, range 20–112). A total of 121 patients (91.7%) were diagnosed with hyperthyroid disease, 6 (4.6%) with hypothyroidism, and 5 (3.8%) were euthyroid disease. Fifty-five patients (41.67%) were tobacco smokers and 27 (20.5%) were involved in some kind of physical activity. The medical history and habits of the study population are listed in Table 1.

THYROID BLOOD TESTS

The mean TSH level at first TED clinic visit was 2.33 mIU/L compared to 2.76 mIU/L at the last visit ($P = 0.08$, *t*-test). The mean level of TSI activity was 4032.61 at the first visit, which decreased to a mean of 1258.22 at the last follow-up visit ($P = 0.332$, *t*-test). The thyroid hormone levels at the first TED clinic visit compared to the last follow-up visit are summarized in Table 2.

The CAS at the first clinic visit was significantly, positively correlated with the level of TSI activity at the first clinic visit (0.905, $P < 0.01$). However, no correlation was found between the CAS and the levels of TSH, fT3, and fT4 at the first clinic visit ($P = 0.588$, $P = 0.863$, and $P = 0.203$, respectively). The CAS and the level of TSI activity significantly, positively correlated at the last follow-up visit (0.773, $P = 0.02$), as did the CAS and TSH (0.443, $P = 0.04$). . However, there was no correlation between the CAS and fT4 levels ($P = 0.931$) and the CAS and the fT3 levels ($P = 0.07$).

Table 1. Characteristics of the study participants

Variable	Number (%)
Family history of thyroid disease	
Yes	37 (28.03)
No	95 (71.96)
Other endocrinologist problem (e.g., diabetes mellitus, prolactinoma)	
Yes	16 (12.12)
No	116 (87.87)
Myasthenia gravis	
Yes	2 (1.51)
No	130 (98.49)
Radiation exposure	
Yes	5 (3.87)
No	127 (96.13)
Cigarette smoking	
Yes	55 (41.67)
No	77 (58.33)
Alcohol drinking	
Yes	4 (3.03)
No	128 (96.97)
Sleeping disorder	
Yes	25 (18.93)
No	107 (81.07)
Physical activity	
Yes	27 (20.45)
No	105 (79.55)

Table 2. Thyroid hormones levels at presentation compared to end of follow-up

	At presentation (mean ± SD)	At end of follow-up (mean ± SD)	*P* value (paired t-test)
TSH (mIU/L)	2.33 ± 10.03	2.76 ± 1.54	0.08
FT3 (ng/dl)	5.64 ± 2.83	4.51 ± 1.51	0.09
FT4 (pg/ml)	14.86 ± 5.65	14.68 ± 3.65	0.82
TSI	4032.61 ± 1031.61	1258.22 ± 1136.96	0.33

fT3 = free triiodothyronine 3, fT4 = free triiodothyronine 4, SD = standard deviation, TSH = thyroid stimulating hormone, TSI = thyroid-stimulating immunoglobulins

MANAGEMENT

Treatment for Graves' disease included: anti thyroid drugs (80 patients, 63%), radioiodine therapy (28 patients, 22%), and thyroidectomy (19 patients, 15%). Eye specific treatment for TED in the multidisciplinary clinic included medical treatment (48 patients, 36.3%) and surgical interventions (56 patients, 42.4%). The distribution of treatments is summarized in Table 3. There

Table 3. Treatments at a thyroid eye disease multidisciplinary clinic

Variable	Number	Percent
Medical treatment		
Any medical treatment	37	28.03
IVGC: High dose*	5	13.51
IVGC: EUGOGO	26	70.27
Immunosuppressive	6	16.21
Radiotherapy	0	0.00
Surgical treatment		
Any surgery	32	24.24
Decompression surgery	16	50
Strabismus surgery	4	12.5
Eyelid surgery	12	37.5

EUGOGO = European Group on Graves' Orbitopathy, IVGC = intravenous glucocorticoids

*IVGC: high dose intravenous infusion of methylprednisolone 1 gram daily for 3 days with a subsequent tapering dose of oral steroids over the next weeks

was a significant correlation between worse VA at the first clinic visit and a higher number of medical treatment (-0.193, P = 0.042). However, there was no correlation between worse VA at the first clinic visit and the number of surgical interventions (P = 0.449).

OCULAR CLINICAL CHARACTERISTICS

Five patients (3.8%) had acute optic neuropathy secondary to thyroid disease that was diagnosed and treated at the TED clinic. Optic nerve function and ocular characteristics at the first visit compared to the last follow-up visit is summarized in Table 4.

CLINICAL ACTIVITY SCORE

The mean CAS was 1.5 (1.5 ± 1.89, range 0–7) at presentation and 0.41 (0.41 ± 0.94, range 0–10) at the last follow-up visit 0.41 (P < 0.01). There was a significant positive correlation between number of pack years and the CAS among the smokers (0.720, P = 0.05). There was a significant negative correlation between CAS and color vision at the first clinic visit (-0.347, P < 0.01, Pearson correlation), but not significant correlation between the CAS and VA or visual field (P = 0.711 and P = 0.230, respectively). At the last follow-up visit, no correlation was found between the CAS and optic nerve visual function (i.e., VA, color vision, and visual field; P = 0.404, P = 0.494, and P = 0.983, respectively).

QUALITY-OF-LIFE QUESTIONNAIRE

The mean GO-QOL score at the first visit to the TED clinic was 54.06, which increased to 67.18 by the last follow-up visit (P = 0.141). There was a significant negative correlation between changes in the QOL score and the CAS score. (-0.240, P < 0.01). There was a significant positive correlation between changes in the QOL score and the number of surgical procedures (0.253, P < 0.01), as well as a positive but non-significant correlation between changes in the QOL score and the number of medical treatments (0.154, P = 0.07). Last, smokers had lower TED-QOS scores than non-smokers at the final follow-up (44.90 vs. 59.09, respectively, P = 0.05).

DISCUSSION

TED is one of the most common autoimmune inflammatory disorders of the orbit. The management of TED is challenging and requires the involvement of numerous medical and surgical specialties. Therefore, the UGOGO recommended the establishment of multidisciplinary TED clinics to provide the optimal tailored treatment for TED patients. In this study, we present the results of the first 3 years of a multidisciplinary TED clinic at a tertiary referral medical center.

Over 130 patients were examined in the clinic, with a mean of 12 patients per clinic. Patients underwent various laboratory tests and clinical examinations and responded to questionnaires about their QOL and self-esteem. We found that the level of TSI activity was the only blood test that predicted the CAS during follow-up. TED-QOS, which is based on a questionnaire that provides information about the patient's self-esteem, was also correlated with the CAS, but the CAS was not correlated with optic neuropathy. As a result, none of these examinations can serve as the sole test for predicting the severity of the disease, further confirming the need for a comprehensive assessment of all TED patients.

More than 70% of the patients in this study were women, and most of them had hyperthyroidism. These values correlate with those of earlier reports of TED being six times more likely in women than men and that most of the patients had Graves' disease [14].

More than 40% of the patients were current tobacco smokers, and there was a positive correlation between the number of pack years and a higher CAS. This finding was also in accordance with an earlier report which stated that tobacco smoking is the strongest modifiable risk factor for TED (an odds ratio of 7.7 for smokers vs. nonsmokers) [15]. The current study results also revealed a positive correlation between smoking and a lower GO-QOL score.

Laboratory tests are required to verify the diagnosis of TED and to help estimate the severity of the condition as well as assist in planning therapy. The routine blood tests for all the patients in our TED clinic measure TSH, fT3, fT4, and TSI levels. We do not recommend the thyrotropin binding inhibiting immunoglobulins (TBII) test since its inability to predict the existence or the severity of the disease has been demonstrated in several studies [16,17]. TSH, fT3, and fT4 did not correlate with the CAS in

Table 4. Ocular clinical characteristics

Variables	At first visit	At last follow-up visit	*P* value
Optic nerve function			
VA (LogMAR)	0.12	0.13	0.514
CV	4.97	4.98	0.903
VF- MD	-3.76	-3.15	0.336
RAPD			
Positive, n (%)	3 (2.27)	2 (1.51)	0.448
Negative, n (%)	129 (97.72)	130 (98.48)	0.327
Eye movement			
Eye movement disorder			
Yes, n (%)	55 (41.67)	45 (34.09)	0.199
No, n (%)	77 (58.33)	87 (65.91)	
Strabismus			
Yes, n (%)	20 (15.15)	23 (17.42)	0.327
No, n (%)	112 (84.84)	109 (82.57)	
Eyelid characteristics			
MRD1 (mm)	5.11 ± 2.27	5.30 ± 2.35	0.501
MRD2 (mm)	6.88 ± 2.02	7.32 ± 3.01	0.397
Orbit evaluation			
Hertel exophthalmometry (mm)	21.11 ± 3.48	21.22 ± 4.19	0.914
Naugle exophthalmometer (mm)	20.38 ± 3.46	19.45 ± 3.35	0.086
Slit-lamp evaluation			
Corneal keratopathy			
Yes, n (%)	40 (30.30)	29 (21.96)	0.567
No, n (%)	92 (69.70)	103 (78.04)	
IOP primary gaze (mmHg)	15.99 ± 3.13	16.22 ± 4.24	0.488
IOP upward gaze (mmHg)	20.73 ± 4.24	19.50 ± 5.78	0.201

CV = color vision, IOP = intraocular pressure, MRD1 = margin reflex distance 1, MRD2 = margin reflex distance 2, RAPD = relative afferent pupillary defect, VA = visual acuity, VF = visual field, MD = mean deviation

the visits to our clinic, but TSI activity did correlate with the CAS at presentation and at the end of follow-up. Several earlier studies also found TSI activity to be a functional indicator of GO activity and severity [16,18]. Taken together, these findings may indicate that the most effective blood tests for diagnosing TED are TSH, fT3, and fT4, and that TSI activity was most effective for predicting the severity of the disease and assisting in planning therapy.

Our results showed a correlation between a greater number of medical treatment and worse VA but not between VA and the number of surgical treatments. This finding is because our management protocol is to recommend steroid therapy or immunotherapy for patients who had already undergone steroid therapy in cases of worsening visual functions. Surgery is usually delayed until the disease is quiescent, and the patient is stable and weaned off all immunosuppression. Worsening visual functions is not the only indication for surgical intervention, and cosmetic problems may lead to surgery.

New immunological treatments have been introduced including cyclosporine, azathioprine, rituximab, and teprotumumab [19]. The new EUGOGO clinical practice guidelines recommended those treatment as second line treatments for moderate to severe disease [19]. Further studies are needed to examine the efficacy of those treatments on patient clinical features and QOL.

The CAS is used worldwide to identify active TED that requires corticosteroid therapy [12]. In the current study, there was no correlation between most of the visual function tests and the CAS. This finding may indicate that the disease can deteriorate and lead to significant complications, such as optic neuropathy or severe corneal exposure, while the CAS will still be low. More-

over, patients with high CAS scores may have long-standing congestive changes that are unresponsive to any immunotherapy but that respond best to decompression surgery. Therefore, clinicians should be aware that the CAS may be a confusing assessment score when decisions are being made about treatment, and that it cannot be the sole assessment on which to rely such decisions. There is, therefore, a need for TED physicians worldwide to consider a new assessment score for active TED, especially in the era of new treatments for the disease.

TED is a highly stigmatizing disease, which can affect both quality and length of life. Gerding et al. [20] reported that TED can impact lifestyle more severely than chronic lung disease or diabetes mellitus. Even mildly to moderately severe GO has a great influence on the QOL of these patients. Therefore, we require that our patients complete the GO-QOL questionnaire at each visit to the TED clinic. Analysis of the results of their responses for the purposes of this study revealed a significant positive correlation between a higher QOL score and more surgical intervention and a trend toward a positive correlation between a higher QOL score and more medical management. We consider that this finding probably stems from the fact that those treatments not only improve the patient's visual function and appearance but also self-esteem and QOL. The quality of life of the patients should also be considered regarding the timing of the treatment and the modality of treatment.

We demonstrated a correlation between the CAS and the QOL score. This finding may be explained by the fact that the CAS includes an assessment of disfiguring characteristics, such as proptosis, conjunctival edema, and others, as well as functional elements, such as strabismus and reduced VA. Those criteria are highly likely to also negatively affect both the self-esteem and the QOL of the TED patients.

CONCLUSIONS

The results of the first 3 years of experience at the first TED multidisciplinary clinic in Israel are described. A total of 132 patients were treated during the study period. To the best of our knowledge, our group of patients comprise one of the largest series treated in a TED clinic to be reported thus far. We recommend that decision making for the best management for TED patients should be based on the combination of clinical examinations by ophthalmologists and endocrinologists, laboratory test findings, CAS results, and QOL scores. A multidisciplinary specialized TED clinic offers an optimal setting for follow-up and management of patients with TED.

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Mistakes are part of the dues that one pays for a full life.

Sofia Costanza Brigida Villani Scicolone, known professionally as Sophia Loren (born 1934),
Italian actress named by the American Film Institute as one of the greatest female stars of Classical Hollywood cinema