Title: What are the psychosocial outcomes of treatment for thyroid eye disease? A systematic review

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Abstract

Background: Thyroid eye disease (TED) causes a number of esthetic and visual problems and its treatment requires close clinical assessment, often for several years. There is evidence to suggest that clinical factors are poor indicators of patient-reported outcomes after treatments that aim to improve appearance, vision, or both. Psychosocial factors can impact on both adjustment to living with TED and also patients' perceptions of their improvements after treatment. There has been growing recognition that it is essential to evaluate treatment efficacy in terms of psychosocial outcomes but, to date, there has been no review that has systematically evaluated psychosocial outcomes following a variety of treatments for TED.

Summary: Fifteen studies were included in the review and 6 were randomized controlled trials (RCTs). The studies varied greatly in methodological rigor; whilst major treatments such as surgery do improve quality of life outcomes, other non-invasive treatments such as intravenous steroids can have a similar impact and show long-term benefits. Only 3 studies reviewed orbital decompressive surgery which showed better psychosocial outcomes than other types of surgery.

Conclusions: The effect of some treatments remains unclear due to poor methodology and poor reporting of results. Clinicians need to be aware when planning rehabilitative treatments such as surgery the influence of psychosocial factors on quality of life outcomes and the lack of a relationship with clinical factors such as disease severity.

Introduction

Thyroid eye disease (TED) is an autoimmune disorder with an annual incidence of 16 in 100,000 women and 3 in 100,000 men (1) and it leads to functional deficits that include dry eyes, double vision, and pain. It can also cause drastic changes in appearance, including redness and swelling of the eyelids, eyelid retraction, and proptosis. These visual limitations and changes in appearance can have a significant impact on a patient's psychological functioning and quality of life. Patients with TED not only report being unable to carry out day-to-day activities – such as reading, driving and watching television (2,3) – but also experience distress in social situations and difficulty maintaining social relationships (4), this leading to social isolation and an altered sense of social identity (5).

There are a number of treatments for active TED including radiotherapy, systemic steroids, or a combination of the two, and other drug treatments such as pentoxifylline, selenium, rituximab and long-acting release octreotide (octreotide-LAR). Once TED has stabilized, patients may be offered surgery to improve appearance and vision: this ranges from 'minor' surgeries, such as eyelid lengthening, to the more intrusive orbital decompression which involves removal of the bony walls or orbital fat to decrease proptosis (6). Although up to four walls of the orbit may be removed during bony decompression (medial, lateral, superior and inferior), it is extremely uncommon to remove the orbital roof (7).

The clinical characteristics before treatment, such as disease duration, severity or activity often do not correlate well with patient reports of how visible they feel their TED is, and the impact the condition has on their lives (8, 9). In fact it appears that psychological processes individual to each patient, such as appearance concerns and a fear of being negatively evaluated in social situations, might better explain psychosocial adjustment to

living with TED (10). It is therefore important to measure psychosocial factors before and after treatment in order to establish the effects of treatment on well-being.

Patients with TED report concerns about changes in their appearance and poor psychological adjustment in the period following diagnosis and there is some evidence to suggest these concerns continue long-term (11). A number of systematic reviews have been conducted in order to establish the impact of radiotherapy (12, 13, 14) and orbital decompression (7) on the quality of life of patients with TED, and radioiodine therapy (RAI) compared to antithyroid drugs on the progression of eye disease for patients with Graves' disease (GD). One study that reviewed orbital decompression found no evidence for quality of life improvement after this surgery (7). Similarly, none of the few studies that examined radiotherapy and quality of life as an outcome measure found any improvement in quality of life (13-15) and patients with TED have not been distinguished from patients with GD in terms of quality of life (12). However with the most recent study included in these reviews having been published in 2005, and with new treatments for TED continually emerging, an updated evaluation of the current evidence is necessary.

The aim of this review was to determine the psychological impact of treatment for TED including drug therapy, radiotherapy, and surgical intervention.

Methods

Inclusion and exclusion criteria

Articles were restricted to those that had recruited adult patients (>16 years) with TED, and had evaluated the impact of some form of clinical treatment for TED on

psychosocial well-being. The tool used to measure psychosocial well-being needed to have been validated and the article needed to be published in a peer-reviewed journal and in English.

Search for relevant studies

An electronic search was performed using Ovid MEDLINE, EMBASE, PubMed, PsycINFO, Web of Science, CINAHL, AMED, PsycARTICLES, Cochrane Library, and SCOPUS in September 2012, using a combination of search terms that included all known medical terms for thyroid eye disease for example “Graves’ ophthalmopathy” and “dysthyroid orbitopathy”, treatment names, and terms to reflect psychosocial adjustment, for example “quality of life” and “depression”. In addition, email alerts were implemented and prominent authors found within this search were contacted for details of any further unpublished related work, or to retrieve elusive articles. The reference lists of all articles included, and relevant systematic reviews, were also searched for additional studies.

Study selection

Once searches had been conducted, clearly irrelevant titles were removed and, if it was unclear from the title alone, the abstracts were screened. All remaining articles were retrieved in full and screened for eligibility. The first author (SW) independently selected the relevant articles and the relevance of these articles was cross-checked by a second reviewer (HM); any disagreements were resolved in collaboration with a third reviewer (SN) until consensus was reached.

Quality assessment

The quality index (QI) developed by Downs & Black (1998) was used to assess the quality of all included articles (15). The QI is a highly regarded tool (16) that has been widely used in healthcare research: it consists of 27 items designed for use with both randomized controlled trials and observational studies and is composed of five subscales reporting, external and internal validity (both control of bias and confounding) and power.

Results

Description of the studies

The database searches identified 440 articles and 2 additional citations were retrieved from other sources, from which a total of 259 titles and abstracts were screened: 71 citations were excluded at this stage (Figure 1). The full texts of 188 articles were retrieved and reviewed for inclusion. After review and consensus, a total of 13 articles remained with an additional 2 articles that were retrieved from the reference lists, resulting in 15 articles included in this review.

The characteristics of the included studies are shown in Table 1. The 15 articles included a total of 1433 patients with TED and most participants were female (1267; 88%) although not all the studies reported sex distribution. Six of the studies were randomized controlled trials (RCTs) and 5 out of 6 were double-blind randomized trials where the patients and treating clinicians were blind to the type of treatment (17, 18, 19, 20, 21). One of the 6 trials was single-blind due to the nature of administering intravenous (IV) steroids (22). Three out of the 15 studies compared pre-treatment quality of life of TED patients to a healthy control group (23, 24, 25), 5 included a control group of patients with untreated TED

(18-21, 26) and the remaining studies had no group for comparison. In addition, two studies compared patients with GD without symptoms of eye disease to those with TED (24, 27)

A total of 14 treatments were evaluated (Table 1); methimazole, radioiodine (RAI), intravenous (IV) glucocorticoids (methylprednisolone), oral glucocorticoids (methylprednisolone, prednisone, and an unspecified corticosteroid), orbital radiotherapy, a combination of radiotherapy and oral glucocorticoids, a combination of radiotherapy and IV glucocorticoids, octreotide-LAR, selenium, pentoxifylline, orbital decompression, eye muscle surgery, eyelid lengthening, and blepharoplasty. Three studies reported administering, in addition to the main drug evaluated in the trial, methimazole and other anti-thyroid drugs in order to stabilize thyroid function (18, 20, 21): unfortunately the efficacy of the main treatment in each of these studies might have been overestimated (or underestimated) if methimazole independently alters eye symptoms and quality of life outcomes.

Quality of life was a primary outcome measure in 7 out of 15 articles (11, 24, 25, 26, 27, 27, 28) and secondary to clinical outcomes in the remaining 8 (18-23, 29, 30). The SF-36^{TM} was used as an outcome measure in 8 studies (11, 20, 21, 23-27). Two studies used the Sickness Index Profile (SIP) and the EQ-5D as outcome measures (11, 20); one study used the full EQ-5D (11), and the other used the visual analogue scale (20). Various versions of the GO-QOL were used in 9 out of 15 articles (11, 18-22, 26, 30, 31).

Quality assessment

The results of the quality assessment (16) indicate that the quality of studies varied considerably (mean = 20/32; range 14/32 to 31/32), but overall was reasonable (see supplementary file for additional details). The most common issues relating to quality were

omission of details about recruitment (such as exclusion criteria, sources of recruitment, or participant characteristics), the use of incorrect statistical analysis or lack of such analysis, and lack of either the reporting of statistical power, or inadequate recruitment to reach statistical power. In addition, the descriptions of treatment and its administration were often inadequate.

Methimazole

Abraham-Nordling *et al.* (24) found no significant difference, at any point between baseline and 4 years after treatment, in the physical or mental health-related quality of life between patients who received RAI and those that received methimazole. Both groups did, however, experience a significant improvement in quality of life after treatment and from 3 to 48 months after treatment the quality of life scores for physical health were equal to those of a Swedish general population reference group. Notably however, it took 12 months for mental health subscale scores to reach the same average for the reference population. This study also compared patients with GD with and withoutTED, and found that patients with TED at 2 years after methimazole treatment had significantly worse physical health-related quality of life as compared to patients without eye disease. At one year follow up, the authors found “no clear correlation” (p.655) between objective eye scores and physical health or mental health subscale scores, however correlation coefficients have not been provided. Elberling *et al.* (27) found that, after a year of methimazole treatment, patients with GD (both those with and those without TED) had significantly lower mental and physical quality of life as compared to a healthy control group from the general population; these authors did not examine the differences between patients with GD with and without TED.

Orbital radiotherapy

Using the GO-QOL, Prummel *et al.* (20) showed that patients at a year after orbital radiotherapy had similar quality of life scores to those receiving placebo radiotherapy, although this comparison was descriptive only. Terwee *et al.* (11) did not find a significant improvement in the visual functioning subscale of GO-QOL at 6 months after radiotherapy (p=0.05). Compared to orbital decompression, eye muscle surgery, eyelid lengthening or blepharoplasty, orbital radiotherapy led to the least improvement in appearance-related quality of life (11). Low correlation coefficients were found between changes in GO-QOL subscale scores and changes in clinical characteristics in this study. For the GO-QOL visual function subscale these include r = 0.27 for visual acuity and r = 0.27 for diplopia, and for the GO-QOL psychosocial function subscale these were r = 0.04 for lid aperture, r = 0.25 for proptosis and r = 0.28 for soft tissue involvement (11). In a cross-sectional study looking at long-term quality of life outcomes (up to 11 years) Terwee *et al.* (26) compared SF-36^{TM} scores for patients that had received radiotherapy, steroids (or both treatments) with the scores for patients that completed the SF-36^{TM} before the start of radiotherapy or orbital surgery: they found that the treated group experienced significantly better quality of life than those newly diagnosed, except on the physical functioning and general health perceptions subscales. The treated group also reported significantly better quality of life on the GO-QOL appearance and visual functioning subscales. Notably these findings are for "GO patients after treatment" and are not reported by treatment type. The radiotherapy group experienced worse functional quality of life than the steroid treated group, but scored better on the GO-QOL appearance subscale: no analysis of statistical significance was reported for this finding however.

Systemic corticosteroids

Using the SF-36™, Kahaly *et al.* (23) reported a significant improvement in physical and mental health-related quality of life after IV methylprednisolone, but no significant changes after oral methylprednisolone. Bartalena *et al.* (22) found that after 12 weeks of medium or high-dose IV methylprednisolone, there was a significant improvement in the GO-QOL visual function subscale and a significant improvement in appearance-related quality of life for those on low dose therapy. Likewise, Aktaran *et al.* (30) found that, after 3 months, 85% of the IV steroid group experienced significant improvements in vision-related quality of life and 81% had an improvement in the appearance subscale. In a group receiving oral steroids, 76% showed improvement in visual function subscale scores and 78% showed improvement in appearance subscale scores. IV treatment led to significantly more improvements in quality of life scores than oral therapy.

Of the participants in the study by Terwee *et al.* (26), 32% received prednisone, although it is unclear if this was oral or intravenous treatment. As compared to those receiving radiotherapy, participants who received prednisone had a better overall quality of life, with the exception of the appearance subscale of GO-QOL and the SF-36™ vitality score. Kashkouli *et al.* (28, 29) studied the effects of corticosteroids on quality of life, but the method of administration is unclear in both studies. In 2009 the authors reported the change in mean scores from baseline to 6 months after treatment and suggest significant improvement in both GO-QOL subscale scores. In the later study, both GO-QOL visual function and appearance subscales significantly improved after steroids, this contrasting with orbital decompression whereby only the appearance subscale scores improved. In both the steroid and the decompression groups, over two-thirds achieved the minimum

clinically important difference in quality of life, with no significant difference between the two groups. In both studies Kashkouli *et al.* failed to show any significant relationship between quality of life scores (before and after treatment) and clinical variables (including duration of disease, severity, or activity) (28, 29); however exact correlation coefficients have not been reported.

Kulig *et al.* (25) reported that patients with TED had significantly reduced quality of life, assessed by the SF-36™, as compared with a healthy group of volunteers from the general population. They found that orbital radiotherapy, combined with methylprednisolone, improved quality of life in relation to physical functioning, bodily pain and vitality; it is unclear if these changes were statistically significant however. The authors also found no correlation between quality of life and demographic or clinical variables; the authors have not reported the correlation coefficients found, however.

Long-acting octreotide (octreotide-LAR)

Dickinson *et al.* (18) reported a significant improvement in visual-related quality of life from pre-treatment to 16 weeks after administration of octreotide, and a significant improvement in appearance-related quality of life at 32 and 54 week follow-up, however significance levels were not reported. Wémeau *et al.* (21) used both the SF-36™ and GO-QOL, but merely report no significant changes in either quality of life score after treatment; exact data is not presented.

Pentoxifylline and selenium

Marcocci *et al.* (19) found no significant difference between the placebo and pentoxifylline on any of the GO-QOL subscales at 6 and 12 months after treatment. A

significantly greater proportion of patients in the selenium group did exhibit an improvement in quality of life at 6 months, compared with those receiving a placebo (19). An improvement of 6 or more points on the appearance subscale was reported in 84% of those taking selenium, 72% on the visual function subscale and 81% in overall scores. Selenium led to a significant reduction in deterioration of quality of (as compared with those given placebo). Selenium had a beneficial effect on quality of life that continued up to 6 months after treatment finished, both over time and when compared to the placebo group. However, the authors appear not to have analyzed the differences in quality of life improvements between the pentoxifylline and selenium groups.

Surgery

The EUGOGO consortium (31) investigated the impact of 18 different approaches to orbital decompression on quality of life using the GO-QOL. They observed improvements in the appearance subscale scores of between 17.4 and 39.9 points in all treatments, except for the translid and endoscopic approaches to decompression, in which the change was no more than 1.8 points. Although no significance testing was performed, improvements appear to be substantial for a number of approaches, with many changes in scores reaching a minimal clinically important difference (MCID) for the GO-QOL (see Table 2). Although the coronal approach led to the biggest improvement in appearance related quality of life, this approach caused the most frequent and serious complications.

Terwee *et al.* (11) reported a significant improvement in the GO-QOL visual function subscale where orbital decompression was performed for sight loss, and an improvement in the appearance subscale when decompression was performed for disfiguring proptosis. The authors have highlighted that improvement on the GO-QOL can be seen in either the visual

function subscale, or appearance subscale, or both, depending on the type of treatment (11). For example the effect size for decompression for sight loss in the GO-QOL visual function subscale is 0.9 and the effect size for decompression for appearance in the GO-QOL appearance subscale is 0.45; for the SF-36™ physical and mental health subscales these are 0.15 and 0.13, respectively. Eyelid lengthening resulted in a lower mean change in appearance-related quality of life compared to the other treatments, although this was not significant. Blepharoplasty (which included 8 patients who had eyelid lengthening at the same surgery) led to significant improvements in the appearance subscale, these improvements being comparable to those after orbital decompression.

Summary

This is the first systematic review to evaluate the impact of treatment including drugs, radiotherapy and surgery for patients with TED. In summary, radiotherapy was found to improve vision-related quality of life, but had the least improvement in appearance-related quality of life compared to surgery. Intravenous methylprednisolone led to better quality of life outcomes than oral methylprednisolone and, even at low doses; the former improved appearance-related quality of life. These studies also reported fewer adverse effects for IV corticosteroids as compared to oral, thereby making IV steroids a more favorable treatment both clinically and psychologically. Long-term benefits in quality of life were found for octreotide-LAR, methimazole and selenium at up to 4 years after treatment. Eyelid lengthening and blepharoplasty were both found to improve appearance-related quality of life, although these findings need to be considered in light of the poor quality of studies. Orbital decompression was found to have a larger effect on vision-related quality of

life when it was performed for failing vision, and a larger effect on appearance-related quality of life when surgery was performed for esthetic improvement.

The reporting of participant characteristics varied greatly between studies, with many studies failing to report disease severity (27) or previous treatments (27, 28). The severity of TED and prior treatment are important clinical factors that might contribute to a patient's psychosocial adjustment and their subsequent quality of life. The reporting of smoking status also varied, with only 6 of 15 studies reporting this data. Smoking is an important factor in the onset and severity of TED, and the response of TED to treatment, and therefore smoking status might affect both the clinical and psychological quality of life outcomes; a recent systematic review provides some evidence for this contention (31). The inclusion of a "no treatment" control group varied between RCTs, although this is not always possible in health research. Where particularly important confounding variables have not been accounted for – such as whether patients smoked, or if they were taking treatments additional to that under investigation – this could potentially affect the results of these studies. Limitations of some of these studies make it impossible to give definite recommendations about the most effective treatments for improving quality of life. Furthermore not all of the studies reviewed included the TED-specific GO-QOL as a measure of quality of life in the population. Generic HRQL measures, such as the SF-36™, include items that are often too broad to capture the specific experiences of patients with TED, unlike the GO-QOL which is able to detect clinically important changes in scores from baseline to post-treatment follow-up (11). The GO-QOL has previously been recommended as a primary outcome measure in RCTs (33) and the present authors would like to

emphasize the importance of assessing the impact of treatments on the quality of life of patients.

It is worth noting the limited number of studies that have examined quality of life after treatment, particularly in relation to orbital decompression: given how costly and physically invasive such procedures are, this is somewhat surprising. Despite the GO-QOL being recommended as an independent primary outcome measure in TED clinical trials (32), very few of the reviewed studies included this measure.

The authors acknowledge that the exclusion of 33 foreign language articles could be a limitation of this review as one of these studies measured quality of life pre- and post-orbital radiotherapy using the GO-QOL (34) and may have been eligible to include in the present findings.

Conclusions

The present review has brought together the results of a range of recommended treatments for TED on quality of life. It appears that whilst major treatments such as surgery do improve quality of life, other non-invasive treatments, such as IV steroids can have a similar impact and lead to long-term benefits. There remain few studies that have investigated how invasive surgical procedures such as orbital decompression impact on the quality of life of patients over the longer term.

This review has also shown that the relationship between clinical and psychosocial outcomes remains unclear. There are a number of previous studies that suggest that a relationship does exist, for example Yeatts (35) found a correlation between quality of life

and the objective severity of TED characteristics such as diplopia and dry eye symptoms. However, the tool used to measure quality of life in this population; the Graves Ophthalmopathy Quality of Life Scale (GO-QLS), had been developed by choosing the items that correlated highly with clinical severity so this finding would be expected (35). Park *et al.* (2) found that poorer quality of life was associated with more severe disease; however the authors conclude that their research might have been overrepresented by severe cases. Interestingly, Moss (36) has described a possible 'U' shaped curve where at the extreme ends of severity, i.e. in the least and most severe cases, objective and subjective ratings would be likely to correlate. Choi, Lim, Lee, Lee *et al.* (37) provide some evidence for this relationship having found that GO-QOL visual and appearance scores were significantly negatively correlated with clinical characteristics including soft tissue involvement, proptosis, severity score (NOSPECS) and activity (CAS). It might be likely that psychological processes rather than objective clinical measurements can better explain quality of life variability in patients with visibly disfiguring conditions (10), with some previous research supporting this notion in TED (8, 9) . However, there remain few studies that have investigated this relationship specifically in TED and, with mixed findings to date, further research is needed.

Definite conclusions about the best treatment options and the overall effects of some treatments on quality of life remains unclear; due to poor reporting of methodology and results. However, with the growing recognition that quality of life outcomes are an essential component of the outcome set for clinical trials, more robust evidence for quality of life changes will become available. As the GO-QOL has been found to be highly sensitive

to detecting changes after treatment for TED (11), it is recommended for use as a primary outcome measure in clinical trials for TED (33).

Clinicians need to be aware when planning rehabilitative treatments such as surgery that there is variability in the effects they have on quality of life. The GO-QOL is recommended for use in the routine assessment of TED in order to identify patients that might benefit from psychological support (33). Patients need to be fully informed that whilst the aim of treatment is to improve clinical symptoms, not all treatments will improve their quality of life.

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Author Disclosure Statement

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Table 1. The main characteristics of the studies included in the review

Authors	Country	Design	Control group	Sample population	Sample size	Exclusion criteria	Treatment type & administration	Follow-up periods
Bartalena *et al.* (2012)	The Netherlands, Belgium, France, Italy, Switzerland, and Greece	RCT	No	Moderate to severe, active TED	159	CAS less than 3/7, optic neuropathy, patients not recommended for GC therapy, pregnancy, no informed consent, increased liver enzymes by a factor of 2 or more above upper normal limits.	Three different doses of IV GC: 2.25g (low dose), 4.98g (middle dose), 7.47g (high dose)	6, 12 and 24 weeks
Dickinson *et al.* (2004)	UK & Germany	RCT	Yes	Moderately severe, active TED	50	Patients with sight-threatening disease (NOSPECS 5b, 5c, or 6)	Octreotide-LAR (30 mg by injection at 4 week intervals); placebo (prepared in ampoules of same volume and appearance as octreotide-LAR).	16, 32, 44, and 56 weeks
Kahaly *et al.* (2005)	Germany	RCT	No	Untreated, active, severe TED	70	*Not reported*	Oral GC (cumulative dose of 4.0g after 12 weeks); IV GC (cumulative dose of 4.5g).	12 weeks and 6 months

Marcocci *et al.* (2011)	Holland, Germany, Switzerland, Italy, Greece	RCT	Yes	Mild TED	152	NOSPECS class 2c1, exophthalmos >22 mm, diplopia and/or ocular torticollis, mono-ocular duction in any direction of less than 20 degrees, optic neuropathy, pregnancy, drug and/or alcohol abuse, severe concomitant illness, inability to comply with the study protocol, no informed consent, current use of selenium- or PTX-containing preparations.	Selenium (100 µg orally twice daily for 6 months); PTX (600 mg orally twice daily for 6 months); placebo (tablets twice a day for 6 months that looked identical to selenium and PTX)	12 weeks, 6 months and 12 months
Prummel *et al.* (2004)	Holland	RCT	Yes	Mild TED	88	Severe periorbital swelling, proptosis > 25 mm, moderate or severe motility disturbances, optic neuropathy, contraindications for radiotherapy (mostly diabetes), severe concomitant disease, no informed consent	Orbital radiotherapy (2 Gy daily over 2 weeks); sham irradiation (patients underwent the same procedures and the sound of the accelerator was simulated)	12 weeks, 6 months & 12 months
Wémeau *et al.* (2005)	France	RCT	Yes	Mild, active TED	51	Any other eye problem, gallstones, a history of treatment with systemic corticosteroids, immunosuppressive drugs, radiotherapy, or chemotherapy.	Octreotide-LAR (2ml treatments by IM injection); placebo (2 ml treatments by IM injection)	4 week intervals throughout the 16 week treatment period, and again 6 months after the

								beginning of treatment
Abraham-Nordling *et al.* (2010)	Sweden	Prospective randomized trial	Healthy (did not receive treatment so only compared at one time point)	Graves' hyperthyroidism	313 GD patients. 41 patients had TED on entry into treatment groups. 76 patients developed TED during the study (diagnosed during post-treatment assessments).	Previous history of treatments with ATDs, Iodine 131, or thyroid surgery, severe TED requiring treatment with corticosteroids, incipient toxic crisis, large goiters, CHD, pregnancy, breast-feeding or planned pregnancy	Methimazole; radioiodine (one administration for an absorbed dose of 120Gy)	12 weeks, 12, 24 and 36 months (48 months if eye symptoms continued to develop/ deteriorate)
Aktaran *et al.* (2007)	Turkey	Prospective, randomized, single-blind trial	No	Active, moderately severe TED	52	Corneal involvement (e.g. exposure keratitis), patients not recommended for GC therapy, a history of treatment with GCs, surgery or radiotherapy.	IV GC (cumulative dose of 4.5g); high dose Oral GC (cumulative dose of 4 g)	12 weeks
EUGOGO consortium (2009)	11 European centres: Holland, Italy, Greece, UK, Germany, France,	Prospective cohort	No	Inactive TED patients seeking surgery	118	*Not reported*	OD (17 different approaches)	12 weeks

	Switzerland							
Terwee *et al.* (2001)	Holland	Prospective cohort	No	TED patients	164; radiotherapy (n=23), OD for sight loss (n=10), OD for exophthalmos (n=38), EMS (n=31), EL (n=43), and blepharoplasty (n=19).	*Not reported*	Orbital radiotherapy; OD; EMS; EL; blepharoplasty (dose and administration of each not reported)	12 weeks after surgery, 6 months after radiotherapy
Terwee *et al.* (2002)	Holland	Cross sectional	Healthy (did not receive treatment so only compared at one time point)	TED patients currently receiving radiotherapy treatment	163	*Not reported*	Orbital radiotherapy; oral GC (prednisone); a combination of both immunosuppressive treatments (dose and administration not reported)	Duration of follow-up was calculated as the time between the first visit to the clinic and the follow-up visit for this study. Average follow-up was 11.7 years
Kashkouli *et al.* (2009)	Iran	Cross-sectional	No	TED	61	Absence of clinical and biochemical euthyroid state, presence of other chronic disorders such as diabetes mellitus, incomplete follow-up, and incomplete	'Corticosteroids' (dose and administration not reported)	6 months

						questionnaires (more than 10% missing data).		
Kashkouli *et al.* (2011)	Iran	Cross-sectional	No	TED	67	Absence of clinical and biochemical euthyroid state, presence of other chronic disorders such as diabetes mellitus, and incomplete follow-up	'Steroids' (dose, type and administration not reported); OD (specific type not reported)	6 months
Elberling *et al.* (2004)	Denmark	Before and after study	Yes	Graves' thyrotoxicosis	27 GD patients. 9 patients with toxic Graves' disease also had signs or symptoms of TED as classified by NOSPECS on entry into the study	Unable to read Danish, prior thyroid disease or psychiatric disorders, neurologic disorders known to influence neuropsychiatric functions, and other co-morbidities	Methimazole (dose and administration not reported)	1 year
Kulig *et al.* (2009)	Not stated - authors are in Poland & Denmark	Before and after study	Healthy (did not receive treatment so only compared at one time point)	Progressive infiltrative TED	29	Other autoimmunological disease, previous treatment with oral steroids, orbital irradiation only or cyclical administration of methylprednisolone only, patients whose treatment was ceased because of complications, cessation of oral treatment with prednisone, patient's	Combined IV GC and orbital radiotherapy (6 cycles of IV methylpred. sodium succinate)	6 weeks

						refusal to be examined after completing the full therapy, relapsing form of TED		

Acronyms: CHD = coronary heart disease, EMS = eye muscle surgery, EL = eyelid lengthening, IV GC = Intravenous glucocorticoid steroids, Oral GC = oral glucocorticoid steroids, Octreotide-LAR = Long-acting repeatable octreotide, OD = orbital decompression, PTX = pentoxifylline, RAI = radioiodine

Table 2. Scores representing the mean change from pre-treatment to post-treatment follow-up for each quality of life outcome measure

Treatment	Author	N	Length of follow up	GO-QOL Visual Function†	GO-QOL Psychosocial Function†	SF-36 Mental Component Score†	SF-36 Physical Component Score†	EuroQol†
Methimazole	Abraham-Nordling et al. (2010) *N.B Authors did not test for statistical significance*	145	48 months	-	-	21*♦	16*♦	-
	Elberling et al. (2004)	30	12 months	-	-	8.1*♦ **	8.6* ♦**	-

RAI	Abraham-Nordling et al. (2010)	163	48 months	-	-	17*♦	14*♦	-
Radiotherapy	Terwee et al. (2001)	23	6 months	8.1 (18.6)**	2 (17.9)	-	-	-
	Prummel et al. (2004)	26	12 months	8.2 (15.8)	6.7 (17.2)	-	-	1.2 (14.5)
	Terwee et al. (2002)*N.B authors combined treatment scores*	21	Various	*Not Reported*	*Not Reported*	*Not Reported*	*Not Reported*	*Not Reported*
IV Methylpred.	Bartalena et al. (2012) *N.B HD group showed the biggest change in mean scores*	52	3 months	12.8 (7.2; 18.3) ** ♦	9 (4.5; 13.5) ** ♦	-	-	-
	Kahaly et al. (2005)	35	3 months	-	-	0.5‡ **	0.4‡ **	-
	Aktaran et al. (2007)	25	3 months	*Not Reported*	*Not Reported*	-	-	-
Oral Methylpred.	Aktaran et al. (2007)	27	3 months	*Not Reported*	*Not Reported*	-	-	-
	Terwee et al. (2002) *N.B authors combined treatment scores*	52	Various	*Not Reported*	*Not Reported*	*Not Reported*	*Not Reported*	*Not Reported*
	Kahaly et al. (2005)	35	6 months	-	-	0.3 **	0.1	-

Other GCs	Kashkouli et al. (2009) *N.B authors combined treatment scores*	61	6 months	*Not Reported*	*Not Reported*	-	-	-
	Kashkouli et al. (2011)	61	6 months	20.1 **♦	24.4 **♦	-	-	-
Radiotherapy & GCs combined	Terwee et al. (2002) *N.B authors combined treatment scores*	90	Various	*Not Reported*	*Not Reported*	*Not Reported*	*Not Reported*	*Not Reported*
	Kulig et al. (2009) *N.B authors combined treatment scores*	29	6 weeks	-	-	*Not Reported*	*Not Reported*	-
Octreotide-LAR	Dickinson et al. (2004)	23	14 months	*Not Reported*	*Not Reported*	-	-	-
	Wémeau et al. (2005)	26	6 months	*Not Reported*	*Not Reported*	*Not Reported*	*Not Reported*	-
PTX	Marcocci et al. (2011) *N.B Authors did not test for statistical significance*	48	12 months	-0.64	-0.9	-	-	-
Selenium	Marcocci et al. (2011) *N.B Authors did not test for statistical significance*	54	12 months	11 (15.3)♦	12.6 (11.8)♦	-	-	-

OD (sight loss)	Terwee et al. (2001)	10	3 months	20.3 (19.5) **♦	4 (9.3)	-	-	-
	Kashkouli et al. (2011)	6	6 months	34.6♦	36 **♦	-	-	-
OD (exophthalmos)	Terwee et al. (2001)	38	3 months	3.2 (23.9)	11 (15.5) **♦	-	-	-
	EUGOGO et al. (2009) *Swinging eyelid transcar (3 wall)*	26	3 months	17.5 (20.8)♦	17.4 (24.5)♦	-	-	-
	Coronal (3 wall)	14	3 months	-1.7 (35.9)	39.9 (27)♦	-	-	-
	Translid endo (3 wall)	14	3 months	-0.8 (9.5)	1.8 (9.5)	-	-	-
	Swinging eyelid transcar (2 wall)	25	3 months	8.5 (20.9)	19.9 (22.9)♦	-	-	-
	Transcon transcar (2 wall)	18	3 months	7.9 (21.8)	9.7 (18.9)	-	-	-
	Endo (2 wall)	10	3 months	2.3 (30)	34.5 (30.4)♦	-	-	-
	Translid (2 wall)	11	3 months	13.6 (18.7)♦	22.1 (25.3)♦	-	-	-

EMS	Terwee et al. (2001)	31	3 months	2.8 (25.4)	2.6 (22.2)	-	-	-
EL	Terwee et al. (2001)	43	3 months	3.7 (15)♦	4.2 (13.9) **♦	-	-	-
Bleph.	Terwee et al. (2001)	19	3 months	0.2 (19.7)	10.2 (17.5) **♦	-	-	-

** Findings were statistically significant

♦ Minimal clinically important difference (MCID) achieved

*Scores include GD and TED patients combined,

‡ Authors reported change in age- and gender-adjusted z scores for the SF-36

† Scale runs from 0 to 100 (higher scores indicate better QoL outcomes)

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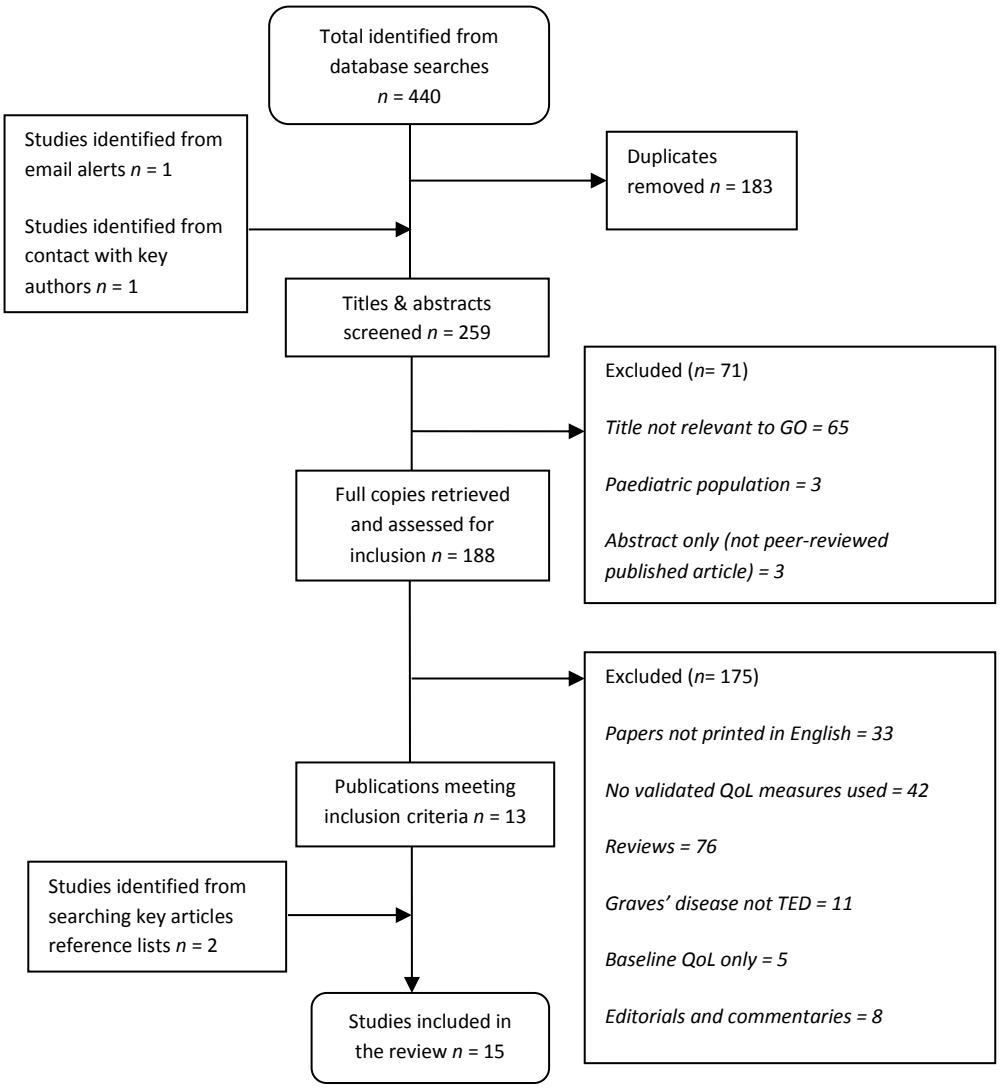

Figure 1. A flow diagram showing each stage of the study selection process

Supplementary File. Results of the quality assessment for the 15 studies included in the review

Source	**Abraham-Nordling et al (2010)**	**Aktaran et al (2007)**	**Bartalena et al (2012)**	**Dickinson et al (2004)**	**Elberling et al (2004)**	**EUGOGO et al (2009)**	**Kahaly et al (2005)**	**Kashkouli et al (2009)**	**Kashkouli et al (2011)**	**Kulig et al (2009)**	**Marcocci et al (2011)**	**Prummel et al (2004)**	**Terwee et al (2001)**	**Terwee et al (2002)**	**Wémeau et al (2005)**
Aims and objectives clearly described	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Main outcomes clearly described in the Introduction or Methods section	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Patient characteristics clearly described (i.e. Inclusion and exclusion criteria are given)	✓	✓	✓	✓	-	✓	✓	✓	✓	✓	✓	✓	-	✓	✓
Interventions clearly described	✓	✓	✓	✓	✓	-	✓	-	-	✓	✓	✓	-	-	✓
Distributions of principal confounders in each group clearly described	✓	✓	✓	✓	✓/ -	-	✓	✓	✓	✓	✓	✓	-	✓/ -	✓

Main findings clearly described	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Estimates of random variability in the data provided	-	-	✓	-	✓	✓	-	-	✓	✓	✓	✓	✓	✓	-
Adverse events have been reported	-	✓	✓	✓	✓	✓	✓	-	-	-	✓	-	-	-	✓
Characteristics of patients lost to follow-up have been described	✓	✓	✓	✓	✓	✓	✓	✓	-	✓	✓	✓	✓	✓	✓
Actual probability values have been reported except where p< 0.001	✓	✓	✓	-	-	-	✓	✓	✓	✓	✓	-	✓	-	✓
The subjects approached for the study were representative	-	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
The subjects who were prepared to participate were representative	-	-	✓	✓	✓	-	-	-	-	-	✓	-	-	-	-

The staff, places, and facilities where the patients were treated were representative	✓	✓	✓	✓	-	✓	✓	-	-	✓	-	✓	✓	✓	-
Subjects were blinded	-	✓	✓	✓	-	-	-	-	-	-	✓	✓	-	-	✓
Those measuring the main outcomes were blinded	-	✓	✓	✓	-	-	✓	-	-	-	✓	✓	-	-	✓
Any unplanned analyses were reported (if done)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
The analyses adjust for different lengths of follow-up of patients	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	-	✓
Statistical tests were appropriate	-	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	-	-
Compliance with the interventions was reliable	-	✓	-	✓	-	✓	✓	✓	✓	✓	-	✓	-	-	-
Outcome measures were valid and reliable	✓	✓	✓	✓	✓	✓	✓	-	-	✓	✓	✓	✓	✓	✓

Subjects in different intervention groups were recruited from the same population	✓	✓	✓	-	✓	-	✓	✓	✓	✓	✓	✓	✓	✓	-
Subjects in different intervention groups were recruited over the same period of time	✓	✓	✓	-	-	✓	✓	✓	✓	✓	✓	-	-	-	✓
Subjects were randomised	✓	✓	✓	✓	-	-	✓	-	-	-	✓	✓	-	-	✓
Randomisation was concealed from both patients and health care staff	-	✓	✓	✓	-	-	-	-	-	-	✓	✓	-	-	✓
Adequate adjustment for confounding in the analyses	✓	✓	✓	✓	-	-	-	✓	✓	✓	✓	✓	-	✓	✓
Losses of patients to follow-up were taken into account	✓	✓	✓	✓	✓	-	✓	✓	✓	✓	✓	✓	✓	✓	✓
The study had sufficient power	-	-	✓	-	-	-	-	-	-	-	-	-	-	-	-
Total score /32	**18**	**25**	**31**	**23**	**16**	**15**	**22**	**17**	**17**	**21**	**25**	**23**	**14**	**14**	**21**

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